EPIDEMIOLOGY OF COCA LEAF CHEWING IN THE 21st CENTURY PERU

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ABSTRACT

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Despite thousands of years of coca leaf chewing by rural inhabitants of the Andes Mountains, there is much to explore in the epidemiological research on this ancient habit. This is the first study about the epidemiology of coca leaf chewing and its health consequences that uses both a large representative random sample of the Andean rural highlanders of Peru, and the new ICD-10 diagnostic criteria for dependence syndrome. This secondary data analysis study has three specific aims: (1) to estimate basic epidemiologic parameters of the quantity of coca leaf chewing. (2) To estimate subgroup variations of the epidemiological parameters of the quantity of coca leaf chewing according to characteristics of person and place. (3) To estimate the degree to which coca leaf chewing might cause ICD-10 dependence syndrome and impairment in the quality of life.

The results show that coca leaf chewing is common and not evenly distributed among the Andean highlanders. Males, elders, and Ayacuchans are the most active coca leaf chewers. Furthermore, 2.3 percent of ever coca leaf chewers have ICD-10 dependence syndrome, and this dependence syndrome has compromised their quality of life. It is still premature to conclude that coca leaf chewing produces addiction. These initial findings should be followed by rigorous causal studies to assess the clinical features of coca leaf chewing dependence syndrome and its potential harmful physical consequences for the users.

This thesis is dedicated to my parents who thought me to love knowledge, freedom, and integrity; to my family for having bestowed their valuable time upon me to build my dreams; and to the children of the world for not stop dreaming of a better life based upon in the cultivation of knowledge.

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1.1 Introduction

The cultivation of plants is an ancient activity that almost certainly promoted a more advanced development of human civilization, and might be a distinctively human form of adaptation to environmental circumstances (Harlan & de Wet, 1973). This activity joined with the invention of tools, enhanced successful adaptation even under harsh life-threatening conditions. Furthermore, the cultivation of plants and the fashioning of tools have converged to yield fascinating patterns of human behavior. It seems to be the case for the chewing of coca leaf in the Andean regions of the world. Coca plants can grow wild, but it has thrived best when it has been cultivated by humans using simple tools such as spades and stone terraces.

Curiously, the reason for the cultivation of coca plants does not seem to be the typical reason for human cultivation of plants. Humans cultivate bananas, palm, maize, wheat, or other plants for its nutritional and nutrient value, ultimately discovered to be essential sources of vitamins in the late 19th century. The coca plant does not seem to be a vital source of a vitamin or a major nutrient compared to other plants eaten by humans (Penny et al., 2009). Chewing the leaf of the coca plant is not enough to keep a human alive in the way that chewing bananas, maize, or wheat might keep a human alive. Instead, we may understand the human cultivation of coca leaf as something more similar to the fashioning of a tool that might enhance life, particularly under harsh conditions of life in the Andean highlands, with benefits in the form of human life-form viability. Coca leaf chewing seems to have instrumental value in ways quite different from the instrumental value of other plants grown as a food.

An apt analogy might be to the coffee plant and the coffee bean, or the cannabis plant and its derivatives. Like drinking coffee from the coffee bean, the chewing of coca leaves can serve an instrumental function, yielding human benefits in the form of mental and physical stimulation. In addition, like smoking cannabis from the cannabis leaf or resin, the chewing of coca leaves serves a reinforcing function, and in some individuals, may function as a euphoriant - "lifting the spirits" as might be needed during times of distress, or trouble, or when hard work requires additional energy. Coca leaf chewing can also suppress appetite and has been used when nutritional food supplies are low. Finally, the coca leaves and coca products (e.g., soap, tea, etc.) can be useful as material tools serving other non-nutritive instrumental purposes.
This is the context for the present Master of Science thesis and the background that motivates this research on the epidemiology of coca leaf chewing in the highland communities of Peru.

1.2 Objective

The overall purpose of this research project has been to contribute new epidemiological survey evidence on coca leaf chewing in Peru, its patterns of use, and some possible complications, especially in the form of a coca leaf dependence syndrome, as well as an exploration of the association of coca leaf chewing with neuropsychiatric disturbances, including PTSD and other conditions often associated with political violence. Potential confounders and moderators of these associations have been taken into account to the extent possible.

1.3 Specific Aims

There is a handful of prior studies that have tried to study the ancestral tradition of chewing coca leaf among Peruvian aborigines, the prevalence, patterns of use, and the consequences in terms of the health of this population. None of these prior studies were carried out using an epidemiological probability sample of the study population. None has investigated coca leaf dependence syndrome. None has tried to estimate the association of coca leaf chewing with exposure to political violence and terrorism in this region during the 1980s and 1990s of the last century.

In order to fill these gaps in available evidence, this research addressed the following specific aims:

1. To estimate basic epidemiological parameters such as cumulative incidence proportions as observed for survey respondents in the study population, as well as prevalence proportions, and other parameters that reflect the persistence of coca leaf chewing once it starts.

2. To estimate the age of onset of coca leaf chewing and the degree to which the history of coca leaf chewing, the persistence of coca leaf chewing, and recently active coca leaf chewing might show variation across subgroups of the study population, with focused attention to variation in relation to characteristics of person and place, especially testing for personal characteristics of:

    2.1. Possible male-female differences,

    2.2. Variation across age groups,

    2.3. Variations across ethnic subgroups,

    2.4. Variation across the levels of exposure to traumatic events associated with political violence and terrorism, and

2.5. Variation across the history of posttraumatic stress disorder (PTSD).

3. To estimate the degree to which coca leaf chewing might have hazards in the form of coca leaf chewing harmful use or coca leaf chewing dependence, as can be detected by standardized field assessments such as the Mini-International Neuropsychiatric Interview (MINI) developed by Sheehan and colleagues (Sheehan et al., 1998). The possibility of impairment of quality of life among the coca leaf chewers in relation to a gradient of coca leaf chewing is considered, with due attention to possibly confounding effects of poverty, education, and psychiatric disorders (mood or anxiety disorders). Quality of life is evaluated via the Multicultural Quality of Life Index (MQLI) developed by Mezzich and colleagues and implemented in this epidemiological study (Mezzich et al., 2000).

It is hoped that this survey research project will give more precise and robust evidence under the heading of what the late Professor Jeremy Morris called ‘community diagnosis’ (Morris, 1955) and under epidemiology's rubrics of quantity, location, and mechanisms (Anthony & Van Etten, 1998). It also is hoped that the findings of this research may help policy makers in the design and implementation of public health policies based on evidence as a way to protect and improve the quality of health of the highlander populations of Peru.

1.4 Hypotheses

Under Specific Aim number 3, there are two specific hypotheses to be tested as part of the thesis research, stated here in the null form:

Within the coca leaf chewing (CLC) population of Peru, there is no evidence of a coca leaf-associated dependence syndrome. In effect, the estimated occurrence of dependence on coca leaf is zero.

If detected, any observed coca leaf-associated dependence syndrome has no apparent effect on the quality of life of the Peruvian highlanders, as measured by the standardized MQLI assessment described in specific aim number 3.

One interesting feature of this research involves the focus on the quality of life. It is possible that the CLC dependence syndrome exists at a non-zero value. However, it also is possible that dependence on coca leaves has no substantial effect on the quality of life. If so, there must be future research on the public health significance of coca leaf chewing dependence. (If the coca leaf chewing dependence syndrome exists, but has no clinical significance, then perhaps it does not belong in any classification of neuropsychiatric disorders. It might be a human experience without implications for human health and disease.)

Organized in relation to these specific aims, this thesis research project will serve as the first descriptive epidemiological survey research on coca leaf chewing in the 21st century. The project has been made possible by completion of a probability sample survey of inhabitants of the Andean highlands of Peru, which was one of a series of related epidemiological field surveys carried out by the Peruvian National Institute of Mental Health "Honorio Delgado – Hideyo Noguchi" throughout Peru. This particular survey studied inhabitants living in the highland rural areas of the Peruvian departments of Ayacucho, Ancash, and Cajamarca, and was completed in 2008 (Saavedra et al., 2009). The author (VC) was part of the leadership team for the field survey, which was completed under a protocol approved by the cognizant human subjects

research committee at the Noguchi Institute. For this thesis research project, he has been granted access to de-identified datasets from the original survey and has completed the thesis research project under a secondary data analysis protocol approved by the Michigan State University committee for the protection of human subjects in research, which judged the protocol to qualify as 'exempt' research as described in Chapter 3.

In outline form, the thesis report includes five chapters, starting with the present first chapter and a presentation of specific aims and hypotheses to be tested. The next chapter serves to present background information and to add more detail about the potential clinical or public health significance of the thesis research project if it proves to be successful. The third chapter describes the 'materials' of the research project and its methods as implemented in the Noguchi Institute field survey and the secondary analyses completed for this project. The fourth chapter describes the results and findings of these analyses, organized into parts according to the specific aims stated above. (The null hypotheses to be tested are covered in the fourth part of Chapter Four, part and parcel with results from analyses on suspected hazards of coca leaf chewing and associations with neuropsychiatric disturbances such as PTSD, as well as exposure to traumatic events.) The fifth chapter provides a discussion of the findings in light of the handful of prior studies on coca leaf chewing and human health, but with a thorough review of limitations of the research as might be strengthened in future research. The final chapter of the thesis is a succinct overview of main conclusions and directions for the future, including any implications for clinical or public health practice, if any are warranted.

CHAPTER 2 BACKGROUND AND SIGNIFICANCE

2.1 Introduction to Chapter 2

This chapter of the thesis is divided into five parts. In the first section, there will be an introduction of useful concepts for understanding the principal scope of this study, such as the concepts of coca leaf chewing, dependence on coca leaf chewing, and potentially associated neuropsychiatric disturbances such as posttraumatic stress disorder. In the second part, there will be a review of the history of coca leaf chewing as we know it from the published literature of the social sciences and epidemiology. In the third section, there will be a presentation of the current knowledge on the epidemiology of coca leaf chewing based on the framework of the five rubrics of epidemiology outlined by Anthony and Van Etten (Anthony & Van Etten, 1998), and then applied to drug dependence (Anthony, 2002). For instance, the rubrics of quantity, location, mechanisms, causation, and prevention will be reviewed, but in fact, there is little published epidemiological evidence on these topics, as will be shown in the thesis research report. In the fourth part, there will be an identification of the current gaps in the knowledge of the epidemiology of coca leaf chewing that I intend to fill in with the present thesis research project. Finally, in the fifth part of this chapter, there will be an identification of the potential contribution to the knowledge of the epidemiology of coca leaf chewing that this thesis might offer to the scientific community and policy makers, including reflections upon potential 'significance' or 'impact' as these terms currently are used in NIH grant reviews.

2.2 Coca Leaf Chewing Research: Organizing Concepts

This part introduces concepts of coca leaf chewing, dependence on coca leaf chewing, theories of drug dependence that now guide 21st-century research on this syndrome.

2.2.1 Coca Leaf Chewing

Generally, coca leaf chewing involves the intensive and persistent chewing of dried coca leaves. Prior research carried out among the Peruvian coca leaf chewers found that they use between 10 and 100 gm of dried coca leaves per day, with a mean of 30 gm per day. Roughly chewers swallowed the half part of the chewed coca leaves, and they throw the rest away. They chew coca leaf three times per day, especially before working (C. Gutierrez-Noriega & Von Hagen, 1950). They often chew coca leaf with a pinch of llipta or cal. Llipta is the name for the ashes of the stalks of the Andean grains knows as quinoa or cañiua, and cal is a powder made from calcium-containing rocks that were previously burned and then ground into small particles (Baker & Mazess, 1963).

2.2.2 Coca Leaf Chewing Addiction or Dependence Syndrome

There are various diagnostic criteria for dependence syndromes in the world. Among them, the most important for exhaustiveness and scientific foundation is the Diagnostic and Statistical Manual of Mental Disorders 4th edition, DSM-IV (American Psychiatric Association, 1994), and the International Classification of Diseases 10th revision, ICD-10 (World Health Organization, 1992a). During this thesis research, the American Psychiatric Association produced the Diagnostic and Statistical Manual of Mental Disorders 5th edition, DSM-5 (American Psychiatric

Association, 2013), which is an updated revision of DSM-IV. However, to date, there is no epidemiological research based on DSM-5.

In the present research, the diagnostic criteria for research based on the ICD-10 Classification of Mental and Behavioral Disorders are used (World Health Organization, 1993). Here, the case definition is that a person with dependence should have three or more of the following clinical features for at least one month or 12-months if the symptoms last less than one month:

1. "A strong desire or sense of compulsion to take the substance."
2. "Impaired capacity to control substance-taking behavior in terms of onset, termination or level of use, as evidenced by the substance being often taken in larger amounts or over a longer period than intended or any unsuccessful effort or persistent desire to cut down or control substance use."
3. "A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms."
4. "Evidence of tolerance to the effects of the substance, such that there is a need for markedly increased amounts of the substance to achieve intoxication or desired effects, or that there is a markedly diminished effect with continued use of the same amount of the substance."
5. "Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a

great deal of time being spent in activities necessary to obtain the substance, take the substance, or recover from its effects."

6. "Persisting with substance use despite clear evidence of harmful consequences, as evidenced by continued use when the person was actually aware of or could be expected to have been aware of the nature and extent of harm."

The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) substitutes both concepts of 'substance dependence' and 'substance abuse' for the most neutral term 'substance use disorder' (American Psychiatric Association, 2013). The change is trying to resolve an old controversy about the appropriateness of the use of the terms 'dependence' or 'addiction' to describe the compulsiveness of substance use despite clear evidence of its harmful consequences. In the 1980s, an international committee of experts from the American Psychiatric Association and the World Health Organization agreed that compulsiveness or loss of control is the fundamental characteristic of substance use disorder. Nonetheless, they did not get consensus if the term addiction or dependence described better the clinical features of this disorder. Some experts believed that the term addiction conveys better the key clinical feature of compulsion for using the drug. Others believed that the use of the term addiction would stigmatize the treatment of drug users. Finally, the term dependence was adopted over the term addiction just for one vote of difference (C. O'Brien, 2011). In 1987, this agreement was implemented in the Diagnostic and Statistical Manual of Mental Disorders III Edition Revised, DSM-III-R (American Psychiatric Association, 1987). The DSM-III-R stated, for the first time, the current diagnostic criteria of dependence disorder. These clinical features remain almost invariable in the Diagnostic and Statistical Manual of Mental Disorders 4th

Edition, DSM-IV (American Psychiatric Association, 1994), and the International Classification of Diseases 10th Revision, ICD-10 (World Health Organization, 1992a).

Scholars advocated for the substitution of the DSM-IV term 'dependence' for 'addiction' because the use of dependence in psychiatric nosology was creating confusion among clinicians (Maddux & Desmon, 2000; C. O'Brien, 2011; C. P. O'Brien, 2012). It is not a new issue, adducing the same motives Miller in 1991 tried to introduce the term addiction in the DSM-IV instead of the DSM-III-R term of dependence (Miller & Gold, 1991). However, the DSM-IV task force did not take into consideration his recommendations. The confusion arises because dependence means at the same time, both physical dependence and a disorder triggered by the use of psychoactive substances.

Furthermore, physical dependence with its classic symptoms of tolerance and withdrawal is observed in the medical use of substances lacking addiction liability, such as beta-blockers and antidepressants (Miller & Gold, 1991; C. P. O'Brien, 2012). In consequence, it cannot be equated as a substance use disorder. On the contrary, not all the addictive substances trigger significant clinical symptoms of tolerance and withdrawal, such as cocaine (Eddy, Halbach, Isbell, & Seevers, 1965). For this reason, the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition, DSM-III, did not consider ***cocaine dependence*** as a psychiatric disorder(American Psychiatric Association, 1980). Until this moment, most of the experts agree in 'addiction' conveys better the behavioral feature of compulsive use of psychoactive substances than 'dependence' which is more related to the pharmacological features of tolerance and withdrawal (Maddux & Desmon, 2000; Miller & Gold, 1991; C. O'Brien, 2011; C. P. O'Brien, 2012).

However, not everybody agrees with the substitution of the term 'dependence' for 'addiction.' For instance, the eminent British professor Griffith Edwards, who in 1981 introduced the concept and clinical description of 'Drug Dependence Syndrome,' which was adopted by the ICD-10 (Edwards, Arif, & Hadgson, 1981), rejects bringing back the old term 'addiction' in replace of the term 'dependence.' He argues the inexistence of empirical data supporting the adduced confusion triggered by the use of the term 'dependence' in psychiatric diagnoses. If there is any confusion, he believes that it can be corrected by education and not necessarily by changing the term 'dependence.' Finally, he considers that using the term 'addiction' in psychiatry is still pejorative such as the use of the term 'lunacy,' which might contribute to the alienation of the patients with substance use disorders (Edwards, 2012).

Curiously, in 1964, Eddy adduced also confusion in the use of the terms 'addiction' and 'habituation' among clinicians, to foster the change of the term 'addiction' for 'dependence' in the new edition of the International Classification of Diseases (World Health Organization, 1964). Probably, one of the oldest definitions of 'addiction' and 'habituation was made by Tatum and Seevers in 1931. They defined 'addiction' as a state resulting in the continuous use of drugs that trigger abstinent symptoms on withdrawal and sometimes tolerance. In opposite, 'habituation' is a state in which the users need the drug, but there is no evidence of abstinent symptoms on withdrawal (Tatum & Seevers, 1931). These concepts of 'addiction' and 'habituation' were incorporated in the first worldwide International Classification of Diseases 6th Revision, ICD-6 (World Health Organization, 1949), and the first Diagnostic and Statistical Manual of Mental Disorders, DSM-I (American Psychiatric Association, 1952). In 1950, addiction experts of the World Health Organization (WHO) under the chairman of Eddy defined the

clinical characteristics of 'addiction.' They pointed out that compulsion for continuously taking the drug was the critical feature of addiction, following for psychological dependence, tolerance, and sometimes physical dependence. The emergence of abstinent symptoms on withdrawal was considered an expression of physical dependence. Furthermore, they defined 'habituation' as the state in which the continuous use of the substance is provoking social or individual detriment in the absence of addiction symptoms (World Health Organization, 1950). The International Classification of Diseases 7th Revision, ICD-7, incorporated the recommendations of the WHO experts and kept the terms 'addiction' and 'habituation' (World Health Organization, 1957). However, in 1963 the WHO addiction experts under the chairman of Eddy recommends the substitution of the terms 'addiction' and 'habituation' for the term 'dependence' because they found that clinicians were misusing these terms (World Health Organization, 1964). The International Classification of Diseases 8th Revision, ICD-8 (World Health Organization, 1967) and the Diagnostic and Statistical Manual of Mental Disorders 2nd Edition, DSM-II (American Psychiatric Association, 1968) incorporated Eddy's recommendations. Both the ICD-8 and the DSM-II substituted the terms "addiction" and 'habituation' for the term 'Drug Dependence.' However, they continue using the term 'Alcohol Addiction' instead of the term 'Alcohol Dependence.' In the following years, both the International Classification of Diseases 9th Revision, ICD-9 (World Health Organization, 1977) and the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition, DSM-III (American Psychiatric Association, 1980) substituted the term 'alcohol addiction' by the term 'alcohol dependence.' Furthermore, for the first time, alcohol and drug use disorders are classified together into the independent category 'Substance Use Disorders.' Moreover, for the first time in the DSM-III appeared the

'Substance Abuse' disorder, and in the ICD-9 appeared the 'Nondependent Abuse of Drugs' disorder, which is the precursor of the ICD-10 'Harmful Use Disorder.'

Either the ICD-6, ICD-7, ICD-8, ICD-9, DSM-I, and DSM-II did not use specific diagnostic criteria for each disorder; this condition was about to change with the emerging of the DSM-III. Influenced by the pioneering work of Feighner, the DSM-III started using diagnostic criteria for some disorders (Feighner et al., 1972; Kendler, Munoz, & Murphy, 2010). The specific DSM-III diagnostic criteria for substance dependence included: (1) tolerance, or (2) withdrawal symptoms(American Psychiatric Association, 1980). The specific diagnostic criteria for 'substance dependence' was refined in the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition Revised, DSM-III-R (American Psychiatric Association, 1987), which included nine criteria. These nine DSM-III-R criteria of 'substance dependence' remain almost invariable through the Diagnostic and Statistical Manual 4th Edition, DSM-IV (American Psychiatric Association, 1994), the Diagnostic and Statistical Manual 4th Edition Text Revision, DSM-IV-TR (American Psychiatric Association, 2000), the Diagnostic and Statistical Manual 5th Edition, DSM-5 (American Psychiatric Association, 2013), and the International Classification of Diseases 10th Revision, ICD-10 (World Health Organization, 1992a); for more details watch table 2.2.2.1. The only exceptions are: (1) The ICD-10, DSM-IV, DSM-IV-TR, and DSM-5 dropped out the 4th DSM-III-R criterion of "frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home, or when substance use is physically hazardous." (2) The ICD-10, DSM-IV, DSM-IV-TR, and DSM-5 joined the 9th DSM-III-R criterion of "substance often taken to relieve or avoid withdrawal symptoms" with the 8th DSM-III-R criterion of "characteristic withdrawal symptoms." (3) Both the ICD-10 and the DSM-5

included the new criterion Craving manifested by and intense desire or sense of compulsion or urge for the drug.

Finally, although the criteria of drug use disorder remain almost invariable throughout the different editions of the DSMs or revisions of the ICDs, there is still a controversy in the best term 'addiction' or 'dependence' to define this psychiatric disorder. To settle this controversy, the DSM-5 is using the term 'substance use disorder' instead of 'dependence' or 'addiction.' To form the criteria of 'substance use disorder,' the DSM-5 joined the DSM-IV criteria of 'substance dependence' and 'substance abuse.' Although the DSM-5 dropped out of the 3rd DSM-IV criterion of 'substance abuse' "recurrent substance-related legal problems." Professor Edwards has criticized the elimination of 'substance abuse' from the DSM-5 because he considers that there is enough evidence to support the idea that substance use disorder is a two-dimensional concept: (1) "problems" with dependence, and (2) "problems" without dependence (Edwards, 2012).

Table 2.2.2. 1 Clinical features of substance dependence or substance addiction throughout the different Classification Manuals of Mental Disorders

	DSM-III-R (1987)	ICD-10 (1992)	DSM-IV (1994)	DSM-IV-TR (2000)	DSM-5 (2013)
	Substance Dependence criterion number	***Dependence Syndrome*** criterion number	***Substance Dependence*** criterion number	***Substance Dependence*** criterion number	***Substance Use Disorder*** criterion number
CLINICAL FEATURES					
Larger/longer	1	2	3	3	1
Cut down/control	2	2	4	4	2
Time spent	3	5	5	5	3
Intoxicated/withdrawal at work	4	–	–	–	–
Reducing/giving up	5	5	6	6	7
Social/psychological/physical probs.	6	6*	7*	7*	9*
Tolerance	7	4	1	1	10
Withdrawal	8	3	2	2	11
Taken to relieve/avoid withdrawal	9	3	2	2	11
Craving	–	1	–	–	4
Required criteria number	≥3	≥3	≥3	≥3	–
Duration					
Continuous symptomatology	≥1 month	≥1 month	≥12 months	≥12 months	–
Discontinuous symptomatology	≥1 month	≥12 months	≥12 months	≥12 months	–
	Substance Abuse criterion number	***Harmful Use*** criterion number	***Substance Abuse*** criterion number	***Substance Abuse*** criterion number	–
CLINICAL FEATURES					
Failure to fulfill obligations	–	–	1	1	5
Use in physically hazardous situations	2	–	2	2	8
Substance-related legal problems	–	–	3	3	–
Using despite social/interpers. prob.	1**	1**	4	4	6
Required criteria number	≥1	–	≥1	≥1	≥2
Duration					
Continuous symptomatology	≥1 month	≥1 month	≥12 months	≥12 months	≥12 months
Discontinuous symptomatology	≥12 months	≥12 months	≥12 months	≥12 months	≥12 months
Never met criteria for dependence	Required	Required	Required	Required	–
Identifiable physical/psychological harm	–	Required	–	–	–
Severity					
Mild	–	–	–	–	2-3 sympts.
Moderate	–	–	–	–	4-5 sympts.
Severe	–	–	–	–	≥6 sympts.

* It does not consider social problems.

** It also includes psychological or physical problems.

2.2.3 Theories of Addiction or Dependence Syndrome

Contrasting with the considerable advances achieved in the biology, psychology, anthropology, and sociology of drug dependence and addiction there is still a controversy in the conceptual

definition of these syndromes (Foddy, 2011; Shaffer, 1997) or the convenience of use of the term dependence instead of addiction (C. P. O'Brien, Volkow, & Li, 2006). In this situation, It is indispensable to review the current theory of drug addiction, which will give the framework to understand the possible dependence syndrome provoked by the chewing of coca leaves.

The current theories of drug addiction go from the microscale to the macroscale. In the microscale, there are psychobiologic theories. In the macroscale, there are the anthropological and sociological theories of addiction.

2.2.3.1 Psychobiologic Theories of Addiction

2.2.3.1.1 Opponent Process Theory of Addiction

This theory is based on the **opponent-process theory of motivation** of Solomon and Corbit (Solomon & Corbit, 1974). This theory of motivation founded in behavioral, psychological observations postulates that all hedonic, affective or emotional state (the primary a-process) is followed by an opposite hedonic, affective or emotional state (the secondary b-process) which reduces the intensity of the first state. It means if the a-process is pleasant, the opposite b-process will be aversive, or if a-process is aversive, the opposite b-process will be pleasant. Finally, the b-process is strengthened by use and weakened by disuse.

Later, the opponent-process theory of motivation was expanded to explain the phenomenon of drug addiction (G. F. Koob, Stinus, Le Moal, & Bloom, 1989; Solomon & Corbit, 1973). For instance, the pleasurable effect of the drug is the a-process (positive reinforcement), and its subsequent aversive effect of the abstinence syndrome is the b-process (negative

reinforcement). With the continued use of the drug, the pleasurable a-process is weakened, and the aversive b-process is strengthened and last longer. In this context, tolerance is the expression of the weakened pleasurable a-process, and the abstinence or withdrawal syndrome is the expression of the strengthened and last longer aversive b-process(G. F. Koob et al., 1989). The neural substrate of the opponent's theory of motivation is the nucleus accumbens(G. F. Koob, Markou, Weiss, & Schulteis, 1993). The increment of dopamine on the nucleus accumbens exerted by the ingestions of the drug triggers the positive reinforcement of the pleasurable effect of the a-process (G. F. Koob & Bloom, 1988). Using the addictive substance persistently triggers the sensitization of the nucleus accumbens. Then, to compensate for the neurobiological action of the addictive drug, the nucleus accumbens exerts a corrective homeostatic response. This sensitized nucleus accumbens is responsible for the tolerance to the pleasurable effects of the drug and the strengthened of the aversive effects of the abstinence syndrome on withdrawal of the drug. This theory considers that the negative reinforcement effect of the drug use on the presence of the withdrawal syndrome is a necessary and sufficient cause of dependence to the drug(G. F. Koob et al., 1989).

2.2.3.1.2 Psychomotor-stimulant Theory of Addiction

This theory postulates that both stimulant and depressant drugs of abuse have the common property of trigger psychomotor activation after the consumption of it by humans or animals. This psychomotor activation is directly correlated with their ability to produce subsequently positive operant reinforcement effects. Furthermore, the psychomotor activation and the positive operant reinforcement have a common biological substrate in the mesocorticolimbic

dopaminergic system, especially in the activity of nucleus accumbens. This substrate coordinates the motivational activity of approach to the drug, and the subsequent reward of it. At least at the beginning, the repetitive use of the drug produces the sensitization of this psychomotor and rewarding dopaminergic pathway, which is expressed by an enhanced psychomotor response to the drug use, and by biochemical and anatomical changes at the neuronal level. This theory hypothesized that this sensitization at the end produces the craving and the compulsive use of the drug, which are the cardinal symptoms of addiction. Also, tolerance (the opposite phenomenon of sensitization) and withdrawal symptoms of physical dependence are just symptoms of second order in the phenomenon of addiction(Wise & Bozarth, 1987).

2.2.3.1.3 Incentive-sensitization Theory of Addiction

This theory is based on the classical and operant conditioning, by which an adaptive behavior such as drinking water when one is thirsty or eating food when one is hungry take the focus of one's attention and enhance the sensation of the associated sights, sounds or smells. The brain perception of these sensations is represented as "wanted," which at the end will direct the motivated behavior. The attractiveness for one's attention to these sensations, its correspondent "wanted" perception, and its elicited motivated response is called ***incentive salience.*** Furthermore, the mesocorticolimbic dopaminergic system is the biological substrate of the incentive salience. Although the dopaminergic system is also related to the mechanism of pleasure or "liking." The incentive-sensitization theory proposed the dissociation of "wanting" from "liking." The persistent use of the drug causes this dissociation, which subsequently

produces the sensitization of the mesocorticolimbic dopaminergic system. This sensitization enhances the "wanting" perception. The behavioral expression of all these neurological changes is the intense craving for the drug even when consuming in the middle of aversive circumstances such as severe withdrawal symptoms or family, social, or work problems. (Robinson & Berridge, 1993).

2.2.3.1.4 Hedonic-allostasis Theory of Addiction

This theory is based upon in the biologic homeostatic theory developed by Bernard (Bernard, 1957) and Cannon (Cannon, 1963). Homeostasis is a dynamic and integrative process of preserving the biological functions inside of certain boundaries in order to preserve life. However, extreme demanding or stressful circumstances, such as the use of the addictive drug, produces the activation of the hypothalamic-pituitary-adrenal axis. In this situation, the hypothalamus releases the corticotropin-releasing factor (CRF) from the paraventricular nucleus. The CRF stimulates the release of the adrenocorticotropic hormone (ACTH) from the pituitary gland. The ACTH stimulates the release of glucocorticoids from the adrenal gland. Finally, the glucocorticoids via negative feedback decrease the synthesis of CRF in the paraventricular nucleus and stimulate the CRF activity in the central nucleus of the amygdala. This hyperactivity of the CRF will increase the excitability of the amygdala, the reward system, and the corticothalamic-striatal circuit, responsible for compulsive behaviors. In the end, these changes will force the living being to change their physiological parameters to another more rigid, permanent, and narrow boundaries, in order to keep working their biological systems under this abnormal situation. At this adaptive process of maintaining stability via the changing

of the physiological homeostatic parameters is called **"allostasis."** This theory affirm that mild changes in the internal milieu of this new allostatic state will produce the drug craving, withdrawal symptoms, and compulsive use of the drug in order to restore the new pathological equilibrium (allostasis) (G. F. Koob & Le Moal, 2001).

2.2.3.1.5 Aberrant-learning Theories of Addiction

This theory is based on learning and motivational theories. The aberrant-learning theory postulates that the drug of abuse produces a distortion on the normal process of learning, creating an alteration in the motivation of the users. Although the drug of abuse similar to sex or food stimulates the rewarding system at the level of the nucleus accumbens shell, it does not experience habituation upon repeated drug use as instead is the case of sex or food. Thus, the repetitive and non-decremental stimulation of dopamine transmission on the nucleus accumbens shell produces the strengthen of classical conditional learning of cues associated with drug use.

Moreover, the activation of dopamine D2 receptors on the central nuclei of the amygdala promotes the consolidation into the long-term memory of the associated drug cues, which is now resistant to extinction. In the future, these conditioned cues or context will increase the likelihood of drug use by triggering approach-escape behaviors. Subsequently, there is a transition from classical conditional learning to an operant conditional learning mediated by a sensitized nucleus accumbens core, basolateral nuclei of the amygdala and the dorsal striatum (caudate nucleus and putamen), which produces an alteration in the motivation expressed by compulsive drug use in the presence of the drug-associated cues (Di Chiara, 2002;

Everitt et al., 1999). Finally, the unconscious classical and operant learning will turn conscious when the hippocampus collects and relates information from drug-related cues and their associated affective states (declarative memory). This memory system helps the learning process of getting and using the drug to obtain its rewarding effects (Squire, 2004; White, 1996).

2.2.3.1.6 Frontostriatal-dysfunction Theory of Addiction

This theory postulates that the persistent use of the drug of abuse will alter the neurological circuit of rewarding and the circuit of inhibition of behaviors (Jentsch & Taylor, 1999). Drug-related changes in the plasticity of the prefrontal cortex and nucleus accumbens are responsible for the uncontrollable drive to drug use. Diminution of dopamine D2 receptors (D2R) and increasing activity of dopamine D1 receptors (D1R) in the prefrontal cortex is responsible for the loss of the rewarding and motivational effects of other unconditional stimuli such as sex, allowing only intense stimulus such as drug-related cues, or drug use to activate the rewarding circuit. Moreover, the subsequent hyperactivation of glutamate from the neuronal projections of the prefrontal cortex to the nucleus accumbens is responsible for the uncontrollable drive to drug use (Kalivas, Volkow, & Seamans, 2005). This uncontrollable craving and compulsive drug use are not going to be inhibited by the orbitofrontal cortex due that the persistent hyperactivation of the rewarding system by the drug use disturbs the normal inhibitory activity of behaviors of the orbitofrontal cortex via the striatal-thalamic-orbitofrontal circuit (N. D. Volkow & Fowler, 2000).

2.2.3.2 Anthropological Theories of Addiction

2.2.3.2.1 The Social Production of Suffering Theory of Addiction

First cultural ethnographic studies tend to diminish the deleterious effects of drug use, especially the effects of alcohol use. The study results show that alcohol consumption of isolated cultural groups has different socio-cultural meanings than in western societies. For instance, in the Camba population of Bolivia, alcohol consumption is a source of social solidarity, rapport, and group health, and the pernicious effect of alcohol use watched in western societies is almost inexistent (Heath, 1958). However, in the 1980s, the critical medical anthropology model was developed as a direct critique of the formerly cultural model. This new anthropological model considers that the consumption of drug use is not only modeled by the culture at which the consumers belong but also by the context of macro-social structures such as the economic structure, political structure, institutions of social control, social classes, the relationship with international corporations and overseas nations (Singer, 1986). Under the critical medical anthropology model, researchers have found that the social suffering of the weaker and impoverished populations is more important than the psychological or biological factors to explain the epidemics of drug use in the twenty century (Bourgois, 2003; Singer, 2012; Stebbins, 1987).

2.2.3.3 Sociological Theories of Addiction

2.2.3.3.1 The Structural Functionalist Theory of Addiction

This theory affirms that addiction is an expression of social deviance of persons who cannot incorporate their cultural norms, values, goals, and means. It usually happens in times of quickly social changes or crisis, where prevails the social disorganization, with weakened or inexistent norms or rules, which is called anomie. In these circumstances, the people display four forms of anomalous adaptations: ***Innovation***, these persons accept the social goal of success, but reject the social means to get it; for instance, these people might accept to be a drug dealer in order to achieve economic success. ***Ritualism,*** these people accept just the means but reject the social goal; for instance, they work routinely and poorly. ***Retreatism***, these people reject the social goals and means; and they are usually addicts to drugs. ***Rebellion***, these people try to change the social goals and means for another set of values (Merton, 1938, 1968). In general, people expressing the retreatism category accounts for drug addiction, but people expressing the other adaptational categories also have some levels of drug addiction (Adrian, 2003).

2.2.3.3.2 Symbolic Interactionist Theory of Addiction (Social Psychological Theory of Addiction)

This theory supports the idea that addiction is a socially learned deviant behavior (Bandura, 1986). As deviant behavior has negative connotations, the learners must use some rationalization to calm their conscience (Akers, 1985). The members of society learn culturally

deviant behaviors in the process of socialization or interaction with others. In this process, someone labels as an "alcoholic" or "drug addict" to the other person. It usually happens when the labeler has power or influence over the labeled. In this process, the labeled will be aware of how others perceive him or her and eventually will integrate into his mind the imaging that he is an addict and will conduct as an addict behave in his culture (Adrian, 2003).

2.3 Historical Background on Coca Leaf Chewing

The human interest for the stimulant effects of plants is as old as its interest in the nutritional value of the plants. There is archaeological evidence of the use of addictive plants from the Neolithic period (Vetulani, 2001) when humans started the domestication of plants (Fedick, 1995). However, the first use of these plants has more a religious and medical purpose than a hedonic purpose (Vetulani, 2001). For instance, there are some archeological pieces of evidence of the use of marihuana and opium 6,000 years ago in the middle east (Adrian, 2002). A study in the remains of ancient Peruvian settlements has shown vestiges of the use of coca leaf and lime (calcite) about 8,000 years ago (Dillehay et al., 2010).

Current evidence suggests that coca leaf was chewed for the first time by nomadic hunter-gatherers of the eastern Andes before the beginning of agriculture. In the beginning, coca leaf might be used as a source of human nutrition, but it soon gets popularity among the highlanders more for the coca stimulant and healing properties than for its nutritional value. When the growing population of coca leaf chewers exceeded the gathering capabilities, the highlanders had to transplant the coca shrubs from the wild close to their human settlements.

This innovation would guarantee the availability of coca leaves to the members of their community (Plowman, 1984).

There is plenty of evidence that this habit of chewing coca leaf prevailed during the pre-Columbus period (Martin, 1970). For instance, coca leaves (Erythroxylum spp) were identified via anatomical and histological analysis in the wool bags ("chuspas") of pre-Hispanic graves from the Tiwanaku period (320 AD), regional development period (1100-1300 AD), and Inca period (1400 AD) (Molina, Torres, Belmonte, & Santoro, 1989). On the western coast of Peru and inside of Moche's graves, it was found ceramics showing the faces of men chewing coca leaf dating from 300 AD (Lumbreras, 1974). It was also found coca leaf "quid" in the oral cavity of Maitas Chiribaya's mommies (figure 2.3.1) dating from 500 AD (Cartmell et al., 1994; Cartmell, Aufderheide, Springfield, Weems, & Arriaza, 1991).

Figure 2.3.1 Maitas Chiribaya mummy showing a coca leaf quid in his mouth (500 AD)

Source: Cartmell, L.W. et al. The frequency and antiquity of prehistoric coca leaf chewing practices in northern Chile: Radioimmunoassay of a cocaine metabolite in human-mummy hair. Latin American Antiquity, 1991 Sep., 2(3): 260-268.

The first writing evidence of the extended habit of chewing coca leaf among the ancient Peruvian aborigines comes from Spaniard conquer Pedro de Cieza-de-Leon. He arrived for the first time to South America in 1553 and described his experiences on a chronicle of his travel through the new land just discovered (figure 2.3.2), which is called Peru by the aborigines (De Cieza-de-Leon, 1864).

Figure 2.3.2 Pedro de Cieza-de-Leon Chronicle of Peru, 1553, where he described the rites and customs of the Indians

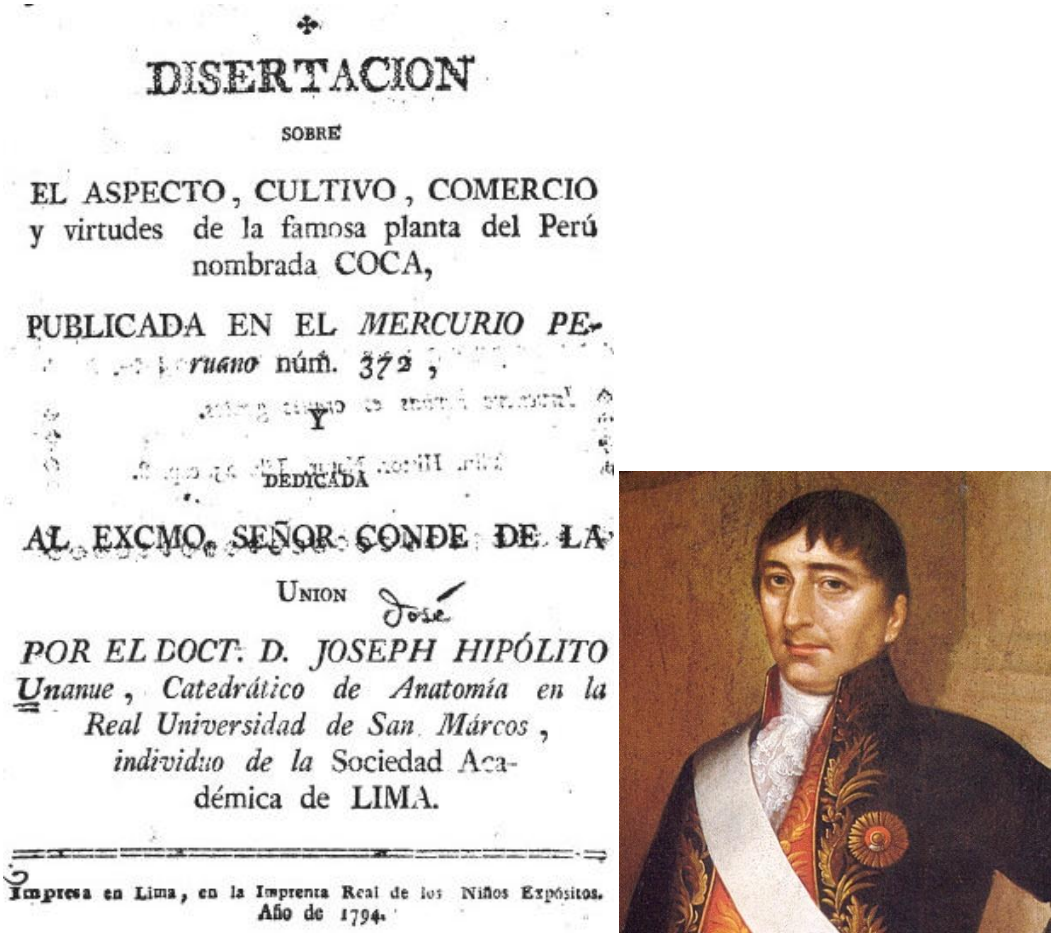
Source: Wikipedia, the free encyclopedia:
http://commons.wikimedia.org/wiki/File:Cronicadelperu.jpg
Source: Collaborative encyclopedia in the Cuban Red (Ecured):
http://www.ecured.cu/index.php/Pedro_Cieza_de_Le%C3%B3n

The first reaction of the Spaniards to coca-leaf chewing was of rejection of this habit among the Indians. The promoter of this rejection was the Catholic Church, which considers that coca-leaf chewing was a central part of the Indian pagan religious life. In this way, the first

ecclesiastical council of Lima condemned it in 1551. Furthermore, Andres Hurtado-de-Mendoza, the Marquis of Cañete and fifth Spanish viceroy of Peru enacted in 1556, the first law aiming to eradicate the plants of coca and substitute it for alternative crops, which nowadays is the hallmark policy of the governments in the world (Gootenberg, 1999). However, after observed that the Indians could do more work with less food, they start to stimulate its extensive use among miners or other hard workers. This activity became so profitable for the businessperson and the authorities that forced the Catholic Church to change its initial point of view. In consequence, the Viceroy Toledo removed the official prohibition on coca leaf cultivation in 1573; this policy aimed to get more revenue from the taxation of the trade of coca leaf. Although the Spaniard considers that coca-leaf chewing was a habit of lower-class, they continue producing and selling it among the Indians during the next three centuries of their reign in the new world (Allen, 2002).

At the end of the eighteen century and under the influence of the enlightenment and the scientific revolution of that century, Hipolito Unanue (figure 2.3.3), the father of the Peruvian Medicine and Founded Father of the Republic of Peru, published one of the best dissertations about the aspect, cultivation, trade, and virtues of the coca leaf shrub (Unanue, 1794). In this paper, Unanue imbued with the ideas of the famous botanist and physician Carl Linnaeus, the father of the modern taxonomy, postulate the potential utility of coca-leaf in medicine. He thinks that chewing coca-leaf or drinking coca-leaf infusion like tea might be useful for respiratory diseases, colic, constipation, asthenia, as well as to keep healthy teeth. He also prognosticates that in the future, the coca leaf might be sold at a large scale worldwide as tobacco after the world recognize its medicinal virtues (Unanue, 1794).

Figure 2.3.3 Hipolito Unanue Dissertation about the Aspects, Cultivation, Trade and Virtues of the Famous Plant of Peru Called Coca, 1794



DISERTACION

SOBRE

EL ASPECTO, CULTIVO, COMERCIO y virtudes de la famosa planta del Perú nombrada COCA,

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Y

DEDICADA

AL EXCMO. SEÑOR CONDE DE LA UNION

POR EL DOCT. D. JOSEPH HIPÓLITO Unanue, Catedrático de Anatomía en la Real Universidad de San Márcos, individuo de la Sociedad Académica de LIMA.

Impresa en Lima, en la Imprenta Real de los Niños Expósitos. Año de 1794.

Source: Google Books: http://books.google.com.pe/books?id=lY4aAAAAYAAJ
Source: Wikipedia, the free encyclopedia: http://en.wikipedia.org/wiki/File:HipolitoUnanue.jpg

In the nineteenth century, with the beginning of the industrial revolution and the influence of positivism as a source of scientific knowledge through observation, the entire world started paying attention to coca leaf as a potential source of medicine for different diseases. This interest was pushed forward with the identification of the active ingredient of Peruvian coca leaf in 1859. Albert Niemann discovered it in Gottingen, Germany, and he called the new alkaloid substance cocaine (Gootenberg, 1999). The subsequent discovery of the

clinical utility of cocaine as an anesthetic for eye surgery by Karl Koeller in 1884, transform the local use of coca leaves by the Andean Indians in a worldwide industry of cocaine. At the end of the nineteenth century, cocaine was sold in drugstores as miracle medicine in the form of pills, tonics, paste, etc. for almost all the diseases.

The late nineteenth-century worldwide awareness of the medical use of cocaine transform the conservative point of view of the Peruvian society that coca-leaf consumption was just a primitive expression of uneducated and underclass Indians. The impact of this discovery was high among the Peruvian academics of the School of Medicine "San Fernando" of the Major National University of San Marcos. One of the prominent scientists of this period was the French-Peruvian Alfredo Bignon, who, between 1884 and 1887, published several papers of his experiments with cocaine in local and international journals (Gootenberg, 2007). The same period in which the young physician Sigmund Freud published in Europe a famous paper about the medical use of cocaine (Freud, 1885). The main contribution of Bignon to the boon on the business of cocaine was the discoverer of a new simple and economical method of extraction of cocaine directly in fields of coca crops. He used lime, kerosene, and soda ash to extract cocaine in the form of cocaine sulfide with 60% of pureness. Without knowing it, Bignon created the foundation of the future cocaine paste, which will be the major Peruvian cocaine product of exportation for the illegal market in the twenty century (Gootenberg, 2007).

In this context by 1900, Peru became the first leading legal exporter of raw coca leaves and cocaine in the form of sulfites of cocaine worldwide (Gootenberg, 1999). Other countries soon entered the business of cultivation of coca leaves and the production of cocaine in different parts of the world such as the Netherlands and Japan. The Netherlands started the

cultivation of coca leaf in 1883 in its East Indies Colony, current Indonesia, especially in the islands of Java, Madura, and in lesser scale in Sumatra. In 1911, Peru was displaced from his position as the first world exporter of coca by the Dutch East Indies colony (Gootenberg, 1999). In 1916, Japanese companies started the cultivation of coca leaf in Taiwan (then Formosa), Iwo, Jima, and Okinawa, and in 1929 its production of coca leaf was sufficient to supply the Japanese manufactures of cocaine (Gootenberg, 1999).

At the end of the nineteenth century, with the recognition of addiction as a medical disease, cocaine started changing from panacea to toxic substance in medicine. The concept of addiction was developed first around the use of opium than cocaine. Because Sertuner isolated morphine, the active substance of opium, in 1803 time before the discovery of cocaine (Gootenberg, 1999), and in the half part of the nineteenth century, with the invention of the hypodermic needle its use became widespread. After ten years of using it with needles, the physicians started describing the first cases of addiction to morphine, where the physiological or physical dependence symptoms were the prominent feature. In the beginning, the physiological symptoms of tolerance and abstinence observed in morphine addicts were mild or absent among the cocaine users, which was take as a fact to affirm that the use of cocaine does not cause addiction. However, in the following years, physicians observed intense craving and compulsive use of cocaine, which was named psychological dependence. After observed other physical harmful consequences concomitant with the use of cocaine such as high blood pressure, cardiovascular arrest, stroke, transitory psychosis, and brain damage the professional organization of physicians started to organize a civil movement in the United States to regulate the selling of cocaine and other drugs in the field of medicine. The principal argument of this

movement was that the pharmaceutical industry sold cocaine and other drugs without enough evidence of their utility and safety. All this movement foster the federal regulation of the cocaine and morphine market via different laws such as the Food and Drug Acts enacted in 1906 and the Harrison Tax Act enacted in 1914. The first one has the aim of labeling the medicine with all its constituents (Gootenberg, 1999), and the second one had the aim of regulate and tax the production, importation, and selling of coca products and opiates (Cantor, 1961). Nonetheless, it was not until 1922 in which the import of cocaine was completely prohibit in all the USA territory via the Jones-Miller Act (Gootenberg, 2003).

The early twenty-century worldwide awareness of the harmful consequences of the use of morphine and cocaine raised the concern of the Peruvian researchers about the medical consequences of the chronic and widespread habit of chewing coca leaf by the Andean highlanders. In this topic, the researchers did not arrive at a consensus. One group consider to have enough evidence to prove that coca-leaf chewing produces addiction such as cocaine, and another group considers that these findings were weak evidence to affirm that coca-leaf cause addiction in a similar way than cocaine (for more information read the section 2.4.3). To resolve this controversy in 1947, the United Nations send a commission of inquiry to Peru and Bolivia to disentangle this controversy. The Peruvian government requested the United Nations the establishment of this commission (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

2.4 Epidemiological Evidence on Coca Leaf Chewing

The presentation of the current epidemiology evidence of coca leaf chewing will be based on the framework of *five rubrics of epidemiology* (Anthony & Van Etten, 1998):

2.4.1 Rubric of Quantity

Across the centuries, coca leaf chewing has impassioned researchers around the world. However, none of them has accurately measure via epidemiological surveys the frequency of this old habit of the Andean highlanders and other local populations. Current data support the idea that this habit was widespread and remain steady across time.

2.4.1.1 Ever Coca-leaf Chewing or Cumulative Incidence Proportion (Lifetime Prevalence)

Researchers via radioimmunoassay measured the presence of cocaine or its metabolite benzoylecgonine in the hair of 163 pre-Columbus mommies dating from 3,000 BC to 1,500 AD; they found a cumulative incidence proportion of coca-leaf chewing of 46.6 percent on the coast and low valleys of the north of Chile (Cartmell et al., 1991). The same researchers using the same methodology and expanding the sample size of pre-Columbus mommies from 163 to 254 found a cumulative incidence proportion of coca-leaf chewing of 45 percent on the coast and low valleys of the south of Peru and the north of Chile (Cartmell et al., 1994). Other researchers working with 86 pre-Columbus human remains from 800 AD to 1350 AD on the southern coast of Peru found a cumulative incidence proportion of coca leaf-chewing of 40.7 percent (E. Indriati & Buikstra, 2001). In this last study, the researchers used the physical characteristics of

the teeth and the identification of benzoylecgonine, a metabolite of cocaine, in the hair of the human remains as a way to identify chewers from non-chewers of coca leaves.

In 1950, the United Nations Commission of Enquiry on the Coca Leaf estimated the at least 45 percent of the Quechuas or Aymaras population of Peru chews coca leaf. This result is just a tentative estimation due that they did not have a reliable and accurate data to reach their goal (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

Perhaps the most serious attempt to measure the prevalence of coca leaf chewing was the survey carried out in 1965 by the Peruvian Ministry of Health with the technical assistantship of the United Nations. They used a representative random sample of the Peruvian population. Unfortunately, this survey never reached the end, and Caravedo-Carranza and Almeida-Vargas published a report with the partial results of this study. They found a cumulative incidence proportion of coca leaf chewing of 50 percent among the rural population of Peru aged 14 years or higher (Caravedo-Carranza & Almeida-Vargas, 1972). At the departmental level, including urban and rural areas, the cumulative incidence proportion was lower than the rural area alone.

In 1965, a team of researchers from the John Hopkins School of Public Health researched four rural Peruvian villages to evaluate the health and disease of this population. They found a cumulative incidence proportion of coca-leaf chewing of roughly three, 26, 29, and 72 percent among the population aged 20 years and over in each one of these four villages located in the jungle, highland, and coast of Peru. They got levels of participation above 90 percent in these communities, and they used a nonrandom sample design in their study (Alfred A. Buck, Sasaki, & Anderson, 1968).

Finally, studies carried out in 1998 among a non-probability sample of 210 Aymaras reported a cumulative incidence proportion of coca-leaf chewing of 69 percent. The participants in this study were residents of the Aymara communities from the Ingavi province of Bolivia and the Parinakota province of Chile (Etty Indriati, 1998).

2.4.1.2 Recent Coca Leaf Chewing (12-months Prevalence)

In the existent literature, there is no evidence of the magnitude of 12-months prevalence of coca-leaf chewing.

2.4.1.3 Active Coca Leaf Chewing (30-days prevalence)

In the existent literature, there is no evidence of the magnitude of 30-days prevalence of coca-leaf chewing. However, the everyday coca-leaf chewing estimation of 20.5 percent reported by Indriati in a study among the Aymaras communities of Bolivia and Chile may be used as a proxy of active coca-leaf chewing (Etty Indriati, 1998). In another study, the estimation of everyday coca-leaf chewing prevalence varies roughly from zero to 52.5 percent, with a lower prevalence in communities located at a lower altitude and with a scarce population of Quechuas and Aymaras. For instance, the prevalence of everyday coca-leaf chewing was zero percent in the village of San Antonio, district of Nauta. Five percent in the village of Yacango, district of Torata. 21.9 percent in the village of Cachicoto, district of Monzon. Moreover, 57.6 percent in the village of Pusi, district of Pusi (Alfred A. Buck et al., 1968).

2.4.2 Rubric of Location

This section will describe the distribution of coca-leaf chewing according to characteristics of person, place, and time. There will also be a description of the age of onset of coca leave chewing.

2.4.2.1 Subgroup Variations of Coca Leaf Chewing According to personal characteristics

2.4.2.1.1 Subgroup Variations of Coca Leaf Chewing by Sex

The current evidence is still not clear if there is some degree of male-female differences in the prevalence of coca-leaf chewing. Some researchers affirm that coca-leaf chewing prevalence is less frequent in females than in males, other researchers found not male-female differences, and others report that coca-leaf chewing is a little more prevalent among females than males.

Researchers such as Zapata-Ortiz and Negrete found that the prevalence of coca-leaf chewing is significantly lower in females as compared to males (Negrete, 1978a; Zapata-Ortiz, 1952). The United Nations commission of researchers found that the cumulative incidence proportion of coca-leaf chewing is lower among females, with no more than 20 percent of female coca-leaf chewers as compared to 45 percent of coca-leaf chewers among the general Indian population (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

Buck et al. found variable results, considerably lower cumulative incidence proportion of coca-leaf chewing among females as compared to males in two Peruvian villages. For instance, 10.4 percent among females as compared to 45.4 percent among males in the rural village of

Yacango, district of Torata, province of Mariscal Nieto, department of Moquegua and 21.8 percent among females vs. 35.7 percent among males in the village of Cachicoto, district of Monzon, province of Huamalies, department of Huanuco. Nevertheless, in the village of Pusi, district of Pusi, province of Huancane, department of Puno, the cumulative incidence proportion of coca-leaf chewing was a little bit bigger among females as compared to males. 74.4 percent among females vs. 68.7 percent among males. Moreover, almost not male-female differences, 2.8 and 2.5 percent respectively in the village of San Antonio, district of Nauta, province of Loreto, department of Loreto (Alfred A. Buck et al., 1968).

Other researchers also found that the cumulative incidence proportion of coca-leaf chewing is a little more frequent among females than males, although these differences were not statistically significant. For instance, among 86 mummies dating 800 AD to 1350 AD, the cumulative incidence proportion of coca leaf-chewing among females was 46.9 percent vs. 32.3 percent among males, although this difference was no statistically significant (E. Indriati & Buikstra, 2001). The same researcher in a more currently sample of 210 Aymaras found a cumulative incidence proportion of coca-leaf chewing of 70.4 percent among females and 67.4 percent among males, although this small difference was not statistically significant (Etty Indriati, 1998).

To sum up, the actual evidence suggests that the cumulative incidence proportion of coca-leaf chewing is significantly lower among females than males or at least similar but not most prominent.

2.4.2.1.2 Subgroup Variations of Coca Leaf Chewing by Age Group

The current evidence suggests that the prevalence of coca-leaf chewing tends to increase with age.

In a study carried out among the residents of the small upper jungle village of Cachicoto, located in the eastern part of the Peruvian Andean Mountain, researchers found a prevalence of coca-leaf chewing of zero percent in the age group of 0-9 years. It was four percent in the age group of 10-19 years, 20 percent in the age group of 20-29 years, 30 percent in the age group of 30-39 years, and 33 percent in the age group of 40 or more years (A. A. Buck, Sasaki, Hewitt, & Macrae, 1968).

This increment on the prevalence of coca-leaf chewing by age is even higher among aborigine communities. Thus, Cachicoto has a lower tendency of the prevalence of coca-leaf chewing by age as compared to the Aymara communities of Bolivia and Chile. Cachicoto has a population of 23 percent of Quechuas and 77 percent of mestizos, while the population of Aymaras en las communities of Bolivia and Chile was close to 100 percent. For instance, a prevalence of 37 percent was found among the Aymaras aged 15-25 years old, and 86 percent among either the Aymaras aged 26-40 years and those older than 40 years old (Etty Indriati, 1998).

2.4.2.1.3 Subgroup Variations of Coca Leaf Chewing by Ethnic Group

Most of the coca-leaf chewers are South American Indian and cholos or mestizos (Indian-Spanish mixed blood) (Carlos Gutierrez-Noriega & Von Hagen, 1951; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

In the 1950s, the United Nations Commission of Enquiry on the Coca Leaf found that 90 percent of the Indian population of Peru and Bolivia chews coca leaf (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Researchers found high consumption of kilograms of coca leaf per year on the regions with a high concentration of Quechuas or Aymaras (Carlos Gutierrez-Noriega & Zapata-Ortiz, 1947; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Researchers from the John Hopkins School of Public Health found a higher prevalence of coca-leaf chewing in Peruvian villages with a high concentration of Quechuas or Aymaras. For instance, Pusi, with a population of Quechuas of 94 percent, had a lifetime prevalence of coca-leaf chewing of 72 percent. Cachicoto, with a population of Quechuas of 24 percent, had a lifetime prevalence of coca-leaf chewing of 29 percent. Yacango with a population of Aymaras of 13 percent and Quechuas of four percent had a lifetime prevalence of coca-leaf chewing of 26 percent. Finally, San Antonio, with a population of Quechuas and Aymaras of 0.2 percent, had a lifetime prevalence of coca-leaf chewing of three percent (Alfred A. Buck et al., 1968).

2.4.2.1.4 Subgroup Variations of Coca Leaf Chewing by Levels of Exposure to Traumatic Events

By way of background to this topic, it should be noted that many people of Peru experienced an unusual set of traumatic experiences during the late 20th century when there was 'terrorism' associated with the "Shining Path" movement and the government response to this movement. The next two sections provide some details about this context for research on coca leaf

chewing, as well as details on the aftermath of exposure to traumatic events in the form of post-traumatic stress disorder (PTSD).

2.4.2.1.4.1 Political Violence in the Peruvian Highlands

In the eighties and nineties of the 20 century, the Peruvians experience the most deadly war than ever seen before. It cost the life of 69,280 persons, which surpassed the number of casualties experienced in all the foreign and civil wars of its almost 200 years of existence as an independent nation. The principal actors of this conflict were the Peruvian Army and the Maoism guerrilla called Peruvian Communist Party "Shining Path" (PCP). The PCP started its popular war against the Peruvian state in the rural highland areas of Ayacucho in 1980. In less than five years, the PCP reached a national presence in almost all the rural areas and some urban areas. In this process, both the Peruvian army and the PCP use extreme methods of violence to reach their goals, such as murders, genocides, torture, rape, and kidnapping. However, the distribution of the casualties was not uniform due that the PCP as Maoism organization concentrates its activity in rural areas of the Peruvian Andean highlands and the jungle. Ayacucho concentrates the 53% of the causalities; Huanuco, Huancavelica, Junin, Pasco and Apurimac concentrate the 25% of the causalities. Other Peruvian departments, such as Ancash and Cajamarca, concentrate much fewer casualties. Moreover, 75% of the casualties were farmers, whose mother language was the Quechua. Among the Quechuas casualties, 24.63% were illiterate, and nearly 50% of them just had elementary education (Truth and Reconciliation Commission of Peru, 2003).

2.4.2.1.4.2 Posttraumatic Stress Disorder (PTSD)

During the eighties and early nineties, the Peruvians experienced traumatic events related to political violence and terrorism. During this period, approximately, 69,280 Peruvians died as a consequence of political violence, and most of these deaths occurred among the rural Andean highlanders (Laplante & Holguin, 2006). A recent meta-analysis of 161 studies has shown that a conflicted-affected population developed posttraumatic stress disorder (PTSD) as a result of torture or cumulative exposition to others war-related traumatic events (Steel et al., 2009). Moreover, PTSD increases the risk of developing abuse or dependence on substances (Breslau, Davis, & Schultz, 2003; Chilcoat & Breslau, 1998b; Reed, Anthony, & Breslau, 2007). In this context, it is crucial to evaluate PTSD among the rural Andean highlanders due to either their history of exposition to war-related traumatic events or the possibility that PTSD might alter the frequency of coca leaf chewing and the odds of developing coca leaf chewing dependence.

In this research, the diagnostic criteria for research of PTSD from the ICD-10 Classification of Mental and Behavioral Disorders were used (World Health Organization, 1993), which consider the diagnosis of PTSD if the person presents the following features:

A. "Exposure to a stressful event or situation (either short or long-lasting) of exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone."

B. "Persistent remembering or 'reliving' the stressor by intrusive flashbacks, vivid memories, recurring dreams, or by experiencing distress when exposed to circumstances resembling or associated with the stressor."

C. "Actual or preferred avoidance of circumstances resembling or associated with the stressor (not present before exposure to the stressor)."

D. "Either (1) or (2):"

(1) "Inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor."

(2) "Persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor) shown by any two of the following:"

a) "Difficulty in falling or staying asleep; "

b) "Irritability or outbursts of anger; "

c) "Difficulty in concentrating; "

d) "Hyper-vigilance; "

e) "exaggerated startle response."

E. "Criteria B, C, and D all occurred within six months of the stressful event, or the end of a period of stress. (For some purposes, onset delayed more than six months may be included, but this should be clearly specified separately.)"

For the present study, the diagnosis of PTSD was made regardless of the period of onset of it. It means that the diagnosis of PTSD in this study included the proper PTSD and the delayed onset of PTSD, after six months of occurred the traumatic event.

With these details about Peru's history and PTSD to set a context for the current research, it must be said that there now is no direct evidence of the variation of coca-leaf chewing according to the levels of exposure to traumatic events. However, studies carried out in the United States have shown that exposure to traumatic events without the presence of

posttraumatic stress disorder (PTSD) is not associated with increased risk of developing substance use disorders such as abuse or dependence of cocaine (Breslau et al., 2003; Chilcoat & Breslau, 1998a, 1998b). As an analogy, the microdoses of cocaine getting by chewing coca-leaf might increase the risk of developing coca-leaf chewing dependence among the people who experience traumatic events as compared to the people who did not experience traumatic events.

2.4.2.1.5 Subgroup Variations of Coca Leaf Chewing by History of Posttraumatic Stress Disorder (PTSD)

Currently, there is no evidence that PTSD increases the odds of developing coca-leaf chewing dependence. Nonetheless, different researchers have consistently found a significant association between PTSD and substance use disorders (SUD) (P. J. Brown & Wolfe, 1994; Jacobsen, Southwick, & Kosten, 2001; Kofoed, Friedman, & Peck, 1993). Other researchers push forward these findings trying to discover some causal relationship between PTSD and SUD. In this regard and trying to assess if this PTSD-SUD association meets the Hill's criteria of causality (Hill, 1965), researchers used a longitudinal study design to evaluate especially the temporality criterion of Hill. These longitudinal studies show that PTSD is a significant suspected causal factor to SUD, but SUD is not a significant suspected causal factor of PTSD (Breslau et al., 2003; Chilcoat & Breslau, 1998a, 1998b).

In conclusion, the findings of this longitudinal studies do not prove that PTSD is a causal factor of SUD, it just extends the evidence of PTSD as a suspected causal factor of SUD and helps to rule out the hypothesis that SUD is a suspected causal factor of PTSD. In consequences

and following these findings, the presence of PTSD among the Andean highlanders who chew coca-leaf might increase the odds of developing coca-leaf chewing dependence.

2.4.2.1.6 Subgroup Variations of Coca Leaf Chewing by Educational Attainment

Coca-leaf chewing directly correlates with illiteracy. In places with a high prevalence of coca leaf chewing, there is between 80 to 90 percent of illiteracy (Carlos Gutierrez-Noriega & Von Hagen, 1951; Zapata-Ortiz, 1952).

Furthermore, illiteracy is higher among Indians. Thus, 75 percent of Quechuas or Aymaras are illiterate (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

In consequence, regions with a higher Indian population have a higher prevalence of illiterates and higher consumption of coca leaf. For instance, Puno (92%), Cuzco (72%), Ayacucho (74%), y Ancash (55%) with the highest aboriginal population have the highest yearly consumption of coca leaf of 1,100,000 Kg, 2,200,000 kg, 700,000 kg, and 500,000 kg respectively. On the contrary, Cajamarca, with just 14 percent of Quechuas, has the same yearly consumption of coca leaf than Ancash. Finally, La Libertad, with a Quechua population of 15 percent, had a yearly consumption of 300,000 kg of coca leaf (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

2.4.2.2 Subgroup Variations of Coca Leaf Chewing According to Place Characteristics

Coca-leaf chewing is highly prevalent in the southern highland departments of Peru, where most of the population speaks Quechua or Aymara (Zapata-Ortiz, 1952). Since the late eighteen

century, there is writing evidence that the high jungles of Paucartambo, Huanta, and Huanuco were the leading center of cultivation of coca leaf (Unanue, 1794). This high availability might have stimulated the use of coca leaf among the locals of the departments of Cuzco, Ayacucho, and Huanuco, where Paucartambo, Huanta, and Huanuco are located.

A researcher also found a direct positive correlation between high altitude and the prevalence of coca-leaf chewing (Monge, 1952). Although, this association seems to be an artifact. In a study carried out in four Peruvian villages located at a different altitude, there was a direct correlation between the prevalence of coca-leaf chewing and altitude (Alfred A. Buck et al., 1968). However, the real nature of this correlation seems to be explained by the fact that Quechuas or Aymaras trend to live in villages located at a high altitude of the Andean mountain, and coca-leaf chewing is highly prevalent among these Peruvian aborigines from old times. In consequence, this differential geographical distribution of coca-leaf chewing is explained more for the uneven distribution of the place where the Quechuas and Aymaras live along the Andean Mountains than for the altitude where these villages are located.

2.4.2.3 Subgroup Variations of Coca Leaf Chewing According to Time Characteristics

The prevalence of coca-leaf chewing seems to be prevalent along the time. The analysis of the presence of cocaine in the hair of pre-Columbian mummies dating from 3,000 years ago, and from the Incas period shows that coca-leaf chewing was practiced by 40.7 to 46.6 percent of those people (Cartmell et al., 1994; Cartmell et al., 1991; E. Indriati & Buikstra, 2001). While a study carried out in the twenty century in the Quechua village of Pusi, found a prevalence of everyday coca-leaf chewing of 52.5 percent (Alfred A. Buck et al., 1968).

2.4.2.4 Age of Onset of Coca Leaf Chewing

There is only one study aiming to assess the age of onset of coca-leaf chewing. This study shows that 75 percent of the Aymaras start to chew coca-leaf at ages between 19 to 25 years, nine percent at ages between 16 to 18 years, and 16 percent at ages between 10 to 15 years (Etty Indriati, 1998). Nevertheless, studies carried out among Pre-Columbian mummies found cocaine in the hair of 54 percent infants (0 - 2 years) and 33 percent children (3 - 14 years). The presence of cocaine in those children might be explained more by the maternal transmission of it through the placenta, breastfeeding or the use of coca tea as medicine than for the chewing of coca leaf (Cartmell et al., 1994; Cartmell et al., 1991).

2.4.3 Rubric of Causes

Although cocaine in the form of cocaine powder or cocaine base is causally associated with psychiatric dependence syndrome (Wagner & Anthony, 2002) and other medical complications (Cregler & Mark, 1986), there is no clear evidence that cocaine getting from chewing coca leaves might produce dependence syndrome or other psychological o physical harm to chewers.

Due to scarce scientific literature about the dependence liability of the cocaine obtained from coca-leaf chewing, this section will start with the description of the rubrics of causation of cocaine powder or cocaine base dependence as proposed by Anthony and Vann Etten (Anthony & Van Etten, 1998). Afterward, and following the causality criterion of analogy postulated by Hill (Hill, 1965), a concise description of the rubrics of causation of cocaine from coca leaf chewing will be provided.

2.4.3.1 Rubric of Causes of Cocaine Powder or Cocaine Base Dependence

"Coca is a far more potent and far less harmful stimulant than alcohol, and its widespread utilization is hindered at present only by its high cost."

Sigmund Freud, Uber Coca, 1885 (Freud, 1885)

At ending the 19 century and beginning of the 20 century, the psychoactive properties of cocaine completed fascinated the world population. Due to its apparent innocuity, physicians used cocaine for the treatment of addiction to morphine or alcohol, depression, constipation, asthma, cachexia, and as aphrodisiac (Cornish & O'Brien, 1996; Goldstein, DesLauriers, & Burda, 2009; Gootenberg, 1999; Petersen, 1977). The absence of the classical clinical features of withdrawal syndrome observed in morphine addicts induced to think in the innocuity of cocaine use (Gawin, 1991). In 1925, even the prestigious journal Science considered that addiction to cocaine is self-limited and of short duration, due to the absence of tolerance and abstinence symptoms on withdrawal ("Science News," 1925). Moreover, Sigmund Freud, the famous Austrian neurologist and the founding father of psychotherapies, encouraged the use of cocaine in medicine because he believes in its safety (Freud, 1885).

Early psychobiological theories support the belief that tolerance was the responsible for escalating drug use and withdrawal the responsible for the lacking of abstinence to the drug use (Badiani, Belin, Epstein, Calu, & Shaham, 2011; Collier, 1968a, 1968b; Solomon & Corbit, 1973, 1974). As cocaine use lacks tolerance and withdrawal syndrome (Gawin & Kleber, 1988), most of the scholars and businesspeople consider cocaine a not addictive drug until the enaction of the United States' Harrison Narcotics Tax Act in 1914. The Harrison Act did not

prohibit the selling of cocaine; instead, it tried to regulate the trade of cocaine, opium, morphine, heroin, and other drugs (Goldstein, DesLauriers, Burda, & Johnson-Arbor, 2009). Maybe, the most important achievement of the Harrison Narcotics Tax Act was the inclusion of cocaine into the list of narcotics substances such as opiates. However, to reach this inclusion was not an easy task, it was the product of an intense social movement, where the professional organizations, such as the American Medical Association (AMA), local and federal agencies, such as the Boards of Health or Pharmacy, muckraking journalists, and temperance organizations had a preponderant role (Gootenberg, 1999). Physicians were the first to recognizing and report the potential addictive properties of cocaine, such as the early report of MD from Boston in 1898. In this report to The Boston Medical and Surgical Journal, he described the deleterious effect of the nostrum "Birney's Catarrh Snuff," containing two percent of cocaine, on the health of two young men. Those young men started using compulsively three to six bottles of "Birney's Catarrh Snuff" per day for the treatment of their catarrh, which was causing them huge expenses and the ruin of their careers (Gilbert, 1898). The other pioneers on the recognition of cocaine as an addictive substance were the muckraking journalists from whom Samuel Hopkins Adams was one of its prominent representatives. Adams, in his reports, criticized the selling of medicines without the scientific probe of their safety, efficacy, and effectiveness. His 11 series of articles entitle "The Great American Fraud" published on the Collier's Weekly (Adams, 1906) had a huge impact on the public health field, and triggered the passage of the 1906 Pure Food and Drug Act, which settle the creation of the future Food and Drug Administration (FDA) and obligated to add labels on the medicines with its active ingredients (Fee, 2010). The lacking of cocaine selling regulations

compels the enaction of state policies via the Boards of Health. A remarkable example of this effort to control the trade of cocaine in the benefit of public health was the law that Massachusetts enacted on September 1, 1906. This law strictly prohibits the selling or prescription of any product containing cocaine or its derivatives to everybody, including physicians and pharmacists into the state of Massachusetts ("Miscellany," 1907).

Cocaine use in the United States declined from 1920 because of the local and federal policies, public awareness, and the rising of the popularity of amphetamine among the drug users in 1930. However, even until the 1980s, the academics and the general population still believed in the innocuity of cocaine (Gawin & Kleber, 1988). For instance, the famous treatise of Psychiatry of 1980 "Kaplan and Sadock's Comprehensive Textbook of Psychiatry third edition" considered that moderate use of cocaine two or three times per week did not cause serious medical problems (Gawin & Kleber, 1988; Kaplan, 1980). Furthermore, the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (American Psychiatric Association, 1980), from 1980 did not consider that cocaine causes Dependence Disorder due to the inexistence of the standard tolerance and withdrawal symptoms among the cocaine users. Is not until the epidemiologic outbreak of crack cocaine in the early 1980s (Cornish & O'Brien, 1996) when cocaine starts been considered an addictive drug with the same potentiality to cause physical and psychological harm to the users than depressant drugs (opiates, alcohol, benzodiazepines) or stimulant drugs (amphetamines and nicotine). In response to the epidemics of crack cocaine, researchers started the study of the clinical features and the psychology of cocaine use disorders in a systematic way.

The first definition of drug addiction of the World Health Organization considered craving or compulsion for the drug together with tolerance and psychological or physical dependence symptoms as clinical features of drug addiction (World Health Organization, 1950). Subsequent works on the field of drug addiction trended to emphasize the importance of tolerance and withdrawal symptoms on the definition of drug dependence syndrome; although, they do not deny the clinical feature of compulsion. In this period, most of the researchers study depressant drugs such as morphine and alcohol, which cause their bias toward tolerance and withdrawal symptoms of addiction. For instance, Edwards, in his clinical research with alcohol addicts, generated a rigorous and detailed description of dependence syndrome to alcohol where the abstinence symptoms on withdrawal was a prominent clinical feature of it (Edwards & Gross, 1976). Edwards' pioneering work provided the foundation for the modern definitions of dependence syndrome. There were other significant contributions to the understanding of drug addiction to depressant drugs, such as the clinical research developed by Himmelsbach on the physical dependence or withdrawal to morphine (Himmelsbach, 1942). These and other findings seemed to contribute to the belief that abstinence syndrome was a prominent clinical feature of drug dependence. Indeed, the opponent-process theory of addiction considers that the negative reinforcing effects of the drug under the presence of abstinence symptoms on withdrawal are a necessary and sufficient cause for the phenomenon or dependence (G. F. Koob et al., 1989).

With the 1980s epidemic of crack cocaine in the USA, there was a switch on the research focus from depressant drugs to stimulant drugs. Researchers became more aware of the subtle clinical features of the "abstinence symptoms" upon withdrawal to cocaine.

Researchers described that cocaine abstinence syndrome has three phases after cessation of cocaine binge: (1) ***The phase of the crash:*** the individual starts feeling depressed, agitated, anxious, and with an intense craving to cocaine, and half of them experience also paranoia. After one to two hours, the cocaine user becomes severely exhausted, and the craving for sleeping displaced the craving for cocaine. In this situation, they strongly reject the use of cocaine, and instead of it, they start using sedatives, hypnotics, alcohol, or opiates to induce sleep. At the end of this phase, the individuals experience severe hypersomnolence and hyperphagia for several days. The crash phase resembles more the alcohol hangover than the classical withdrawal to opiates or alcohol. (2) ***The phase of withdrawal:*** after the half to four days, the individuals experience a marked dysphoric syndrome characterized by severe anhedonia, absence of motivation, boredom, and anxiety. In this situation, the remainders of the euphoric effects of cocaine trigger severe cocaine craving. As this period is close related to intense cocaine craving and a high probability of relapsing into cocaine use, it is called the withdrawal phase and has a duration of one to 10 weeks. This withdrawal phase resembles the withdrawal symptoms to opiates or alcohol, although it is notorious the absence of the classic physiological symptoms of abstinence to opiates or alcohol. (3) ***The phase of extinction*** it is not clear when this phase starts, but the euthymic mood and the normalization of the hedonic experiences characterized this phase. However, conditional cues still can trigger intense craving and the resume of cocaine use (Gawin, 1991; Gawin & Ellinwood, 1989; Gawin & Kleber, 1986, 1988).

As a consequence of this advance on the knowledge of cocaine dependence, the American Psychiatric Association (APA) starts describing the clinical features of dependence

based upon on the behaviors that users of the drug exhibit and the degree to which this drug controls the users' behaviors, rather than the degree of the withdrawal symptoms that the users experience (Jaffe & Jaffe, 1989). The APA embodied this concept for the first time in the Diagnostic and Statistical Manual of Mental Disorders third edition revised (DSM-III-R) (American Psychiatric Association, 1987).

Epidemiologic studies also contributed to the characterization of the clinical features of dependence on cocaine as an entity a little bit different from the dependence on opiates. Initially, clinical studies have shown that there is no difference in the ascription of the clinical features of dependence syndrome, as defined by DSM-III-R. Mainly, it did not find differences in the ascription of the clinical feature of tolerance and withdrawal among cocaine dependents as compare to heroin dependents (Hasin, Grant, Endicott, & Harford, 1988). However, Anthony et al., using the data of the Epidemiologic Catchment Area Surveys (ECA), found that the symptoms of tolerance and withdrawal were considerable less prevalent among cocaine users than among heroin users (Anthony & Petronis, 1989).

Parallel to the advances on the study of the clinical features of cocaine dependence syndrome, researchers also found strong evidence that cocaine use can produce dependence syndrome according to the clinical features of DSM-III-R (American Psychiatric Association, 1987), Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (American Psychiatric Association, 1994), and the International Classification of Diseases 10th edition (ICD-10) (World Health Organization, 1993). For instance, Anthony et al. using the data of the National Comorbidity Survey (NCS) found that 16.2 percent of the US population have ever used cocaine, and 2.7 percent of the general population and 16.7 percent of the ever cocaine

users have the diagnosis of cocaine dependence as defined by the DSM-III-R. This cocaine liability to dependence among cocaine users was almost similar to the liability to the dependence on alcohol and heroin with the prevalence of 15.4 percent and 23.1 percent among the users of alcohol and heroin, respectively (Anthony, Warner, & Kessler, 1994). Moreover, Wagner and Anthony found that cocaine dependence syndrome develops more explosive among cocaine users than the dependence syndrome on alcohol or marijuana among the users of each of these substances (Wagner & Anthony, 2002). Also, between four to six percent of the recent cocaine users develop cocaine dependence as defined by the DSM-IV within the 24 months after first use. Females, young adults, African-Americans, crack-cocaine users, intravenous cocaine users, and early onset of cocaine use have an excess risk of developing cocaine dependence (M. S. O'Brien & Anthony, 2005; Reboussin & Anthony, 2006).

Finally, many researchers have found that cocaine produce severe medical and psychological harm to users. For instance, the consumption of cocaine powder or cocaine base can induce cardiac complications such as acute myocardial infarction, myocardial ischemia, coronary vasospasm, cardiac arrhythmias, cardiomyopathies, ventricular hypertrophy, tachycardia, blood hypertension, and rupture of the Ascending Aorta (Cregler & Mark, 1986; Goldfrank & Hoffman, 1991; Schindler, 1996). Moreover, it can induce neurologic complications such as ischemic and hemorrhagic stroke, subarachnoid and intracerebral hemorrhages, cerebral infarction, transient ischemic attack, seizures, movement disorders, migraine headache, headache, transient loss of consciousness, cerebrospinal fluid rhinorrhea, fungal cerebritis, and vasculitis (Buttner, Mall, Penning, Sachs, & Weis, 2003; Fessler, Esshaki, Stankewitz, Johnson, & Diaz, 1997; Goldfrank & Hoffman, 1991; Lowenstein et al., 1987; Spivey

& Euerle, 1990). Moreover, the use of cocaine powder or cocaine base increases the odds of developing psychiatric complications such as agitation, anxiety, depression, psychosis, paranoia, suicidal ideation, suicide attempt, and suicide (Lowenstein et al., 1987). It is also associated with an increment in the likelihood of gastrointestinal complications such as mesenteric ischemia or infarction, intestinal ischemia, hepatic necrosis, and gastrointestinal perforation (Goldfrank & Hoffman, 1991; Thompson, Shuster, & Shaw, 1979). Pulmonary complications, such as pulmonary edema and infarction, were also reported (Goldfrank & Hoffman, 1991). It is also associated with obstetric complications such as abruptio placentae or spontaneous abortion (Goldfrank & Hoffman, 1991). Neonatal complications such as prematurity, growth retardation, especially in head circumference, developmental delays, and congenital abnormalities, were also reported (Eyler, Behnke, Conlon, Woods, & Wobie, 1998; Goldfrank & Hoffman, 1991). At last, cocaine increases the risk for the development of sexually transmitted diseases such as the infection with the human immunodeficiency virus (HIV) (Edlin et al., 1994).

2.4.3.2 Rubric of Causes of the Suspected Dependence Liability of Coca Leaf Chewing

"The influence of the drug (coca-leaf chewing) through many generations may have some importance as a creative factor in psychological disturbances and racial degeneration."

Carlos Gutierrez-Noriega, Coca–The Mainstay of an Arduous Native Life in the Andes, 1951 (Carlos Gutierrez-Noriega & Von Hagen, 1951)

In the world exists over 250 species of the plant Erythroxylum and 200 were detected in the tropical regions of America (Bo Holmstedt, Jäätmaa, Leander, & Plowman, 1977). From all these species of Erythroxylum, two have been cultivated for many centuries due to its stimulant properties. These cultivated species are Erythroxylum coca Lamarck (Erythroxylum coca Lam or just Erythroxylum coca) and Erythroxylum novogranatense Morris (Erythroxylum novogranatense) (Plowman, 1984). Each one of these cultivated species of Erythroxylum has one additional variety, given a whole of four varieties of cultivated Erythroxylum: The Erythroxylum coca var. coca, Erythroxylum coca var. ipadu, Erythroxylum novogranatense var. novogranatense, and Erythroxylum novogranatense var. truxillense. From them, the Erythroxylum coca var. coca, commonly known as Huanuco coca or Bolivian coca, is the most important because it originated the other species and varieties of cultivated Erythroxylum via its adaptation to new environments outside of its natural habitat (Plowman, 1984).

Furthermore, the Erythroxylum coca var. coca is the most cultivated variety of coca in South America, with crops on the high jungle of the eastern Andean mountains of Colombia, Ecuador, Peru, Bolivia, and Argentina. Its cultivation began approximately 7,000 years ago to supply the coca chewers with this commodity, and nowadays, it is the principal source of coca

leaf for the illegal trade of cocaine in the world (Plowman, 1984). The other varieties of Erythroxylum are cultivated in less scale. Erythroxylum coca var. ipadu (Amazon coca) is cultivated in the northeastern jungle of Peru and the adjacent jungles of Colombia and Brazil. Erythroxylum novogranatense var. novogranatense (Colombian coca) is cultivated in the western valleys of Colombia, and Erythroxylum novogranatense var. truxillense (Trujillo coca) is cultivated on the river valleys of the northwestern coast of Peru (Plowman, 1984).

Until this moment, researchers have identified the alkaloid cocaine in only two species of Erythroxylum: the Erythroxylum coca and his variant ipadu, and the Erythroxylum novogranatense and his variant truxillense (Bo Holmstedt et al., 1977). The dry leaves of Erythroxylum coca var. coca (Huanuco or Bolivian coca) have 0.23 to 0.96 mg of cocaine per 100 mg of the dry mass of coca leaves (mean 0.63 mg percent). The dry leaves of Erythroxylum coca var. ipadu (Amazon coca) have 0.11 to 0.41 mg of cocaine per 100 mg of the dry mass of coca leaves (mean 0.25 mg percent). The dry leaves of Erythroxylum novogranatense var. novogranatense (Colombian coca) have 0.47 to 0.93 mg of cocaine per 100 mg of the dry mass of coca leaves (mean 0.77 mg percent). Moreover, the dry leaves of Erythroxylum novogranatense var. truxillense (Trujillo coca) have 0.42 to 1.02 mg of cocaine per 100 mg of the dry mass of coca leaves (mean 0.72 mg percent) (Moore & Casale, 1994; Plowman, 1984). In contrast, the concentration of the alkaloid cocaine is much higher in cocaine powder and crack-cocaine, the two most abused forms of cocaine in the United States (Chen & Kandel, 2002; J. Dunn & Laranjeira, 1999; Rouse, 1991). Cocaine powder (cocaine hydrochloride) is obtained from the combination of coca paste with hydrochloric acid, and it is abused via intranasal administration (sniffing it) or intravenous administration (injecting it in aqueous solution) (U.S.

Department of Justice, 2002). The cocaine powder has a concentration of 43 to 64 percent of the alkaloid cocaine (Darke, Kaye, & Topp, 2002; Schneider & Meys, 2011). Crack-cocaine is made from the combination of cocaine powder, water, and baking soda. The hitting of this combination transforms it into a solid mass. Crack-cocaine has a concentration of 89 percent of the alkaloid cocaine and it is abused by smoking it (U.S. Department of Justice, 2002).

It seems that it is not plausible that coca-leaf chewing can cause dependence syndrome due to its minimum concentration of the alkaloid cocaine. The most common coca leaf chewed in the Andean mountains is the leaves from the shrub Erythroxylum coca var. coca. The concentration of the alkaloid cocaine in the leaves of Erythroxylum coca var. coca is approximately 100-fold times lower than in cocaine powder or crack-cocaine. Sun-dried coca leaf contains 0.63 to 0.73 percent of cocaine (Plowman, 1984), while cocaine powder (cocaine hydrochloride) contains 43 to 64 percent of cocaine (Darke et al., 2002; Schneider & Meys, 2011), and crack-cocaine contains 89 percent of cocaine (U.S. Department of Justice, 2002). Nonetheless, Fischman and Foltin in laboratory studies carried out among humans showed that low doses of intravenous cocaine (4 mg) are systematically chosen over placebo even in the absence of the characteristics psychological or physical effects produce for higher doses of cocaine (Fischman, 1989; Fischman & Foltin, 1992). It means that low doses of cocaine can induce compulsive use in humans even in the absence of its positive reinforcing euphoric effects.

Furthermore, blood concentrations of cocaine similar to those obtained via sniffing cocaine powder were detected among coca leaf chewers. Peak concentrations of cocaine of 10 to 150 ng/ml of plasma were detected after chewing 4.4 g of sun-dried coca leaves of the shrub

Erythroxylum coca Lamarck (Homstedt, Lindgren, Rivier, & Plowman, 1979). While, concentrations of cocaine of 40 to 88 ng/ml of plasma were detected after snoring 32 mg of cocaine powder (cocaine hydrochloride) (Cone, 1995). Initially sniffing cocaine powder was considered to be safe, clinical and epidemiological studies have demonstrated that it can induce dependence syndrome in less degree than crack cocaine or injecting cocaine powder (Kleber & Gawin, 1984). For instance, between 34 to 37 percent of the cocaine users looking for treatment in addiction centers consumes cocaine powder via intranasal insufflation (Gawin & Kleber, 1985; Schnoll, Karrigan, Kitchen, Daghestani, & Hansen, 1985). Besides, epidemiological studies show that sniffing cocaine powder can trigger an early development of two percent of dependence syndrome between the 24 months after the first use of it (Reboussin & Anthony, 2006). Although this excess risk for early onset of dependence syndrome via sniffing cocaine is threefold less than the excess risk observed among crack-cocaine users, it is no less important from the public health perspective due that a population level 95 percent of cocaine users had sniffed cocaine powder and just 21 percent had smoke crack-cocaine (Rouse, 1991).

In sum up, small doses of cocaine can induce compulsive use of it. Furthermore, the chewing of coca leaf produces almost the same blood concentrations of cocaine than sniffing cocaine powder. In consequence, it is still possible that, to some degree, coca leaf chewing might produce dependence syndrome as it was defined in the International Disease Classification 10th edition (ICD-10) (World Health Organization, 1993).

Following the Hill's causality criteria of analogy (Hill, 1965), if sniffing cocaine powder can develop a dependence syndrome, then coca-leaf chewing might also develop dependence syndrome due to its similar pharmacokinetics properties with sniffing cocaine powder. In order

to shed light on the dependence liability of coca-leaf chewing, a summary of the current evidence of its dependence liability according to the two Johanson's requirements of ***positive reinforcement*** and ***toxicity*** for the evaluation of the dependence potential of cocaine (Johanson, 1984) will be presented in the next paragraphs.

Following the first ***Johanson recommendation of positive reinforcement*** properties in the assessment of dependence liability of cocaine, only a few researchers found that coca-leaf chewing could enhance the compulsive use of coca leaves. For instance, Gutierrez-Noriega working in his lab at the Medicine School of the National Major University of San Marcos in Lima, Peru, found that coca-leaf chewers do not develop tolerance to the effects of coca leaves. However, they present long-lasting and slight abstinence symptoms only among the inveterate coca-leaf chewers. However, he found that intense craving for coca leaves is almost always present among coca-leaf chewers (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951). As his results were similar to Tatum pioneer findings on cocaine addiction (Tatum & Seevers, 1931), he concluded that coca-leaf chewing could produce addiction a little bit different than the addiction observed among morphine users who experience high tolerance and intense abstinence symptoms on withdrawal. Gutierrez-Noriega got strong support to his point of view that coca-leaf chewing produces addiction from Wolff, the chief of the Addiction-Producing Drugs Section of the World Health Organization. Wolff was also a member of researchers of the United Nations Commission of Enquiry of the Coca Leaf who arrives in Peru in 1950 to disentangle the controversy of the potential dependence liability of coca-leaf chewing (Wolff, 1949, 1952). Zapata-Ortiz, also working at the school of medicine of the Peruvian National Major University of San Marcos, found almost similar results than

Gutierrez-Noriega. It is an absence of tolerance "most of the coca addicts take practically the same dose of coca throughout their lives" and moderate abstinence symptoms among coca-leaf chewers who consume more than 100 or 200 grams of coca per day. Based in his findings of mild clinical features among coca-leaf chewers as compare to intravenous cocaine powder users, he concluded that coca-leaf chewing is more a habit than an addiction, although he recognized that a chronic and inveterate coca-leaf chewing might produce deleterious effects in the health of the chewers (Zapata-Ortiz, 1952, 1970). In a study carried out among the highlanders of Nunoa, a region of Puno, Peru, Hanna found that chewing coca leaves in quantities that it is used to chew in that community produce just a mild stimulation as compare to no chewers. Moreover, he observed that coca-leaf chewers of the community of Nunoa do not present serious health complications such as the insatiable desire for the drug, paranoia, or other mental complications observed in addicts to cocaine. Based on these findings, he concluded that coca-leaf chewing does not produce dependence syndrome as cocaine powder or cocaine base (Joel M. Hanna, 1971; J M Hanna & Hornick, 1977). Working with coca chewers at the Peruvian National Institute of Andean Biology, Monge found that chewing coca leaves produce the absorption of insignificant quantities of cocaine with a slight stimulation and absences of craving, tolerance, and withdrawal symptoms. He concluded that coca leaf might be used for the highlanders as a slight stimulant to avoid fatigue and not because they are addicts to the effects of coca leaf. However, he recommended future studies to disentangle this gap in the knowledge of the phenomenon of coca-leaf chewing (Monge, 1952). In an individual matching study of chewers with controls in the province of Jujuy, Argentina, Negrete and Murphy found that chewers with recent high consumption of coca leaves perform better on

psychological tests than chewers with the same age and duration of consumption who has recently chewed low quantities of coca leaves. These findings were similar to the improved attention and speed of chronic coca-leaf chewers who chews recently 50 to 80 grams of coca leaves reported by Gutierrez-Noriega (Negrete & Murphy, 1967). Negrete also found light craving and absences of tolerance and abstinence symptoms among chewers and concluded that coca-leaf chewing is an ancient, orderly, moderate, and social use of narcotics which rarely might produce addiction (Negrete, 1978a, 1978b). The United Nations Commission of Enquiry on the Coca Leaf found also just a mild craving and absences of abstinence and tolerance among coca leaf chewers. Based in these findings the commission concluded that coca-leaf chewing is a habit, but they warn about the potential dependence liability of high doses of coca leaves (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950).

In conclusion, current evidence suggests that in general coca-leaf chewing is a slight stimulant lacking tolerance and abstinence symptoms. In consequence, coca-leaf chewing exerts a weak positive reinforcement effect on the use of coca leaves due to its slight stimulant properties. Moreover, the possibility that coca-leaf chewing exerts negative reinforcement effects is almost inexistent due to the lacking of the abstinence symptoms on withdrawal. Then the likelihood that coca-leaf chewing triggers the compulsive use of coca leaves is very low. However, there is some possibility that higher doses of coca-leaf chewing might produce moderate to high stimulation and light abstinence symptoms. The moderate stimulation via positive reinforcement and the light abstinence symptoms via negative reinforcement might trigger the compulsive chewing of coca leaves.

Respect to the second ***Johanson recommendation of toxicity*** in the assessment of dependence liability of cocaine, coca-leaf chewing seems not to be causally associated with the acute and chronic toxicity exerted by the use of cocaine powder or cocaine base. Although, there is some evidence that coca leaf chewing might cause some intellectual impairment and malnutrition. Initially researchers have related different diseases to coca-leaf chewing, such as epilepsy (C. Gutierrez-Noriega & Von Hagen, 1950; Negrete, 1978a, 1978b; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950), liver diseases (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950), cretinism (Carlos Gutierrez-Noriega & Von Hagen, 1951; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950), grow retardation (C. Gutierrez-Noriega & Von Hagen, 1950; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950), racial degeneration (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950), and caries (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). However, almost all these researchers consider that other causal factors different than coca-leaf chewing might be contributing to the development of these diseases. For example, the observed high prevalence of epilepsy in the regions with high prevalence of coca-leaf chewing, might be an artifact due that these zones are high prevalent to helminthiasis such as the neurocysticercosis produced by the larva of the Taenia solium (pork tapeworm). And the most common manifestation of the neurocysticercosis is the epilepsy (Burneo & Cavazos, 2014). The high prevalence of hepatic diseases among

chewers might be the expression of confounding effects of the high consumption of alcohol observed in these areas (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Nowadays, it is well known that a diet lacking of iodine can cause cretinism (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Grow retardation is better explained by malnutrition affecting almost the entire population of Indians of South America (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). The suspected racial decay such as dwarfism, skeletal defects, cranial deformities, and idiocy caused by the practice of chewing coca leaves for many centuries is better explained for the Indian diet lacking of micronutrients, vitamins and proteins observed in this population (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Furthermore, caries is better explain for the absences of adequate hygiene and the lacking of dentist in the area where the Indians live (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Nonetheless, the best evidence of the suspected causal effect of coca-leaf chewing on malnutrition and intellectual impairment comes from individual matching studies (Gordis, 2004) of coca-leaf chewers with controls. For instance Buck et al. found that coca-leaf chewers have significantly more prevalence of malnutrition, inferior personal hygiene and incapacitating illnesses than their pair controls in a rural village of Cachicoto of the region of Huanuco, Peru (A. A. Buck et al., 1968). He measure the nutritional status via anthropometric and biochemical tests. In the anthropometric test, he found non-significant differences on measures of the weight/height ratios and on the skinfold thickness of chewers as compare to controls. However he found significant differences on the measures of biochemical tests of albumin (difference = 0.36 gm %,

p-value = 0.05) and cholesterol (difference = 20.3 mg %, p-value = 0.01). As well as a significant major prevalence of severe hypochromic anemia among chewers (23.5 %) than controls (3.9 %) (p-value < 0.01). Regarding the inferior personal hygiene, there was significant major prevalence of pyoderma among chewers (16.3 %) than controls (2.0 %) (p-value = 0.03), although there were no significant differences on the prevalence of scabies (p-value = 0.10). Finally, more coca-leaf chewers reported to be ill and lost work in the month before the evaluation than controls, although the researchers did not carried out statistical tests to evaluate the significance of these differences. Moreover, in a individual matching study (Gordis, 2004) carried out in a farm workers of Jujuy, Argentina, Negrete and Murphy found that chewers of 200 gm of coca leaves per week during at least 10 years presents a lower performance in five of seven tests evaluating psychological deficit caused by brain damage. The control group of this study was chewers, who never chews more than 10 gm of coca leaves per week (Negrete & Murphy, 1967).

In conclusion, the existing evidence does not support that coca-leaf chewing can cause the same psychological or physical harm than cocaine powder or cocaine base. More of the evidence coming from previous studies are not exempt from bias. As a case in point, almost all the studies reporting physical or psychological harm did not use a control group, and there was selection bias (Dohoo, Martin, & Stryhn, 2003) even in the individual matching studies (Gordis, 2004). For instance, in the individual matching study where Buck found a significantly higher prevalence of malnutrition among chewers, the control group of no chewers was significantly composed for more Protestants than the chewers' group (A. A. Buck et al., 1968). Furthermore, this Christian group of Protestants do not drink alcohol, do not smoke, and have other healthier

habits of life than chewers, which might explain better the presence of proper nutrition in this group than just the fact that they do not chew coca leaves. Similarly, the individual matching study of Negrete and Murphy, where they found evidence that coca-leaf chewing is causing brain damage, the group of inveterate chewers has two times more illiterates than the control group of sporadic chewers (Negrete & Murphy, 1967).

2.4.4 Rubric of Mechanisms

To this date, the body of epidemiological evidence under the heading of the rubric of mechanisms is minimal. However, there is a substantial body of evidence from neurobiological investigations across the scale from intra- and inter-cellular mechanisms (e.g., transcription, and signaling) onward through studies of pharmacokinetics and pharmacodynamics of the cocaine effects at a cellular and molecular level. Because these studies are not per se epidemiological in nature, Appendix A provides a summary of these non-epidemiological studies. Readers of this thesis who are interested in the Epidemiological Rubric of Mechanisms of cocaine addiction may read the appendix materials on these topics.

2.4.5 Rubric of Prevention

There is archeological evidence that the South American Indian starts chewing coca leaf 8000 years ago when the domestication of plants was beginning (Dillehay et al., 2010). The first reaction of the Spaniard conqueror of Soth America was to banish the habit of coca-leaf chewing because they believed that this practice was related to their pagan religious rituals. In 1551, the first ecclesiastical council prohibited the habit of coca-leaf chewing. In 1556, Andres

Hurtado-de-Mendoza, the fifth Spanish viceroy, enacted the first low aiming the eradication of coca leaf and its substitution for alternative crops, which is the principal preventive policy of cocaine consumption until nowadays (Gootenberg, 1999). Notwithstanding, after they became aware that the Indians who chew coca leaf can do more work with less food, they stimulate its extensive use among the aborigines who work in their mines or plantations. The Viceroy Toledo removed the official prohibition of coca leaf cultivation in 1573, aiming to get more revenue from the taxation of coca leaf trade. During its three-century reign in the new world, the Spaniards stimulated the production and selling of coca leaf among the South American aborigines (Allen, 2002). After the discovery of cocaine, the coca leaf active principle, by Albert Niemann in 1859 and the clinical utility of cocaine as an anesthetic by Kark Koeller in 1884, Peru became the first legal exporter of raw coca leaf and cocaine in the form of sulfites of cocaine worldwide in 1900 (Gootenberg, 1999). It is not until 1922 that the selling of cocaine was prohibited in all the US territory via the Jones-Miller Act because the physicians recognized that cocaine produces addiction a little bit different from morphine (Gootenberg, 1999). The United Nations Convention of 1961 banned the cultivation of coca bush in the territory of its all member nations aiming the abolition of coca leaf chewing within the upcoming 25 years. In 1988 the United Nations Convention made an exception to the prohibition of coca bush cultivation to those countries where the traditional licit use of coca leaf has historical evidence (United Nations, 2013).

In 1978 and under mounting pressure from the USA, the Peruvian dictator Francisco Morales-Bermudez enacted the decree-law 22095 mandating the gradual eradication of coca bush, the gradual elimination of coca-leaf chewing, and the sanction of the illegal cultivation of

coca bush with no less of 10 years of imprisonment (Felbab-Brown, 2010; Morales-Bermudez, 1978; Rojas, 2005). In the first year of implementation of this policy, named "Operation Green See," the Peruvian authorities just eradicated 60 of the estimated 12,000 hectares of coca bush in the Upper Huallaga Valley fostering the increase of coca cultivation due to the rise in the price of coca leaf and the subsequent migration of more farmers to the region (Felbab-Brown, 2010). In 1985 and under the U.S. aid of 1,300,000 dollars per year, the Peruvian government launched the Special Project for the Control and Eradication of Coca in the Upper Huallaga Area ("Proyecto Especial de Control y Reduccion de Cultivos de Coca en el Alto Huallaga," CORAH). This year, the CORAH eradicated 5,000 hectares of coca paying 300 dollars per hectare to the farmers for their losses (Felbab-Brown, 2010; McClintock, 1988). Then, the U.S. Agency for International Development (USAID) founded with 3,000,000 U.S. dollars annually the Upper Huallaga Area Development Project (Programa Especial del Alto Huallaga, PEAH). The goal of the PEAH was the substitution of the coca bush by other legal crops.

Notwithstanding, legal crops took too long to become productive, around three to four years for coffee and three to five years for cocoa. Moreover, while coca leaf could be harvest four to six times per year, coffee just one time per year and cocoa one to two times per year. These agricultural factors joined to the declining market prices of the legal crops impoverished many farmers. Thus, PEAH largely failed; it generates much mistrust of the concept of alternative development among the farmers until nowadays (Felbab-Brown, 2010). Successive governments forcefully eradicated 13,800 hectares of coca bush in 1999 and 3,900 hectares in 2001 (Rojas, 2005). In 2007, they eradicated 12,072 hectares; however, this massive effort is a

failure because from 1999 to 2007, the area of coca leaf cultivation in Peru increased by 40 percent (Pruett, 2012).

2.5 Gaps in Epidemiological Evidence to be Filled

In this part, there will be an identification of the current gaps in the knowledge of the epidemiology of coca leaf chewing that I intend to fill in my thesis research project. Mainly, a reflection on the specific aims.

2.5.1 Gaps Related to the Aim One: Estimation of Basic Epidemiological Parameters of Coca Leaf Chewing

Regarding the first aim, estimating basic epidemiological parameters of coca-leaf chewing, with the current existent scientific literature, it is not possible to estimate accurately epidemiological parameters of the quantity of the occurrence of coca-leaf chewing. Methodological research's flaws cause this difficulty. The using of incorrect study design to reach the study goals or the lacking of essential information of the methodology used on the research characterized these flaws.

Most of the studies carried out in the epidemiological rubric of the quantity of coca-leaf chewing were cross-sectional studies with non-random samples of the target population. Therefore, as all the cross-sectional studies with non-random samples, these estimations might have excellent internal validity, but the selection bias of the study population limits its external validity (Dohoo et al., 2003). In consequence, all these cross-sectional studies of coca leaf chewing had considerable selection bias because they did not use random samples. In other

words, the results of the cumulative incidence proportion and prevalence of coca-leaf chewing of these studies must be applied just to the target population but not to an external population.

2.5.2 Gaps Related to the Aim Two: Subgroup Variations of the Basic Epidemiological Parameters of Coca Leaf Chewing

In the same way that the gaps related to the epidemiological rubric of quantity, all the studies in the epidemiological rubric of the location of coca leaf chewing were carried out in a small and nonrandom sample of participants. In consequence, the results of the subgroup variations of coca leaf chewing according to characteristics of the person, time, and place cannot be generalized to the entire source population.

2.5.3 Gaps Related to the Aim Three: Possible Hazards of Coca Leaf Chewing in the Form of Coca Leaf Chewing Dependence Syndrome and Detrimental Quality of Life among Coca Leaf Chewers

With the current scientific evidence, it is not reliable to conclude that coca leaf chewing produces addiction or dependence syndrome. It is because almost all the studies in the rubric of causation of coca leaf chewing were carried out in the fifties, sixties, or seventies of the twenty century when the current diagnostic criteria of dependence syndrome were still not developed. The academics of this period believe that cocaine does not cause dependence syndrome or addiction. Even the renowned treaty of psychiatry of Kaplan in its third edition stated that moderate use of cocaine hydrochloride two to three times per week does not cause dependence syndrome (Gawin & Kleber, 1988; Kaplan, 1980). Moreover, the Diagnostic and

Statistical Manual of Mental Disorders in its third edition did not consider that cocaine produces dependence syndrome; it is because cocaine hydrochloride users almost do not present the classical withdrawal and tolerance symptoms observed among opiates and alcohol users (American Psychiatric Association, 1980).

Recently in the 1980s, with the emergence of the epidemic of crack cocaine in the United States of America, cocaine began to be considered an addictive substance with the same potentiality to produce physical and psychological harm than opiates, alcohol, or benzodiazepines (Cornish & O'Brien, 1996).

It was not until 1987 that the modern definition of dependence syndrome to cocaine emerges in the Diagnostic and Statistical Manual of Mental Disorders third edition revised (DSM-III-R) (American Psychiatric Association, 1987). The DSM-III-R diagnostic criteria or clinical features of cocaine dependence syndrome remain almost unchanged in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (American Psychiatric Association, 1994). The World Health Organization introduced the new DSM-III-R diagnostic criteria of cocaine dependence syndrome in the International Classification of Diseases tenth revision (ICD-10). The ICD-10 developers modified a little bit the DSM-III-R clinical features of dependence syndrome, for instance, they introduced craving as an additional diagnostic criterion of dependence syndrome (World Health Organization, 1992a).

2.6 Potential Significance and Impact of the Thesis Research

Finally, in this part of the chapter, there will be an identification of the potential contribution to the knowledge of the epidemiology of coca leaf chewing that this thesis might offer to the

scientific community and policy makers, including reflections upon potential 'significance' or 'impact' as these terms currently being used in the National Institute of Health (NIH) grant reviews.

This study is significant because it will advance the knowledge of the epidemiology of coca leaf chewing by given current and more valid and reliable estimations of the magnitude, distribution, and possible harmfulness of this old habit of the Andean population.

With the current state of the art, it is impossible to know the real magnitude, distribution, and the health effects of coca leaf chewing. It is because the existent studies did not use a representative random sample of the source population, and they were carried out before the development of the current diagnostic criteria of addiction or dependence syndrome done in 1987. In consequence, this is the first cross-sectional study in using a large representative random sample of the rural Peruvian Andean highlanders to study the magnitude, health effects, and distribution of coca leaf chewing according to personal and place characteristics. Furthermore, to the date, this is the unique research in using the current ICD-10 diagnostic criteria of dependence syndrome to study the coca leaf chewing addiction liability. Evidence supporting the plausibility of coca leaf chewing addiction comes from the identification of cocaine in the blood of coca leaf chewers. Researchers identified cocaine concentrations up to 149 ng/ml in the blood of coca leaf chewers (B. Holmstedt et al., 1979). Although this concentration is approximately ten times less than the concentrations detected in the blood of cocaine hydrochloride, crack-cocaine or cocaine paste users (Jatlow, 1988; Paly et al., 1982), it is plausible that the chronic exposition to low doses of cocaine and its potential fast absorption of cocaine through the oral mucosa while chews coca leaf might produce symptoms

of dependence syndrome. Moreover, some coca leaf chewers might eventually fulfill the ICD-10 criteria for the diagnostic of cocaine dependence syndrome.

The findings of the present study will update the current knowledge of the health effects of coca leaf chewing, which will foster the development of more rigorous causal study designs to evaluate the addiction liability of coca leaf chewing. Furthermore, these findings will guide the development of public health policies to improve the health of this underserved Andean population.

CHAPTER 3 MATERIALS AND METHODS

3.1 Introduction to Chapter 3

This chapter is organized in relation to the 'methods' outline suggested by Professor J. Anthony (http://www.epi.msu.edu/janthony/39%20Sentences.pdf, last accessed 17 June 2015). The elements in that outline follow are shown below. It also should be mentioned that the completion of the field research aspects of this project was not part of the thesis research project, which has been restricted solely to secondary analyses of the field survey data. That is, the original contribution of this thesis research project is concerning the analysis and scientific writing, and is not about the design and conduct of the field operations for the survey, which were completed under the aegis of the Peruvian National Institute of Mental Health "Honorio Delgado - Hideyo Noguchi" before this Master of Science thesis project was contemplated.

3.2 Research Design

The thesis project research design is that of a cross-sectional field survey with an epidemiological sample and standardized assessments of the constructs under study. This thesis research will use the data from the Rural Peruvian Andean Mental Health Survey, 2008. The main aim of this survey was the integral evaluation of the mental health of the Peruvian highlanders, from a negative and positive perspective of mental health. In the negative perspective of the mental health, they evaluated the magnitude and distribution of psychiatric disorders among the highlanders. In the positive perspective of mental health, the researchers assessed psychological constructs, such as resilience, quality of life, and self-esteem.

3.3 Source Population

The source population was all the highlanders 18 years and older living in rural villages of 30 to 400 dwelling units located in the Andean mountains of Peru in 2008. Figure 3.3.1 shows the geographic location of Peru, and figure 3.3.2 shows the geographic location of the Andes Mountains.

Figure 3.3.1 The geographic location of Peru

Legend: Peru
Source: https://en.wikipedia.org/wiki/Peru#/media/File:PER_orthographic.svg

Figure 3.3.2 Andes mountains map

Source: http://ciprofloxacinxcost.com/wp-content/uploads/2018/10/andes-mountains-world-map-los-on-of-chile-bolivia-in-south-america-bigpony-640-x-960-pixels-andes-mountains-world-map.jpeg

3.4 Sampling Approach

The Peruvian National Institute of Mental Health researchers used a multistage random sampling in their survey study. In the first stage, they performed a stratification of the Andean rural highlander by regions. They got three strata, corresponding to the regions of Ancash, Ayacucho, and Cajamarca. Figure 3.4.1, 3.4.2, and 3.4.3 show the geographic location of these regions. In the second stage, they chose census clusters in each region via systematic random selection. Each census cluster had 30 to 400 dwelling units corresponding to small villages. The Peruvian National Institute of Statistics and Informatics built the census cluster based upon in the pre-census of 2005. The census cluster was the primary sampling unit of the sampling

survey. In the third stage, they selected 14 to 16 dwelling units, where just the first dwelling unit was randomly selected. The remaining 13 to 14 dwellings units were adjacent to the first randomly selected dwelling unit. The dwelling unit was the secondary sample unit of the sampling design. Finally, they randomly selected a designed participant in each selected dwelling unit via the modified Kish table of random numbers (Kish, 1949).

Figure 3.4.1 The geographic location of the Ancash region

Source: https://en.wikipedia.org/wiki/Department_of_Ancash#/media/File:Peru_-_Ancash_Department_(locator_map).svg

Figure 3.4.2 The geographic location of the Cajamarca region

Source: https://en.wikipedia.org/wiki/Department_of_Cajamarca#/media/File:Peru_-_Cajamarca_Department_(locator_map).svg

Figure 3.4.3 The geographic location of the Ayacucho region

Source: https://en.wikipedia.org/wiki/Department_of_Ayacucho#/media/File:Peru_-_Ayacucho_Department_(locator_map).svg

3.5 Sampling Size

For the determination of the sample size, the Peruvian researchers used the sample size equation proposed by Lohr in his book "Sampling: Design and Analysis" page 311 (Lohr, 2010), which was based in the previous work of Cornfield (Cornfield, 1951)

$$n = \left(\frac{z}{e}\right)^2 \left(\frac{1-p}{p}\right)(deff)\left(\frac{1}{1-lnr}\right)\left(\frac{1}{1-prd}\right)$$

In this equation, ***n*** is the number of dwelling units included in the survey. ***Z*** is the z value of 1.96 required for the 95% confidence interval of the estimations. The ***e*** is the maximum

allowable error in this survey; they considered a value of e of 10 percent. The ***deff*** is the design effect; they specified deff in 1.5 based upon the values obtained in previous studies. The ***p*** is the proportion; they set a prevalence of psychiatric disorders of 30 percent in this study. The ***lnr*** is the level of no response; they specified the value of 10 percent for the lnr. Finally, ***prd*** is the average mean of designed respondents per dwelling unit. They specified prd in 0.544. Taking into consideration all these values, they got a sample size of 3,276 dwelling units for their survey.

3.6 Participation Levels

In the survey carried out in 2008 among the rural Peruvian highlanders, 245 of them did not consent to participate. Due to this, the effective sample size for the present research is 3,031, and the proportion of designated participants in the present study is 92 percent.

3.7 Ethical Issues

The Rural Peruvian Andean Highlands Mental Health Survey protocol was reviewed and approved by the Peruvian National Institute of Mental Health Institutional Review Board for Protection of Human Subjects in Research. Every participant in this study signed informed consent before starting the interview. Participation in this study was entirely voluntary, and participants had the freedom to not answering the questions that they consider uncomfortable, or they could finish the interview whenever they want. Besides, the entire budget for this survey came from the Peruvian government funds.

On the other hand, the protocol for this master thesis study was reviewed and approved by the Michigan State University Institutional Review Board for Protection of Human Subjects in Research (IRB). As this master thesis study was carried out with de-identified data from the Rural Peruvian Andean Highlands Mental Health Survey, the IRB considered that this master thesis research does not involve human subjects. This decision was made because according to the definition § 46.102(f) from the part 46-Protection of Human Subjects, Title 45-Public Welfare of the CODE OF FEDERAL REGULATIONS (United States Office of the Federal Register, 2008), the present study was not conducted with subjects from whom the researchers obtain (1) data through intervention or interaction with the individual, or (2) identifiable private information.

3.8 Measures

This section describes the measured variables as well as the survey methods for the assessment of these variables.

3.8.1 Study Variables

The study variables are listed as response variables (e.g., coca leaf chewing), covariates (e.g., department or state of residence of the participants), some of which functioned as confounding or moderator variables of the association under study.

3.8.1.1 Response Variables

a. History of Coca Leaf Chewing

History of coca leaf chewing was defined concerning any chewing of coca leaves in the lifetime. Ever coca leaf chewing use data was based on a face-to-face survey carried out among the Peruvian highlanders. Standardize questionnaire was applied by previously training interviewers; all the interviewers were bachelors in psychology, nurse, or midwifery. Participants were asked if they have ever chewed coca leaf, whether by curiosity, pleasure or because they were pressed to do it (not including those who chewed coca leaf by medical prescription). Those who endorsed lifetime coca leaf chewing were asked if they are using in the last 30 days (active coca leaf chewing). Those who did not endorse active coca leaf chewing were asked if they have used it in the last 12 months (recent coca leaf chewing). Furthermore, those who endorsed lifetime coca leaf chewing were asked the age of onset of coca leaf use.

b. Active Coca Leaf Chewing

Active coca leaf chewing was defined as the consumption of coca leaves in the last 30 days. Participants who endorsed ever coca leaf chewing were asked if they have used it in the last 30 days.

c. Recent Coca Leaf Chewing

Recent coca leaf chewing was defined as the use of coca leaves in the last 12 months. Participants who endorsed ever coca leaf chewing were asked if they have used it in the last 12 months.

d. Age of Coca Leaf Chewing Onset

Age of coca leaf chewing onset was defined as the age when the participant chews coca leaf for the first time. Consumption for medical prescription was not taken into consideration. Participants who endorsed ever coca leaf chewing were asked for the age at which they chewed coca leaf for the first time.

e. Coca leaf chewing recency

Coca leaf chewing recency was defined as the period at which happened the last consumption of coca leaf chewing. Participants were asked if their last consumption of coca chewing was in the last 30 days. Participants who did not endorse coca chewing in the last 30 days were asked if their last use was over 30 days but less of one year. Participants who did not endorse coca chewing over 30 days but less of one year were asked if their last consumption was over one year.

f. Persistence of Coca Leaf Chewing

Persistence of coca leaf chewing was defined as the proportion or percentage of ever coca leaf chewers who are active coca leaf chewers in the last 30 days. This proportion was obtained by dividing the number of active coca leaf chewers (30-days users) by the number of ever coca leaf chewers (lifetime users) and then expressed this value in percentage.

g. 12-months Coca Leaf Chewing Dependence

The diagnosis of coca leaf chewing dependence syndrome was made in the last year and based on the clinical features of the International Classification of Diseases 10th Revision (ICD-10) for Mental and Behavioral Disorders: Diagnostic Criteria for Research (World Health Organization, 1993). This nosology defines dependence syndrome as a psychiatric disorder, which has in the

last 12 months three or more symptoms from six clinical features. These clinical features are: (1) A strong desire or compulsion to use the substance. (2) The substance is often being used in large amounts or over a long period than intended or any unsuccessful effort or desire to cut down or control the substance intake. (3) Withdrawal syndrome when the ingestion of the substance is reduced or ceased or use the substance with the intention of relieving or avoiding withdrawal symptoms. (4) Tolerance to the effects of the substance, consequently, a high quantity of the substance is needed to reach the desired effect. (5) Preoccupation with the substance, as manifested by reduction of pleasurable activities because of the substance use; or spending considerable time in activities necessary to obtain, use, or recover from the effects of the substance. (6) Persistent substance use despite clear evidence of harmful consequences.

h. 12-months Coca Leaf Chewing Harmful Use

The diagnosis of coca leaf chewing harmful use was made in the last year and based upon in the clinical features of the ICD-10 for Mental and Behavioral Disorders: Diagnostic Criteria for Research (World Health Organization, 1993). This nosology considers the following clinical features for the diagnoses of harmful use: (A) Clear evidence that the substance was responsible for physical or psychological harm, including impaired judgment or dysfunctional behavior. (B) The nature of the harm should be clearly identifiable. (C) The patterns of use of the substance have persisted for at least one month or have occurred repeatedly within twelve months. (D) This disorder does not meet the criteria for any other mental or behavioral disorder related to substance use in the same period (except for acute intoxication for the substance).

i. Multicultural Quality of Life Index

A multicultural setting of professionals in New York developed the Spanish version of the Multicultural Quality of Life Index (MQLI-Sp). The MQLI-Sp is a brief device for comprehensive, culture-informed, and self-rated assessments of the quality of life. This scale has the following ten dimensions: (1) Physical well-being (feeling energetic, free of pain, and physical problems). (2) Psychological/emotional well-being (feeling good and comfortable with yourself). (3) Self-care and independent functioning (carry out daily living tasks, making one's own decisions). (4) Occupational functioning (able to carry out work, school, and homemaking duties). (5) Interpersonal functioning (able to respond and relate well to family, friends, and groups). (6) Social-emotional support (availability of people you can trust and who offers help and comfort). (7) Community and services support (good and safe neighborhood, availability of resources, and other services). (8) Personal fulfillment (experiencing a sense of balance, solidarity, and empowerment; enjoying sexuality, aesthetics, etc.). (9) Spiritual fulfillment (having a high philosophy of life; religiousness; transcendence beyond ordinary life). (10) The overall quality of life (feeling satisfied and happy with your life in general). These items were obtained through an exhaustive and critical review of the existing literature on the topic (Mezzich et al., 2000). Trained interviewers ask the participants to rate each item by choosing a number on a 10-point line from one (poor) to ten (excellent). The main MQLI-Sp index score is the arithmetic mean of the ten items, with a minimum average score of one (poor) and a maximum average score of ten (excellent) (Mezzich, Cohen, Ruiperez, Banzato, & Zapata-Vega, 2011).

3.8.1.2 Covariates

a. Sex

The variable sex was measured through the interviewer observation into two categories: male and females.

b. Age

The variable age was measured in years via the participants' self-report, and afterward, it was recorded in a new variable with three categories: "18-44 years", "45-64 years," and "65 years or over."

c. Ethnicity

Ethnicity was measured indirectly through the language that they learn from their parents in their early childhood. The participants were asked if their mother language was Spanish, Quechua, Aymara, or others.

d. Education

Education attainment was measured by asking about the last level of formal education that the participant approved. The following levels were considered according to the formal Peruvian education system: "Illiterate" without formal education. "Preschool" with 1 to 3 years of education, it is similar to the USA kindergartens schooling. "Primary" with six years of education, it is similar to the USA elementary schooling. "Secondary" with five years of education is similar to the USA's high school education. "Superior technical" with 1 to 3 years of education, it is similar to the USA vocational-technical education. "Superior university" with five years of education, it is similar to the USA undergraduate university education. "Graduate" with

2 to 4 years of education, it is similar to the USA graduate programs of master or doctoral studies. For this study, the variable education was recorded in the following three categories: "illiterate" without education, "primary" with kindergarten or elementary education, "secondary" with high school education" and "postsecondary" with technical, undergraduate, or graduate education.

e. Poverty

The concept of basic needs was used for the definition of poverty. Basic needs involve the satisfaction of primary needs such as food, health, clothing, housing, and education, and it was measured on a nominal scale. Thus, the participants were classified as poor if they have not satisfied one or more basic needs, and as not poor if they satisfied all their basic needs.

f. Marital Status

The Peruvian researchers evaluated the current marital status based upon in the self-report of participants. In this study, the variable marital status was recorded as "married or cohabiting," "separated/divorced/widowed," and "never married."

g. Region or State

The region is the administrative first-level subdivision of the Republic of Peru, which counts with 24 regions and the Constitutional Province of Callao. In this study, a random sample of participants was taken from the Andean rural highland villages of the regions of Cajamarca, Ancash, and Ayacucho.

h. Exposure to Traumatic Events Associated with Political Violence and Terrorism

The Peruvian researchers evaluated the exposure to traumatic via yes/no questions. They considered the following questions: During the period o high violence and terrorism (1) Have

you lost a close family member (parent, spouse, and children) in a violent event? (2) Have you lost other family members in any violent event? (3) Did you have a disappeared family member as a cause of the violence? (4) Have you witnessed the violent death of any person in a situation related to terrorism? (5) Have your family been arrested for an act related to violence or terrorism? (6) Have you had a family member in prison because of the violence? (7) Did you lose almost all your property because of the violence? (8) Did you have to change of residence a cause of the violence? In the present study, this variable was used as a count variable with a range of zero to eight traumatic events, as well as a nominal variable with yes/no answer if the participants have experienced one or more traumatic events associated with political violence and terrorism.

i. History of Posttraumatic Stress Disorder

The Peruvian researchers measured lifetime posttraumatic stress disorder based upon the clinical features of the ICD-10 for Mental and Behavioral Disorders: Diagnostic Criteria for Research (World Health Organization, 1993). The ICD-10 diagnosis of posttraumatic stress disorder requires the presence of the following criteria: (A) Exposure to a stressful event of exceptional threatening, which is likely to cause pervasive distress in almost anyone. (B) Persistent remembering or "reliving" the traumatic experience via flashbacks, vivid memories, or recurring dreams. (C) Avoidance of circumstances resembling or associated with the traumatic event. (D) Presence of either (1) or (2): (1) Impossibility to recall, either partially or entirely, some crucial aspects of the exposure to the traumatic event. (2) Persistent symptoms of increased psychological sensitivity and arousal shown by any two of the following: (a)

difficulty in falling or staying asleep; (b) irritability or outburst of anger; (c) difficulty in concentrating; (d) hyper-vigilance; (e) exaggerated startle response.

3.8.1.3 Potentially Confounding Variables

a. History of Mood or Anxiety Disorders

In this study, a lifetime history of either mood or anxiety disorders in the participants was used to create a new variable called mood/anxiety, whose affirmative answer represents the presence of one or more of these disorders. The diagnosis of these disorders was based upon the clinical features of the ICD-10 for Mental and Behavioral Disorders: Diagnostic Criteria for Research (World Health Organization, 1993). Lifetime history of depressive episodes and dysthymia were considered for the group of mood disorders. Moreover, a lifetime history of social phobia, panic disorder with or without agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder were considered for the group of anxiety disorders.

In this study, the lifetime history of mood or anxiety disorders was included as a confounder of the suspected detriment of the quality of life of the participants produced by coca leaf chewing dependence syndrome.

b Poverty

The variable poverty was included as a confounder of the suspected detriment of the quality of life index provoked by coca leaf chewing dependence syndrome. This variable was described in section 3.8.1.2(e).

c. Education

The variable education was included as a confounder of the suspected detriment of the quality of life index produced by coca-leaf-chewing dependence syndrome. This variable was described in section 3.7.1.2(d).

To the extent of possible, each of these confounding variables was studied as a potential source of subgroup variation in the observed associations. For the most part, this activity involved the formation of product-terms, and fitting regression models with the product-terms added one by one.

3.8.2 Assessments

The assessment device used for the diagnosis of psychiatric disorders in the Rural Peruvian Andean Highland Mental Health Survey was the Mini-International Neuropsychiatric Interview (MINI) Version in Spanish 5.0.0. The diagnoses of the MINI is based upon in the clinical features of the ICD-10 for Mental and Behavioral Disorders: Diagnostic Criteria for Research (World Health Organization, 1993). The MINI is a short diagnostic interview; it was created to evaluate 17 psychiatric disorders from the ICD-10 (Sheehan et al., 1998). Bobes validated the Spanish version of the MINI (Bobes, 1998), who found a good sensitivity and acceptable specificity for the MINI diagnoses as compare with the diagnoses made by psychiatrists.

Bachelors in psychologist, nurse, and midwifery were trained for the standardized application of the MINI's questions. The MINI was applied in a face-to-face interview.

3.9 Analysis Plan

3.9.1 Aim 1

For the estimation of basic epidemiological parameters, the Stata 12 complex survey commands such as ‘survey: mean,’ ‘survey: proportion,’ ‘survey: table,’ and 'survey ratio' were used (StataCorp, 2015). These survey Stata commands take into consideration the complexity of the sample design of the present study, such as sampling weights, stratification, and the presence of clusters with a homogeneous population. As the subjects living inside of the cluster are correlated, the classic statistical principle of independence of the events is not fulfilled. In this context, using the usual calculation of the variance based on simple random sampling tends to underestimate the real value of the variance, which could affect the reliability of our estimates (Kish, 1957). In order to increase the accuracy of the variance estimates, the Taylor Series Linearization was used to improve the approximation of variances due to the complex sample design of this master thesis study (Heeringa, West, & Berglund, 2010; Rust, 1985).

3.9.2 Aim 2

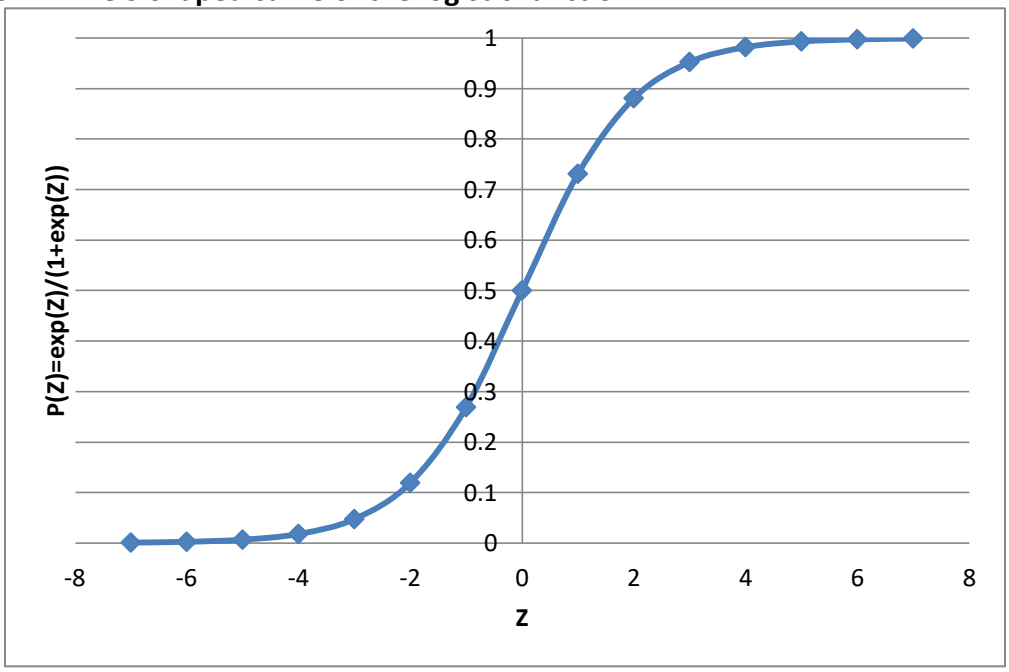
For the estimation of subgroup variation across subgroups, the Stata survey table, mean, ratio, and logit commands were used. The first three commands were described in section 3.9.1. The Stata survey logit command uses what Cramer described as a classic logistic function discovered by Pierre Francois Verhulst in the XIX century (Cramer, 2004) and rediscovered by Pearl and Reed in the XX century (Pearl & Reed, 1920). The Stata logit command models the probability (p) of success of a binary response variable in its logit form (p/1-p) as a function of one or

several covariates which could be categorical or numerical variables, actually known as logistic regression (Hosmer, Lemeshow, & Sturdivant, 2013). Binder, in 1983, expanded the concept of logistic regression to applied it to data from complex surveys (Binder, 1983), which was implemented in the Stata survey logit command used in this study (StataCorp, 2011).

Logistic function = P(Z)

$$P(Z) = \frac{e^Z}{1 + e^Z}$$

Figure 3.9.2.1 The S-shaped curve of the logistic function



Fitting a linear logistic regression model to a binomial data Y:

The data formed by n observations, y_1, y_2, ..., y_n, on a binomial response variable Y where $y_i = 1$ is a success, $y_i = 0$ is a failure, and i=1, 2, ..., n is the number of independent observations of Y. Moreover, Y is a binomial random variable with parameters n and p, Y ~ B(n,p), because n

independent Bernoulli trials Yi constitutes it. The expectation of Y is E(Y) = np, the variance of Y is V(Y) = npq, and q = 1 - p. It means that $Y = \sum_{i=1}^{n} Y_i = number\ of\ success$.

If the random variable $\hat{p}$ is the sample proportion, then $\hat{p} = \frac{\sum_{i=1}^{n} Y_i}{n} = \frac{Y}{n}$. As $\hat{p}$ is a sample mean, then $p = E(\hat{p})$ and $V(\hat{p}) = \frac{\sigma^2}{n} = \frac{pq}{n}$. Then the $se(\hat{p}) = \sqrt{\frac{pq}{n}}$, so the $se(\hat{p})$ is estimated by $\sqrt{\frac{\hat{p}\hat{q}}{n}}$ (Rosner, 2006).

From a statistical model, that is:

$$response\ variable = systematic\ component + residual\ component$$

$$y_i = \hat{y}_i + \epsilon_i = E(Y_i/x_j) + \epsilon_i$$

Where i = 1, 2,..., n is the number of independent observations of the random variable Y, and j = 1, 2, ..., k is the number of predictor variables X of the random variable Y.

In the case of a binomial data, it is more convenient to model the random variable probability of success p_i than the binary random variable y_i

$$p_i = \hat{p}_i + \epsilon_i = E(p_i/x_j) + \epsilon_i$$

Then, the linear regression of the $E(p_i/x_j)$ on k explanatory variables X is

$$\hat{p}_i = E(p_i/x_j) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_k x_{ki}$$

This linear regression has some technical problems, such as (1) the absence of the required constant variance of p_i. It is because $V(\hat{p}_i) = \frac{\sigma_{p_i}^2}{n_i} = \frac{p_i q_i}{n_i}$ Thus, even in the situation where n_i is all equal or $n_i = 1$, such as in the Bernoulli trials, the p_i will be different for each observation of Y. In consequence, the variance $V(\hat{p}_i)$ will also be different for each observation of the binomial random variable Y. Nonetheless, there are some statistical techniques to

correct the absence of constant variance, such as the variance stabilizing transformation or the weighted least square. (2) The assumption of normally distributed response variable Y is no longer fulfilled because Y is now a binomial random variable. However, due to central-limit theorem large sample size tend to normality independent of its underlying distribution (Rosner, 2006) (3) As $\hat{\beta}_j$ could take any value between $-\infty \; and \; +\infty$, then the estimated probability of success $\hat{p}_i$ could also take any value between $-\infty \; and \; +\infty$ because $\hat{p}_i$ is a linear combination of $\hat{\beta}_j$. From all these limitations of fitting a linear regression to a binomial data, the last one is the most important because of the range of the probability $\hat{p}_i$ must be between 0 and 1 and not between $-\infty \; and \; +\infty$ (Collett, 2003). In consequence, the first step for the fitting of a linear model to binomial data is the transformation of a range of the main response variable probability of success p_i from (0, 1) to $(-\infty, +\infty)$. For this purpose, statisticians have developed different transformations of the probability of success p_i such as the *logistic transformation*, the *probit transformation*, and the *complementary log-log transformation*. Although the *logistic transformation* and the *probit transformation* are quite similar, the *logistic transformation* is the most used due to its practicality and the usefulness in epidemiology because it easily allows the estimation of odds ratios (Collett, 2003). The logistic transformation permits the use of many of the desirable properties of linear regression models because the logit(p_i) is linear in its parameters (Hosmer et al., 2013)

The *logistic transformation* is the log odds of the probability of success p_i, which is called the *logit* of p_i:

$$logit(p_i) = \ln\left(\frac{p_i}{1 - p_i}\right)$$

Then, the logistic transformation changes the range of the probability of success p_i from (0, 1) to $(-\infty, +\infty)$. Thus, when p_i tends to zero, the logit(p_i) approaches the $-\infty$, and when p_i tends to one, the logit(p_i) approaches the $+\infty$. Furthermore the function logit(p_i) is linear between p_i = 02 and p_i = 0.8. In general, the function logit(p_i) is a sigmoid curve, that is symmetric in the probability of success p_i equal to 0.5 (Collett, 2003). See figure 3.9.2.2.

Finally, the ***linear logistic model*** or the ***logistic regression model*** of p_i on k explanatory variables X for a binomial response variable Y is:

$$logit(p_i) = \ln\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_{1i} + \cdots + \beta_{ki}$$

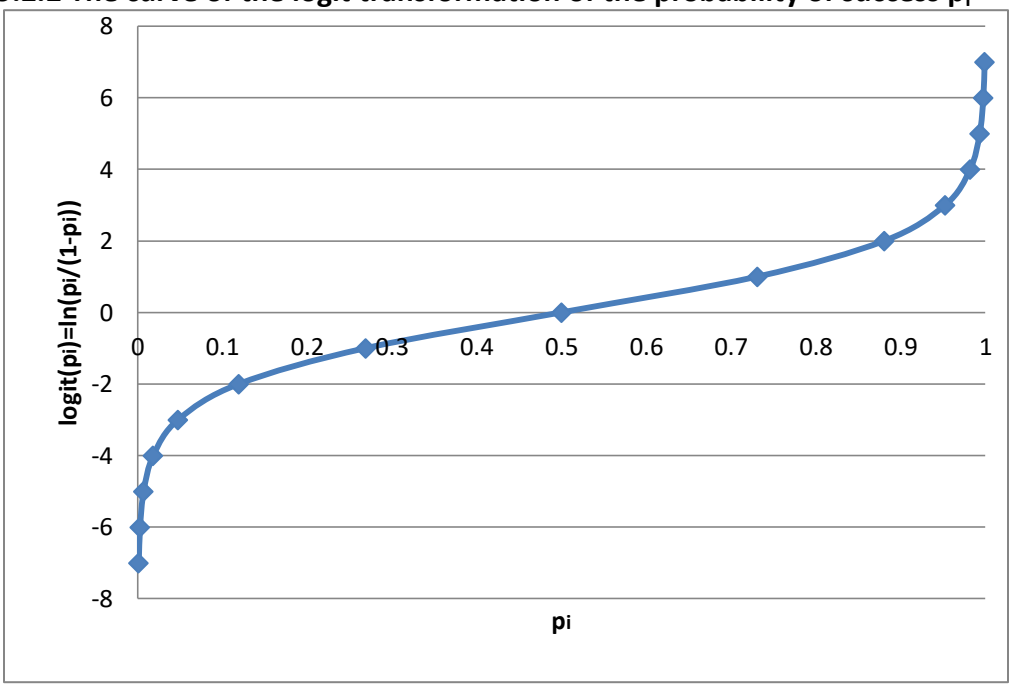
The estimated logit of the probability of success p_i after $\hat{\beta}$ was calculated via the method of *maximum likelihood* is:

$$logit(\hat{p}_i) = \ln\left(\frac{\hat{p}_i}{1-\hat{p}_i}\right) = \hat{\beta}_0 + \hat{\beta}_1 x_{1i} + \cdots + \hat{\beta}_k x_{ki}$$

The fitted probability of success $\hat{p}_i$ can be found from:

$$\hat{p}_i = \frac{e^{\hat{\beta}_0 + \hat{\beta}_1 x_{1i} + \cdots + \hat{\beta}_k x_{ki}}}{1 + e^{\hat{\beta}_0 + \hat{\beta}_1 x_{1i} + \cdots + \hat{\beta}_k x_{ki}}}$$

Figure 3.9.2.2 The curve of the logit transformation of the probability of success p_i



3.9.3 Aim 3

For the estimation of the prevalence of coca leaf chewing dependence, the Stata survey 'proportion' command was used; this command was described in section 3.9.1. Afterward, the Stata post-estimation 'test' of 'survey proportion' was used to test the hypothesis that the prevalence of coca leaf chewing dependence was equal to zero via the Wald test (Rao, 1973; Wald, 1943) as a proxy for the one-sample Z proportion test (Rosner, 2006). Furthermore, the t-test (Eisenhart, 1979; Fisher, 1925; Hagin, 1990; Student, 1908) was used to evaluate the null hypothesis that the mean of the multicultural quality of life index Spanish version (MQLI-Sp) of coca leaf chewers with dependence syndrome was equal to the mean of the MQLI-Sp of never or ever coca leaf chewers without dependence syndrome. The t-test was performed using the post-estimation command 'lincom' of the Stata 12 'survey mean' command (StataCorp, 2011).

Finally, in order to evaluate if the suspected differences in the means of the MQLI-Sp between coca leaf chewers with and without dependence syndrome persist after control for the confounding effects of mood/anxiety disorders, poverty and education, the generalized linear model/Generalized Estimation Equations (GLM/GEE) with identity link was used. Liang and Zeger developed the GLM/GEE (Diggle, Liang, & Zeger, 1994; Liang & Zeger, 1986; Zeger & Liang, 1986; Zeger, Liang, & Albert, 1988). The GLM/GEE regressed the values of each of the ten items of the MQLI-Sp on ever coca leaf chewers with and without dependence syndrome controlling for the probably confounding effects of mood/anxiety disorders, poverty and education. Furthermore, the GLM/GEE allowed the estimation of the relative individual contribution of each of the ten MQLI-Sp items in the impairment of the quality of life of coca leaf chewers with dependence syndrome as compared to the chewers without dependence syndrome. The GLM/GEE was selected because it fits better the correlated items of the MQLI-Sp than the ordinary least squares linear regression. These analyses were performed with the statistical software Stata 12 (StataCorp, 2015).

CHAPTER 4 RESULTS

4.1 Introduction to Chapter 4

The results chapter of this thesis research project is organized into parts, each of which conveys findings under the specific aims. Part 4.2 presents a description of the study sample. Part 4.3 covers Specific Aim #1 and presents estimates of basic epidemiological parameters such as cumulative incidence proportions as observed for survey respondents in the study population, as well as prevalence proportions for recently active behaviors, and other parameters that reflect the persistence of coca leaf chewing once it starts. Part 4.4 covers Specific Aim #2 and presents estimates of the age of coca leaf chewing onset and the degree to which the ever coca leaf chewing and especially the active coca leaf chewing shows variation across subgroups of the study population, with focused attention to variation in relation to characteristics of person and place. Part 4.5 covers Specific Aim # 3 and presents estimates pertinent to the occurrence of cocaine dependence among coca leaf chewers as well as estimates pertinent to the quality of life of coca leaf chewers with dependence syndrome.

4.2 Study Sample Description

A description of the study sample is provided in table 4.2.1. Results show that approximately one of two participants was female. The age group with most participants was the 18-44 years old. Concerning ethnicity, two of five participants belong to the Quechua ethnic group, which is the major Peruvian ethnic group living in the Andean mountains. A low level of education was predominant in this population, with about one-half just having elementary education, and one

of five of them never having a formal education. The disadvantaged conditions of this population are clearer when we examine the privation of the highlanders because nearly nine of ten of them live in poverty.

Table 4.2. 1 Characteristics of the Rural Peruvian Andean Highlands Mental Health Survey, 2008, (n=3,031)

Characteristics	Unweighted No.	Weighted %	SE
Sex			
Female	1,762	49.3	1.1
Male	1,269	50.8	1.1
Age			
18-44	1,735	61.2	1.2
45-64	772	24.4	1.0
65+	522	14.4	0.9
Ethnicity			
Hispanic	1,325	62.4	1.6
Quechua	1,700	37.5	1.6
Other	5	0.1	0.0
Education			
Postsecondary	164	5.0	0.7
Secondary	583	20.7	1.4
Primary	1,541	52.9	1.6
Illiterate	743	21.3	1.2
Poverty			
Poor	2,784	91.7	1.3
No poor	247	8.3	1.3
Marital status			
Married/cohabiting	2,128	73.6	1.1
Separated/widowed/divorced	513	10.7	0.7
Never married	389	15.7	1.0
Region (State)			
Ancash	973	20.5	1.8
Ayacucho	1,023	22.7	1.1
Cajamarca	1,035	56.8	1.8

Abbreviation: SE = standard error, based on Taylor series linearization method

4.3 Specific Aim # 1 Results: Epidemiological Rubrics of Quantity of Coca Leaf Chewing

In the specific aim number one, the basic epidemiological parameter of coca leaf chewing was estimated, such as cumulative incidence proportions, prevalence proportions, and other parameters that reflect the persistence of coca leaf chewing once it starts. Estimates for the prevalence proportion, cumulative incidence proportion, and persistence of coca leaf chewing are provided in table 4.3.1. The result shows a lifetime prevalence or cumulative incidence proportion of coca leaf chewing of 41.2% among the rural Peruvian Andean highlanders (95% CI 38.4, 44.1), which means that 41.2% of the Peruvian highlanders have ever chewed a coca leaf (ever coca leaf chewers). The prevalence proportion of coca leaf chewing in the last 12 months is 26.4% (95% CI 23.8, 29.2), which means that 26.4% of the Peruvian highlanders have chewed coca leaf in the last 12 months (recent coca leaf chewers). The prevalence proportion of coca leaf chewing in the last 30 days is 21.4% (95% CI 19.2, 23.8), which means that 21.4% of the Peruvian highlanders have chewed coca leaf in the last 30 days (active coca leaf chewers). Finally, referring to the persistence of coca leaf chewing, 1 of 2 of 'ever coca leaf chewers' has actively chewed it in the last 30 days (51.9%; 95% CI 48.1, 55.7).

Table 4.3. 1 Prevalence proportion, cumulative incidence proportion, and persistence of coca leaf chewing use – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Prevalence	Unweighted No.	Weighted %	(95% CI)	SE
Coca Leaf Chewing Prevalence				
Ever (cumulative incidence proportion)	1,333	41.2	(38.4, 44.1)	1.5
Recent (12 months)	877	26.4	(23.8, 29.2)	1.3
Active (30 days)	714	21.4	(19.2, 23.8)	1.2
Persistence of coca leaf chewing*	-	51.9	(48.1, 55.7)	1.9

***Percentage of ever coca leaf chewers who are active coca leaf chewers in the last 30 days. Some percentages do not sum to 100% due to rounding.

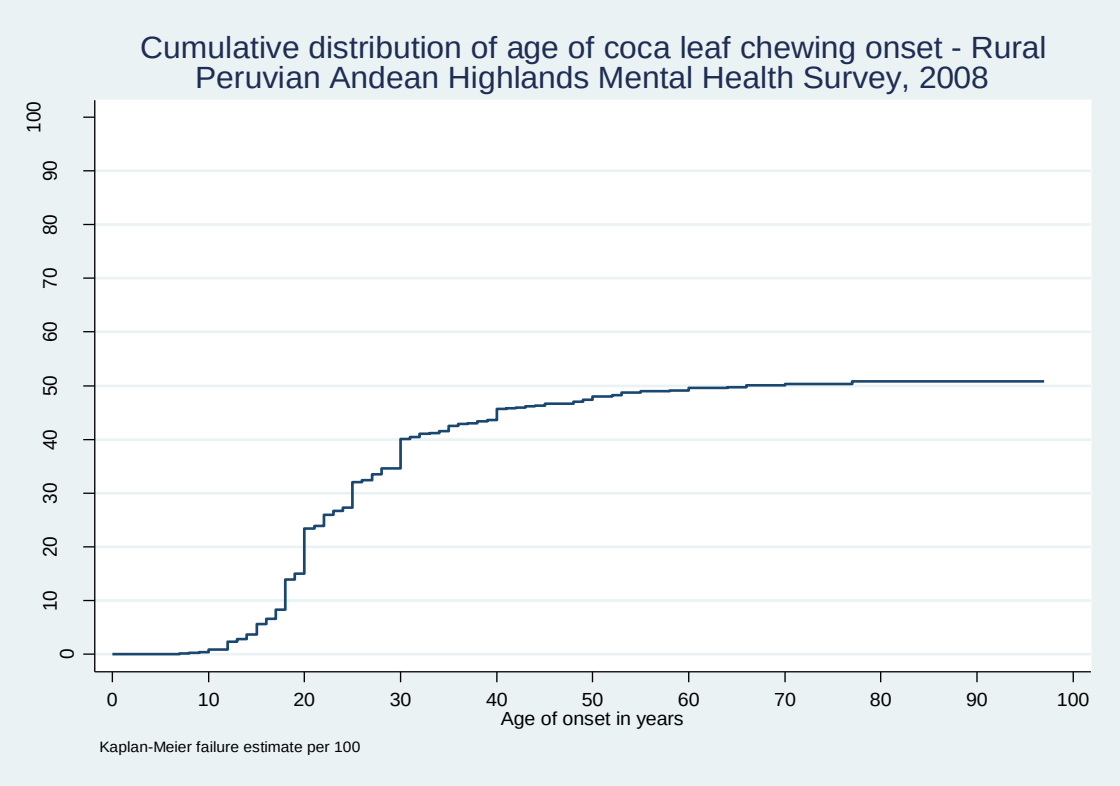
4.4 Specific Aim # 2 Results: Epidemiological Rubrics of Location of Coca Leaf Chewing

Under the specific aim number two, an estimation of the age of onset of coca leaf chewing was provided in section 4.4.1. Estimations of the subgroup variation of ever coca leaf chewing were made in section 4.4.2. Estimations of the subgroup variations of the persistence of coca leaf chewing were done in section 4.4.3. Also, mainly estimations of the subgroup variations of active coca leaf chewing were made in section 4.4.4. Furthermore, estimations of the subgroup variations of coca leaf chewing according to personal characteristics were done in section 4.4.5. Male-female differences of coca leaf chewing in section 4.4.5.1. Age group variations of coca leaf chewing in section 4.4.5.2. Ethnic subgroup variations of coca leaf chewing in section 4.4.5.3. Variations of coca leaf chewing across levels of exposure to traumatic events associated with political violence and terrorism in section 4.4.5.4. Variations of coca leaf chewing across the history of posttraumatic stress disorder in section 4.4.5.5. Finally, estimations of the variations of coca leaf chewing across characteristics of the place were done in section 4.4.6.

4.4.1 Age of Onset of Coca Leaf Chewing

Estimates for the age of coca leaf chewing onset are provided in figure 4.4.1.1. The cumulative proportions show that among these Peruvian highlanders chewing coca leaf generally did not start until about ten years of age, and a great number of highlanders start chewing coca leaf between the age of 12 and 30 years old. After 30 years old, to start chewing coca leaf for the first time is quite rare. By 50 years old, approximately one-half of the highlanders have chewed coca leaf.

Figure 4.4.1.1 Cumulative distribution of age of coca leaf chewing onset - Rural Peruvian Andean Highlands Mental Health Survey, 2008



4.4.2 Subgroup variations of Ever Coca Leaf Chewing

Evidence of subgroup variation in the cumulative incidence proportion or lifetime prevalence of coca leaf chewing is provided in table 4.4.2.1. These results came from survey contingency table analyses, and it shows that males, elders, Quechuas, married or cohabitants, residents in Ayacucho, and highlanders with history of posttraumatic stress disorder, mood/anxiety disorders, or exposure to traumatic events related to political violence and terrorism are subgroups with higher cumulative incidence proportions for coca leaf chewing.

Table 4.4.2. 1 Coca leaf chewing among adults aged ≥ 18 years, estimated cumulative incidence proportions for subgroups – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Characteristic	Unweighted No.	Weighted %	(95% CI)
Total	1,333	41.2	(38.4, 44.1)
Sex			
Female	516	21.3	(19.0, 23.7)
Male	817	60.6	(55.6, 65.4)
Age			
18-44 years	664	36.8	(33.3, 40.4)
45-64 years	372	44.6	(39.9, 49.3)
65+ years	296	54.4	(49.0, 59.8)
Ethnicity			
Hispanic	425	33.3	(29.7, 37.1)
Quechua	905	54.5	(49.8, 59.1)
Other	3	*	(15.6, 88.7)
Poverty			
Poor	1,261	42.2	(39.4, 45.1)
No poor	72	30.0	(21.4, 40.3)
Education			
Postsecondary	52	31.4	(21.9, 42.7)
Secondary	247	39.3	(33.0, 45.9)
Primary	727	45.5	(41.6, 49.4)
Illiterate	307	34.9	(30.6, 39.4)
Marital status			
Married/cohabiting	973	44.1	(40.7, 47.5)
Separated/widowed/divorced	241	40.0	(34.2, 46.1)
Never married	118	28.6	(23.5, 34.4)
Region (State)			
Ancash	240	24.1	(19.4, 29.6)
Ayacucho	791	77.2	(73.8, 80.4)
Cajamarca	302	33.0	(29.2, 37.0)
Posttraumatic stress disorder			
Present (ever)	328	59.8	(52.4, 66.8)
Absent	1,005	38.7	(35.7, 41.7)
Mood/anxiety disorders			
Present (ever)	468	48.3	(43.1, 53.5)
Absent	865	38.7	(35.7, 41.8)
Exposure to political violence			
Yes	644	71.4	(66.5, 75.8)
No	689	33.0	(29.8, 36.3)

Abbreviation: CI = confidence interval. Estimates are not produced for minimal subgroups (n<20)

4.4.3 Subgroup Variations of Persistence of Coca Leaf Chewing

Evidence of subgroup variations on the persistence of coca leaf chewing is provided in table 4.4.3.1. These results came from the Stata survey ratio with an option over to get estimations across subpopulations. It shows that just the persistence of coca leaf chewing in the last 30 days among ever chewers in Ayacucho was two-fold higher than in Ancash, and one and a half-fold higher than in Cajamarca. There were no differences in coca leaf chewing persistence for other sociodemographic and health characteristics according to the 95% confidence interval of its estimations.

Table 4.4.3. 1 Persistence of coca leaf chewing among adults aged ≥ 18 years, by sociodemographic and health characteristics – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Characteristic	Weighted %*	SE	(95% CI)
Total	51.9	1.9	(48.1, 55.7)
Sex			
Female	51.0	3.1	(44.9, 57.2)
Male	52.1	2.3	(47.7, 56.6)
Age			
18-44 years	49.5	2.5	(44.5, 54.5)
45-64 years	55.3	3.7	(47.9, 62.6)
65+ years	54.1	3.9	(46.3, 61.9)
Ethnicity			
Hispanic	46.6	3.0	(40.7, 52.5)
Quechua	57.2	2.6	(52.2, 62.3)
Other	39.1	29.5	(-19.0, 97.2)
Education			
Postsecondary	50.7	11.4	(28.3, 73.1)
Secondary	37.6	4.0	(29.7, 45.5)
Primary	55.5	2.5	(50.5, 60.5)
Illiterate	56.1	3.7	(48.8, 63.4)
Poverty			
Poor	52.9	2.0	(49.0, 56.8)
No poor	35.8	7.2	(21.5, 50.1)
Region (State)			
Ayacucho	64.4	2.3	(59.8, 68.9)
Cajamarca	45.0	3.3	(38.5, 51.5)
Ancash	33.6	4.7	(24.3, 42.9)
Posttraumatic stress disorder			
Present (ever)	53.6	3.5	(46.7, 55.8)
Absent	51.5	2.2	(47.2, 60.6)

*percentage of ever coca leaf chewers who are active coca leaf chewers in the last 30 days

4.4.4 Subgroup Variations in Active Coca Leaf Chewing (within 30 days)

Evidence of subgroup variation in the active prevalence proportion (within 30 days) for coca leaf chewing is provided in table 4.4.4.1. These results came from survey contingency table analyses. It shows that males have a three-fold, more active prevalence proportion of coca leaf chewing than females. Sixty-five years old or older have one and a half-fold more active prevalence of coca leaf chewing than the group of 18-44 years old. Regarding ethnicity, Quechuas has two times more prevalence of active coca leaf chewing than Hispanics. Indigents have a two-fold more prevalence of active coca leaf chewing than not poor highlanders. Ayacucho residents have a six-fold and three-fold more prevalence of active coca leaf chewing than residents of Ancash and Cajamarca, respectively. Highlanders with a history of posttraumatic stress disorder have a two-fold more prevalence of active coca leaf chewing than residents without posttraumatic stress disorder. Highlanders with a history of exposure to political violence and terrorism have a three-fold more prevalence of active coca leaf chewing than residents without a history of exposure to political violence and terrorism. There were no subgroup variations of the prevalence proportion of active coca leaf chewing by other sociodemographic or health characteristics of the highlanders.

Table 4.4.4. 1 Active prevalence proportion (within 30 days) of coca leaf chewing among adults aged ≥ 18 years, by sociodemographic and health characteristics – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Characteristic	Unweighted No	Weighted %	(95% CI)
Total	714	21.4	(19.2, 23.8)
Sex			
Female	272	10.9	(9.1, 12.9)
Male	442	31.6	(27.9, 35.6)
Age			
18-44 years	345	18.2	(15.7, 21.0)
45-64 years	196	24.6	(20.4, 29.5)
65+ years	173	29.4	(25.0, 34.3)
Ethnicity			
Hispanic	195	15.5	(12.9, 18.5)
Quechua	518	31.2	(27.2, 35.5)
Other	1	21.4	(2.8, 71.7)
Poverty			
Poor	686	22.3	(20.1, 24.8)
No poor	28	10.8	(6.8, 16.6)
Education			
Postsecondary	20	15.9	(8.1, 28.9)
Secondary	102	14.8	(11.2, 19.2)
Primary	410	25.2	(22.2, 28.5)
Illiterate	182	19.6	(16.1, 23.7)
Marital status			
Married/cohabiting	524	23.1	(20.6, 25.9)
Separated/widowed/divorced	126	19.5	(15.2, 24.6)
Never married	64	14.4	(10.4, 19.7)
Region (State)			
Ancash	74	8.1	(5.6, 11.5)
Ayacucho	502	49.7	(45.3, 54.2)
Cajamarca	138	14.8	(12.1, 18.1)
Posttraumatic stress disorder			
Present (ever)	182	32.1	(26.3, 38.5)
Absent	532	19.9	(17.6, 22.4)
Mood/anxiety disorders			
Present (ever)	253	25.6	(21.7, 29.8)
Absent	461	19.9	(17.5, 22.6)
Exposure to political violence			
Yes	390	43.5	(38.3, 48.7)
No	324	15.3	(13.1, 17.9)

Abbreviation: CI = confidence interval.

Evidence of subgroup variation of the estimated association of active coca leaf chewing (within the last 30 days) with sociodemographic/health characteristics are provided in table 4.4.4.2. These results came from unadjusted and adjusted survey logistic regression. It shows that males are four-fold more probably to endorse active coca leaf chewing than females. After adjusting for age, ethnicity, poverty, educational attainment, marital status, department of residence, posttraumatic disorder, mood/anxiety disorders, and exposure to political violence, the males are still seven-fold more likely to endorse active coca leaf chewing than females. The 45-64 years old group is one and a half-fold more likely to endorse active coca leaf chewing than the 18-44 years old group; this association remains almost unchangeable after adjusting for the other predictor variables included in the model as was described previously in this section. The 65 years or older highlanders are two-fold more likely to endorse active coca leaf chewing than the 18-44 years old group in the unadjusted and adjusted survey logistic regression model. The Quechua ethnic group is two-fold more likely to endorse active coca leaf chewing than the Hispanics; however, after adjusting for the other predictor variables included in the survey logistic regression model, this association was not statistically significant. The same result was observed with poverty, where indigents were two-fold more likely to endorse active coca leaf chewing than the not poor highlanders; after adjusting for the other predictor variables included in the multivariate survey logistic regression model, this association was not any longer significant. The never-married highlanders are one-half-fold more likely to endorse active coca leaf chewing than the married or cohabiting highlanders; however, after adjusting for the other predictor variables included in the model, this association was not any longer significant. The highlanders who are residents of the regions of Ayacucho and Ancash are six-

fold and one-half-fold more likely to endorse active coca leaf chewing than the residents of the region of Cajamarca respectively. However, after adjusting for the other predictor variables included in the model, only the residents of Ayacucho remain significant with eight-fold more probability to endorse active coca leaf chewing than the residents of Cajamarca. The association of the history of posttraumatic stress disorder, mood/anxiety disorders, or exposure to political violence and terrorism with active coca leaf chewing is only significant in the unadjusted survey logistic regression. In this unadjusted model, highlanders with a history of posttraumatic stress disorder are two-fold more likely to endorse active coca leaf chewing than highlanders without a history of posttraumatic stress disorder. Highlanders with a history of mood/anxiety disorders are one and a half-fold more likely to endorse active coca leaf chewing than highlanders without a history of mood/anxiety disorders. Finally, highlanders with a history of exposure to political violence and terrorism are four-fold more likely to endorse active coca leaf chewing than highlander without a history of exposure to political violence and terrorism.

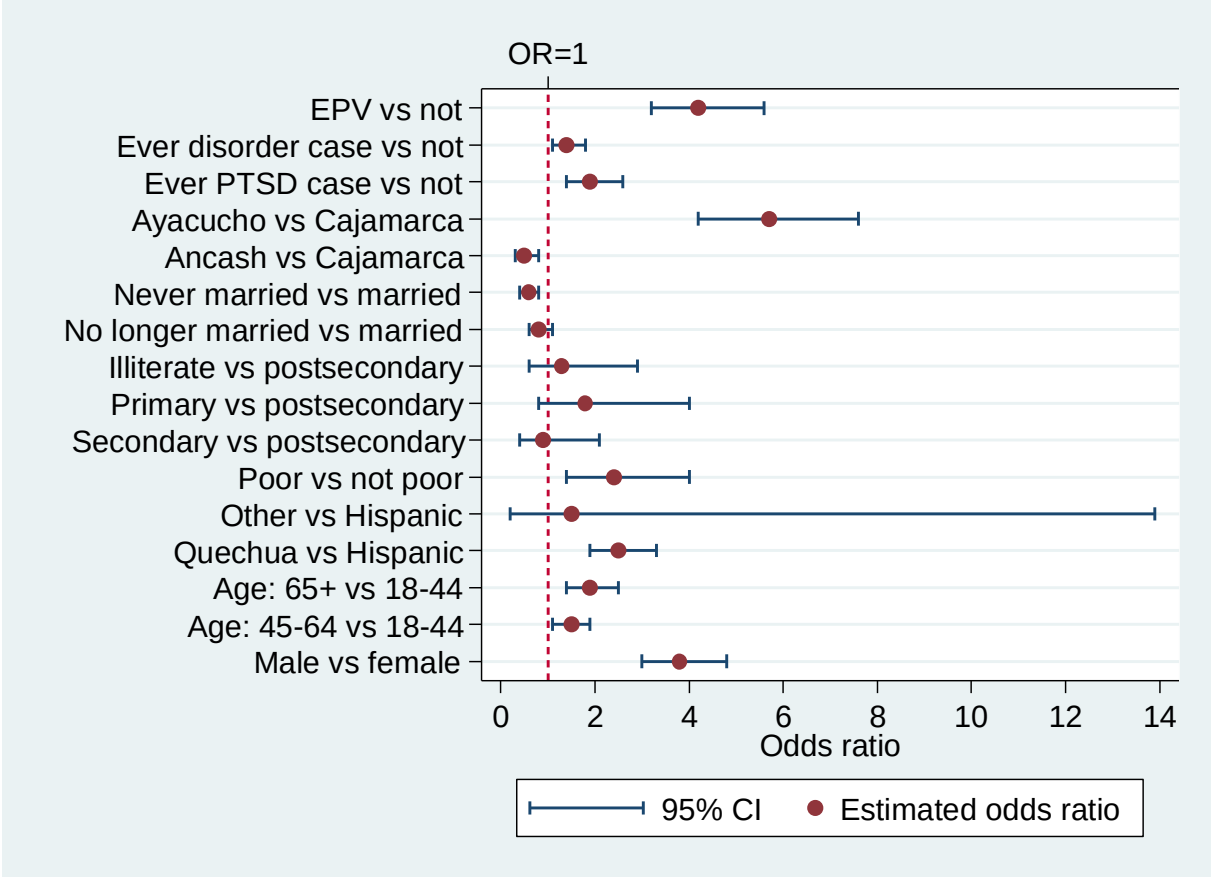
Table 4.4.4. 2 Estimated associations of active coca leaf chewing (within 30 days) with binary logistic regression parameters

Past 30-days coca leaf chewing use	Bivariate association			Adjusted associations		
	U. OR	(95% CI)	p-value	A. OR	(95% CI)	p-value
Sex						
Female	1.0			1.0		
Male	3.8	(3.0, 4.8)	<0.001	7.2	(5.4, 9.5)	<0.001
Age						
18-44 years	1.0			1.0		
45-64 years	1.5	(1.1, 1.9)	0.007	1.5	(1.1, 2.2)	0.016
65+ years	1.9	(1.4, 2.5)	<0.001	1.5	(1.0, 2.3)	0.041
Ethnicity						
Hispanic	1.0			1.0		
Quechua	2.5	(1.9, 3.3)	<0.001	0.9	(0.5, 1.4)	0.574
Other	1.5	(0.2, 13.9)	0.729	1.0	(0.1, 11.6)	0.974
Poverty						
Poor	2.4	(1.4, 4.0)	0.001	1.6	(0.9, 2.8)	0.112
No poor	1.0			1.0		
Education						
Postsecondary	1.0			1.0		
Secondary	0.9	(0.4, 2.1)	0.841	0.5	(0.2, 1.4)	0.169
Primary	1.8	(0.8, 4.0)	0.159	1.2	(0.4, 3.6)	0.678
Illiterate	1.3	(0.6, 2.9)	0.530	1.4	(0.5, 3.9)	0.555
Marital status						
Married/cohabiting	1.0			1.0		
Separated/widowed/divorced	0.8	(0.6, 1.1)	0.188	0.9	(0.6, 1.4)	0.709
Never married	0.6	(0.4, 0.8)	0.003	0.8	(0.5, 1.3)	0.382
Region (State)						
Ancash	0.5	(0.3, 0.8)	0.004	0.6	(0.3, 1.1)	0.113
Ayacucho	5.7	(4.2, 7.6)	<0.001	8.3	(4.9, 14.3)	<0.001
Cajamarca	1.0			1.0		
Posttraumatic stress disorder						
Present (ever)	1.9	(1.4, 2.6)	<0.001	0.7	(0.4, 1.2)	0.244
Absent	1.0			1.0		
Mood/anxiety disorders*						
Present (ever)	1.4	(1.1, 1.8)	0.010	1.5	(1.0, 2.2)	0.058
Absent	1.0			1.0		
Exposure to political violence						
Yes	4.2	(3.2, 5.6)	<0.001	1.4	(0.9, 2.2)	0.096
No	1.0			1.0		

* Depressive episode, dysthymia, posttraumatic stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, social phobia, panic disorder. **Abbreviation**: U. OR = Unadjusted OR, A. OR = Adjusted OR

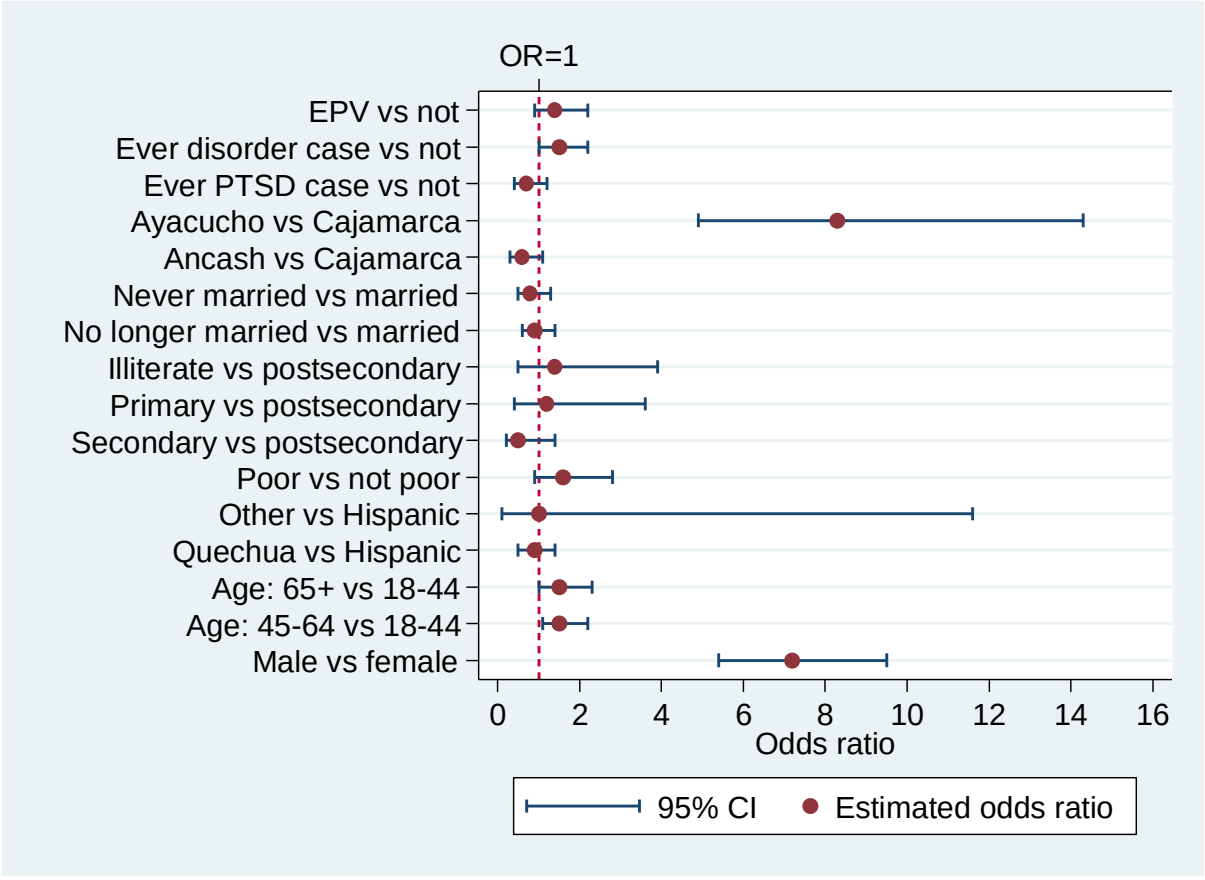
A summary of the unadjusted association of active coca leaf chewing with sociodemographic/health characteristics are provided in figure 4.4.4.1. The results from unconditional logistic regression show that political violence, mood/anxiety disorders, posttraumatic stress disorder, residents of Ayacucho, indigents, Quechuas, 45-64 years group, 65+ years group, and male are direct and significant associated with active coca leaf chewing. In contrast, residents of Ancash and never married are inverse and significant associated with active coca leaf chewing.

Figure 4.4.4.1 Estimated unadjusted associations of active coca leaf chewing (within 30 days) with unconditional logistic regression parameters



Finally, a summary of the adjusted association between active coca leaf chewing and sociodemographic/health characteristics is provided in figure 4.4.4.2. These are results from multivariate unconditional logistic regression with sex, age, ethnicity, poverty, educational attainment, marital status, department of residence, history of posttraumatic stress disorder, history of mood/anxiety disorders, and history of exposition to political violence as predictor variables. It shows that only residents of Ayacucho, 45-64 years group, 65+ years group, and male are direct and significantly associated with active coca leaf chewing.

Figure 4.4.4.2 Estimated adjusted associations of active coca leaf chewing (within 30 days) with binary logistic regression parameters



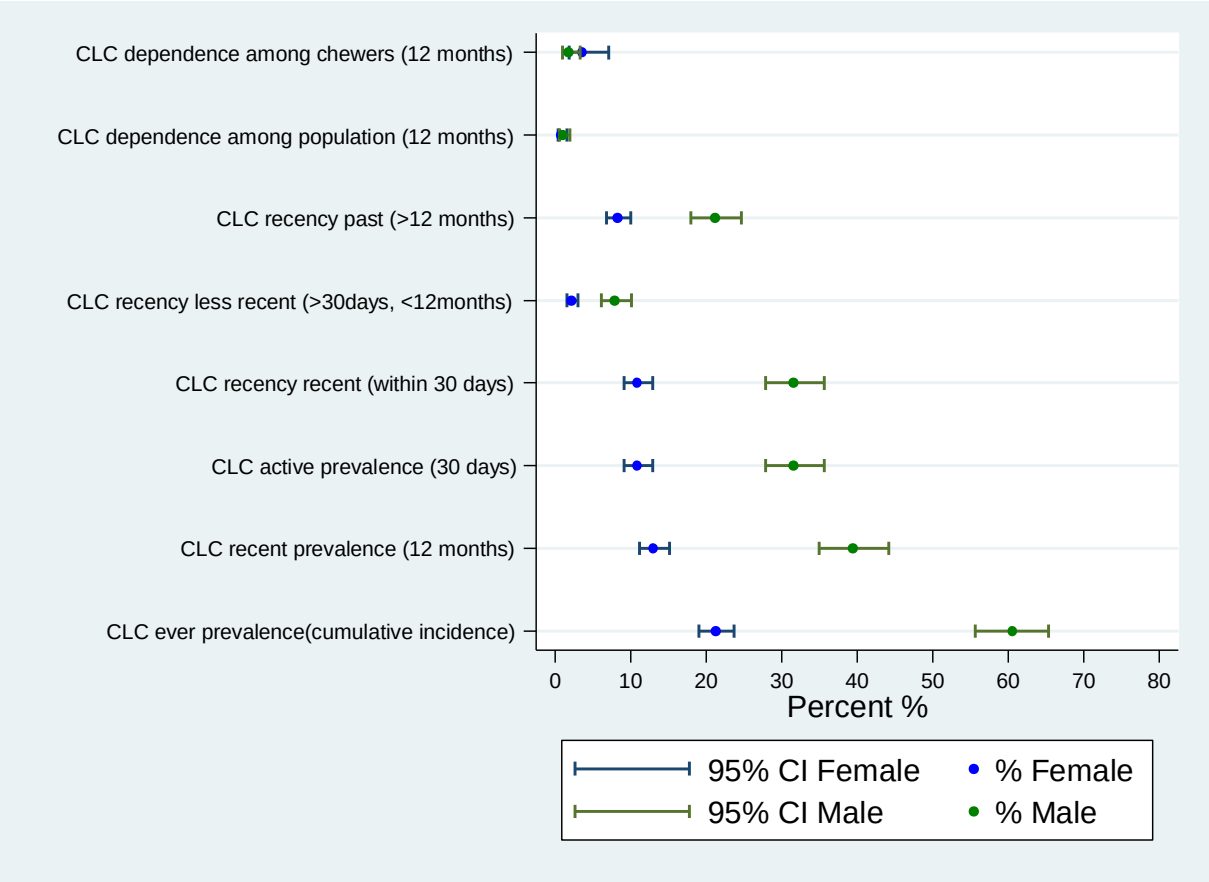
4.4.5 Variations of Coca Leaf Chewing Across Personal Characteristics

Under the variations of coca leaf chewing across personal characteristics, in section 4.4.5.1 estimations of male-female differences of coca leaf chewing was done. In section 4.4.5.2 estimations of age group variations of coca leaf chewing is provided. In section 4.4.5.3 estimations of ethnic subgroup variations of coca leaf chewing was done. In section 4.4.5.4, estimations of the variations of coca leaf chewing across levels of exposure to traumatic events associated with political violence and terrorism were done. Finally, in section 4.4.5.5, estimations of the variations of coca leaf chewing across the history of posttraumatic stress disorder were done.

4.4.5.1 Male-Female Differences

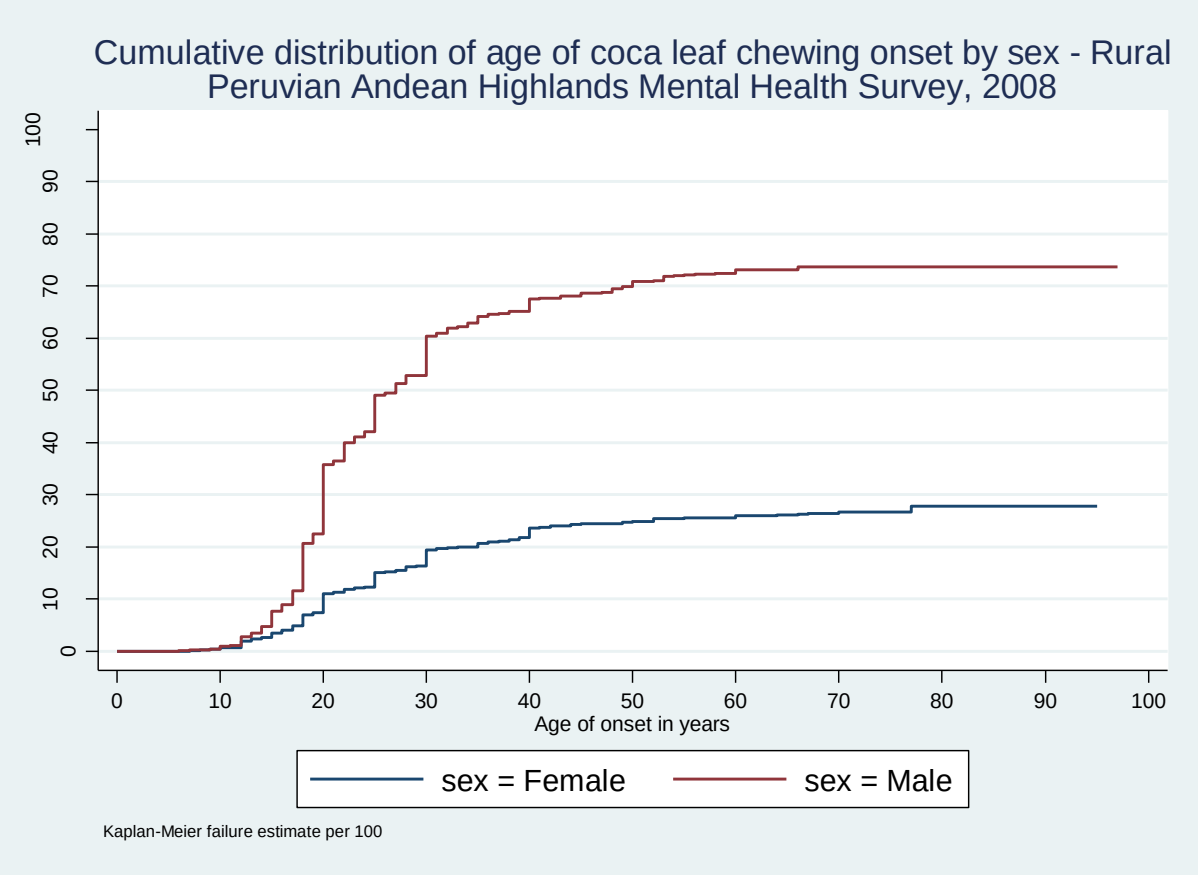
Evidence of male-female differences of coca leaf chewing use and 12-months dependence syndrome is provided in figure 4.4.5.1.1. These results came from survey contingency table analyses. It shows that cumulative incidence proportion, 12-months prevalence proportion, and 30-days prevalence proportion of coca leaf chewing are significantly higher in males than females based upon in its 95% confidence intervals. Moreover, among ever coca leaf chewers, the recency of coca leaf chewing within the last 30 days, between 30 days and 12 months, and over the 12 months was significantly higher among males than females. However, there was a not significant male-female difference in the "12-months dependence syndrome to coca leaf chewing" among the entire population and among ever chewers.

Figure 4.4.5.1.1 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use and 12-months dependence syndrome by sex – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Estimates of male-female differences of the age of onset of coca leaf chewing are provided in figure 4.4.5.1.2. The cumulative proportions show that both males and females start chewing coca leaf by ten years of age; however, the number of highlanders who starts chewing coca leaf for the first time between 12 and 30 years of age grows exponentially in males while in females grow moderately. After 30 years old, starting chews coca leaf for the first time is quite rare for both males and females. By 50 years old, approximately one-fourth of females and three-fourths of males have chewed coca leaf.

Figure 4.4.5.1.2 Cumulative distribution of age of coca leaf chewing onset by sex - Rural Peruvian Andean Highlands Mental Health Survey, 2008



4.4.5.2 Variations Across Age Groups

Evidence of the age group variations of coca leaf chewing use and 12-months dependence syndrome are provided in figure 4.4.5.2.1 and 4.4.5.2.2. These results came from survey contingency table analyses. Figure 4.4.5.2.1 shows that there is not an apparently variation of cumulative incidence proportion, prevalence proportion, recency, and 12-months dependence syndrome to coca leaf chewing across age groups. However, the comparison of extreme age groups (figure 4.4.5.2.2) shows that cumulative incidence proportion, 12-months prevalence proportion, and 30-days prevalence proportion of coca leaf chewing are significantly higher in

highlanders of the age group of '65 years old or over' than the '18-44 years old' group. As well as the recency of coca leaf chewing 'within the last 30 days' and 'over the 12 months' is significantly higher in the age group of '65 years old or over' than the '18-44 years old' group. Finally, the 12-months coca leaf chewing dependence syndrome was only significantly higher in the age group of '65 years old or over' than the '18-44 years old' group for the entire population, but this difference was not significant among ever coca leaf chewers.

Figure 4.4.5.2.1 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use, and 12-months dependence syndrome by age groups – Rural Peruvian Andean Highlands Mental Health Survey, 2008

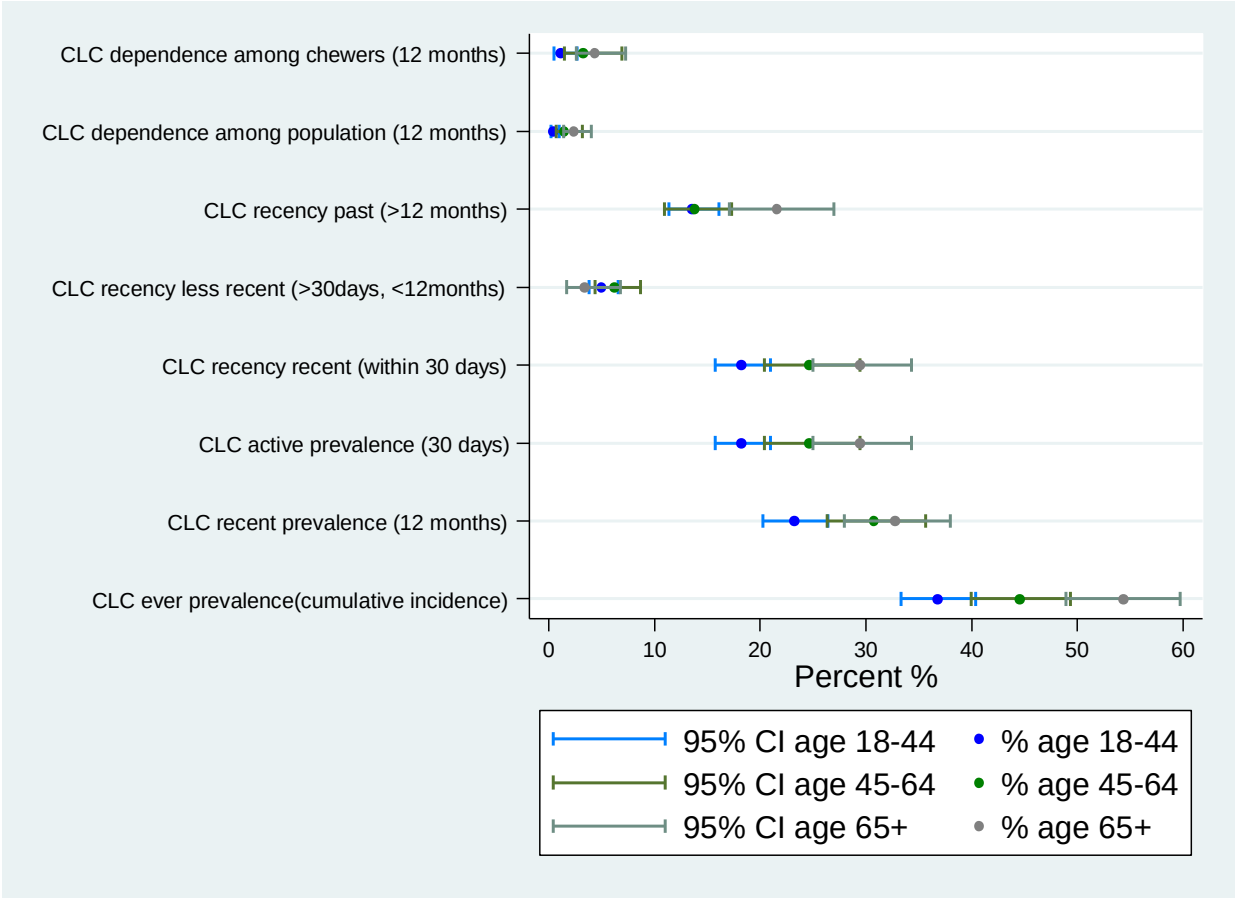
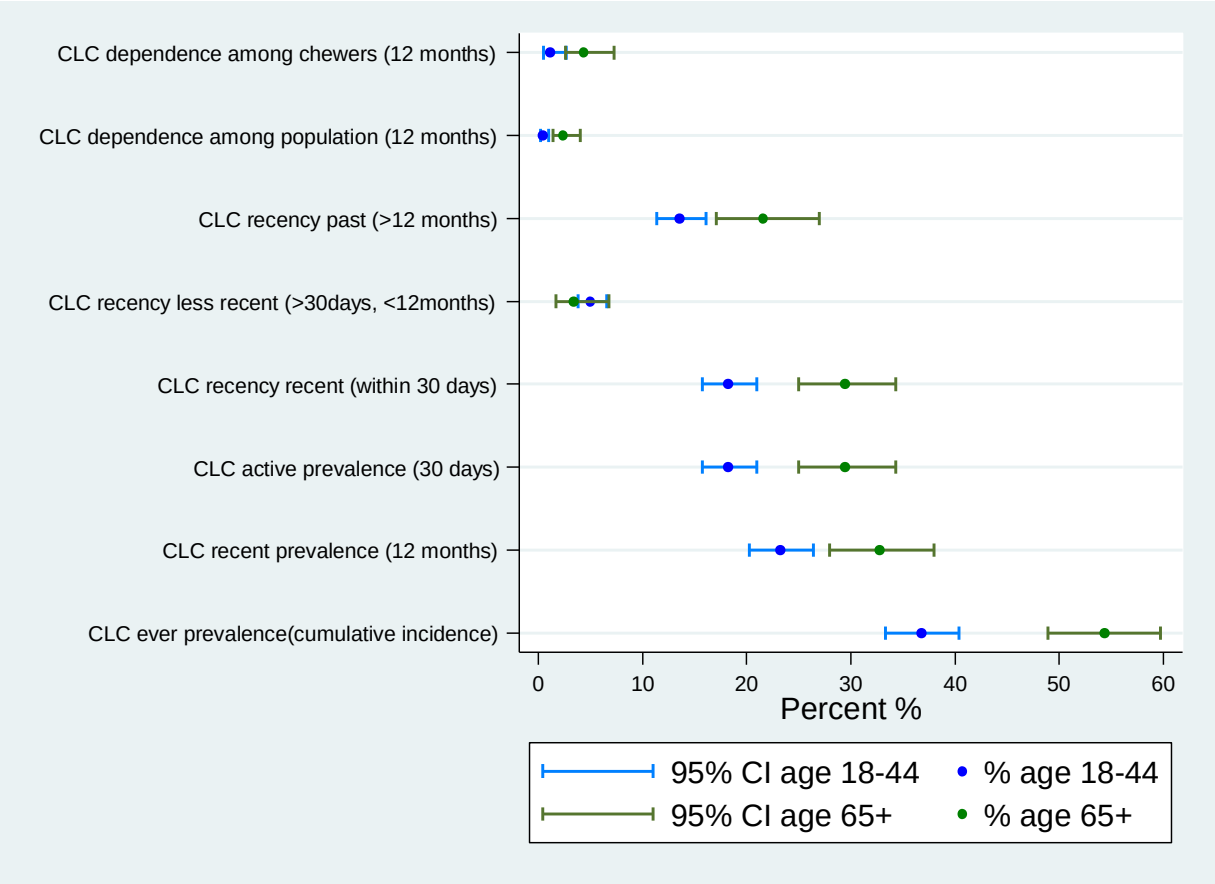
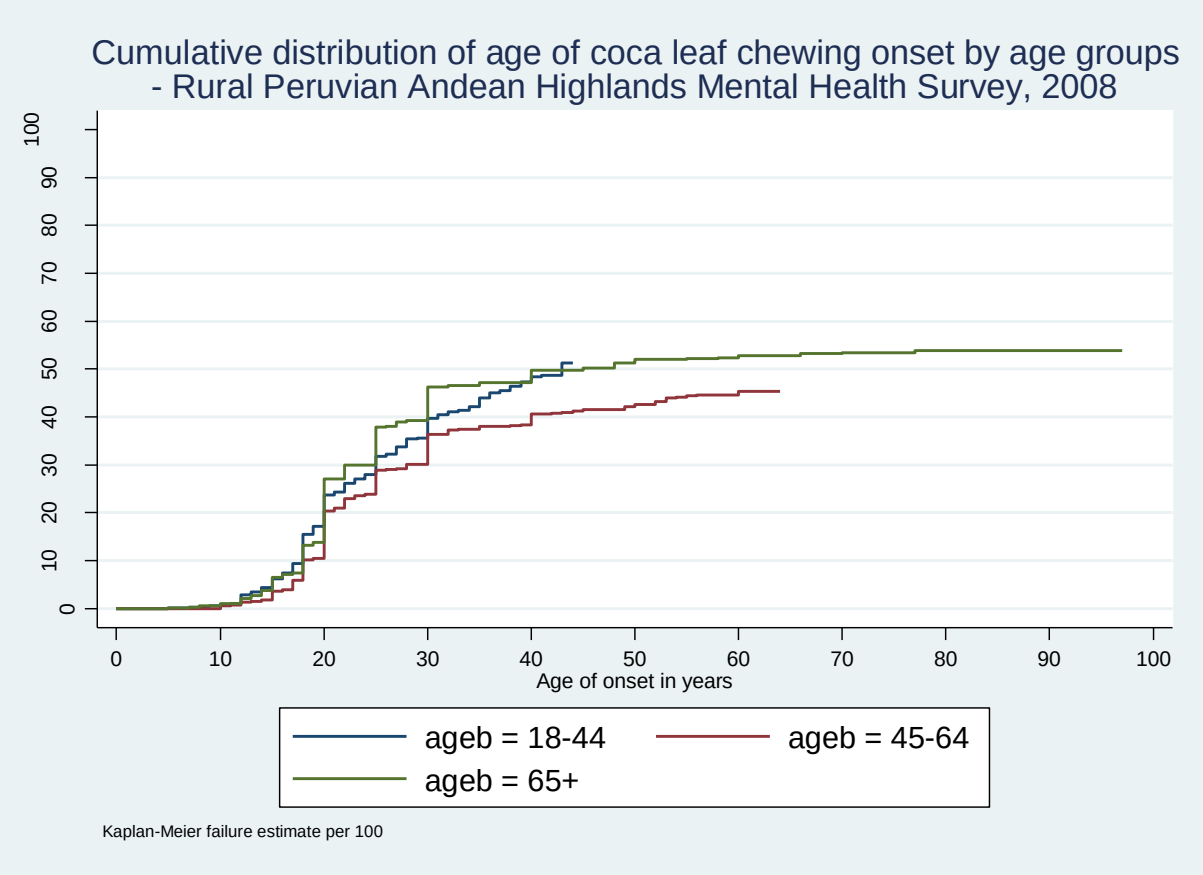


Figure 4.4.5.2.2 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use, and 12-months dependence syndrome by extreme age groups – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Estimates of the variations of age of onset of coca leaf chewing across age groups are provided in figure 4.4.5.2.3. The cumulative proportions show that the three age groups have the same possibility of starting coca leaf chewing for the first time between 10 and 25 years old. However, the possibility of starting coca leaf chewing for the first time after 25 years old is quite higher for the age group of '65 years old or over' than the age group of '45-64 years old,' but it is the same than the age group of '18-44 years old.

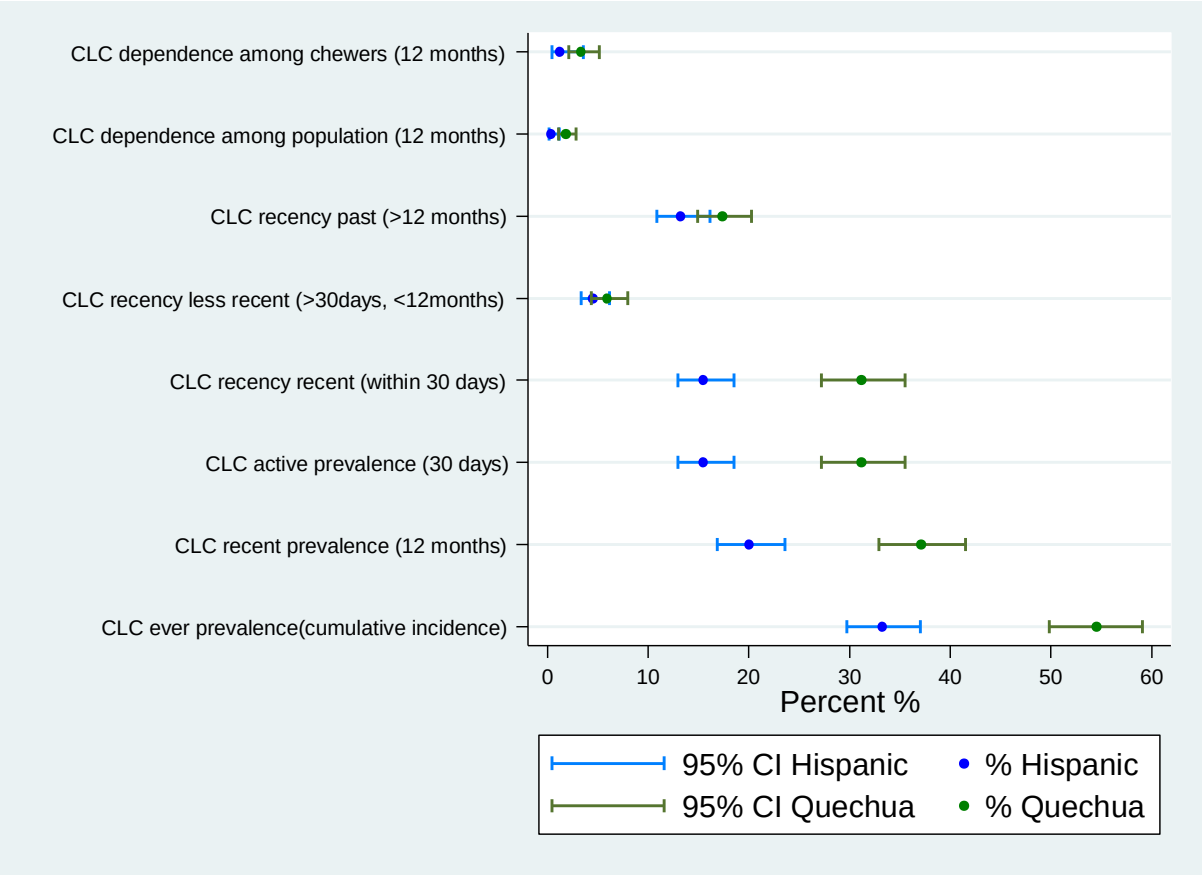
Figure 4.4.5.2.3 Cumulative distribution of age of coca leaf chewing onset by age groups - Rural Peruvian Andean Highlands Mental Health Survey, 2008



4.4.5.3 Variations across Ethnic Groups

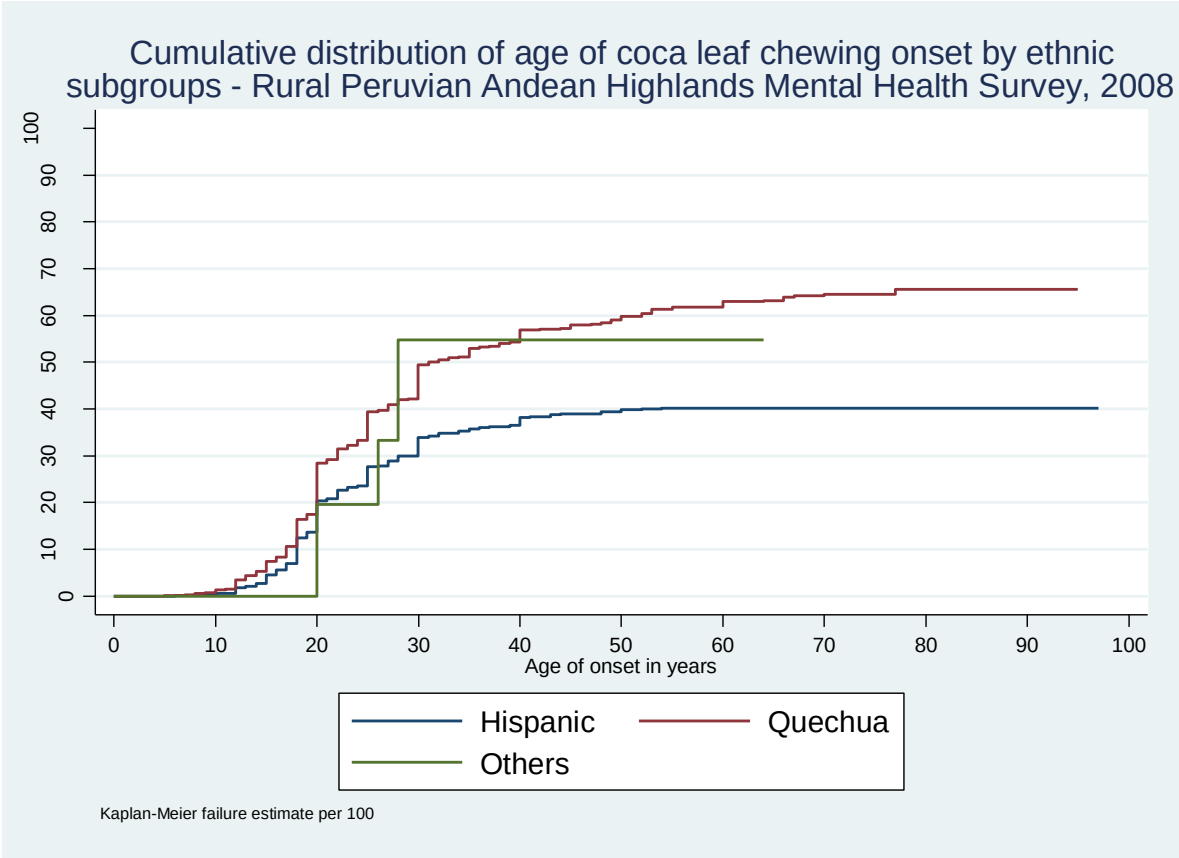
Evidence of the variations across ethnic groups of coca leaf chewing use and 12-months dependence is provided in figure 4.4.5.3.1. These results came from survey contingency table analyses; it shows that cumulative incidence proportion, 12-months prevalence proportion, 30-days prevalence proportion, and 30-days recency of coca leaf chewing are significantly higher in Quechuas than in Hispanics. However, there were not ethnic groups differences in 12-months dependence syndrome, '30 days - 12 months,' and 'over 12 months' recency of coca leaf chewing.

Figure 4.4.5.3.1 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use, and 12-months dependence syndrome by ethnic subgroups – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Estimates of the variations of age of coca leaf chewing onset across ethnic subgroups are provided in figure 4.4.5.3.2. The cumulative proportions show that the Quechuas and Hispanics have the same possibility of starting coca leaf chewing for the first time between 10 and 20 years old of age. However, the possibility of starting coca leaf chewing for the first time after 20 years old is higher in Quechuas than in Hispanics. Around 50 years old, approximately two-fifths of Hispanics and three-fifths of Quechuas have chewed coca leaf.

Figure 4.4.5.3.2 Cumulative distribution of age of coca leaf chewing onset by ethnic subgroups - Rural Peruvian Andean Highlands Mental Health Survey, 2008



4.4.5.4 Variations Across the Levels of Exposure to Traumatic Events Associated with Political Violence and Terrorism

Evidence of variations of the exposure to different types of political violence and terrorism across region of residence is provided in figure 4.4.5.4.1 and 4.4.5.4.2. These results came from survey contingency table analyses. It shows that the cumulative incidence proportions (lifetime prevalence) of exposure to the different types of traumatic events associated with political violence and terrorism was highest among the rural highlanders living in the region of Ayacucho. The rural highlanders living in the region of Cajamarca have the lowest cumulative

incidence proportion of exposure to traumatic events associated with political violence and terrorism, followed by the rural residents of Ancash. They had little more odds of experienced these traumatic events than the residents of Cajamarca.

Figure 4.4.5.4.1 Cumulative incidence exposure to the different types of traumatic events associated with political violence and terrorism by the department of residence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

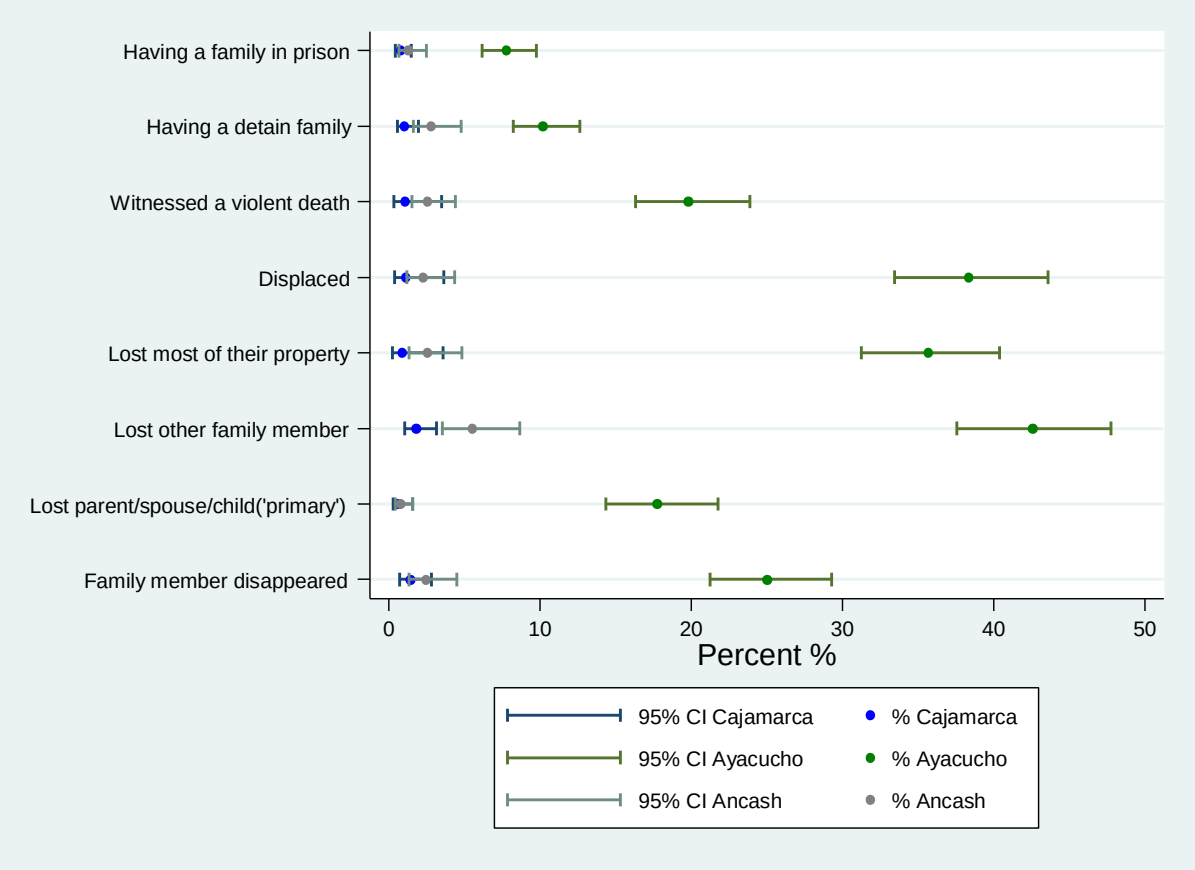
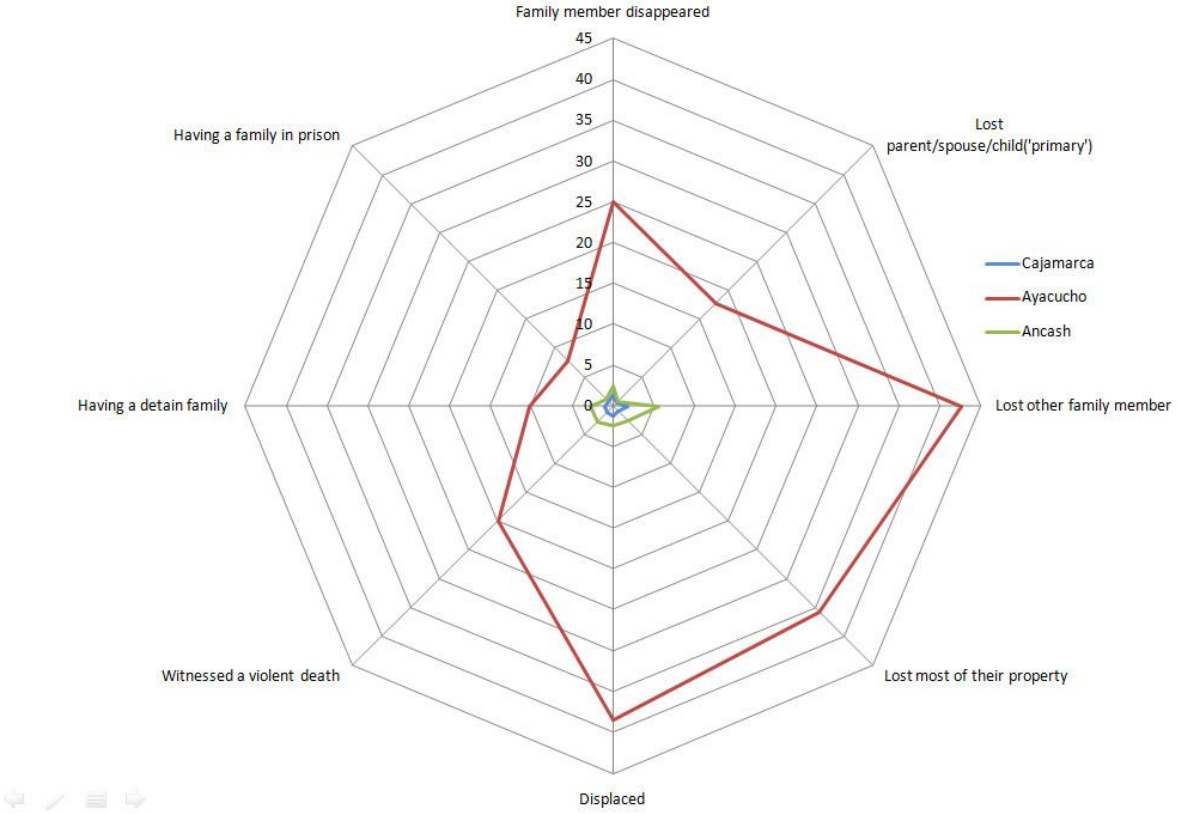


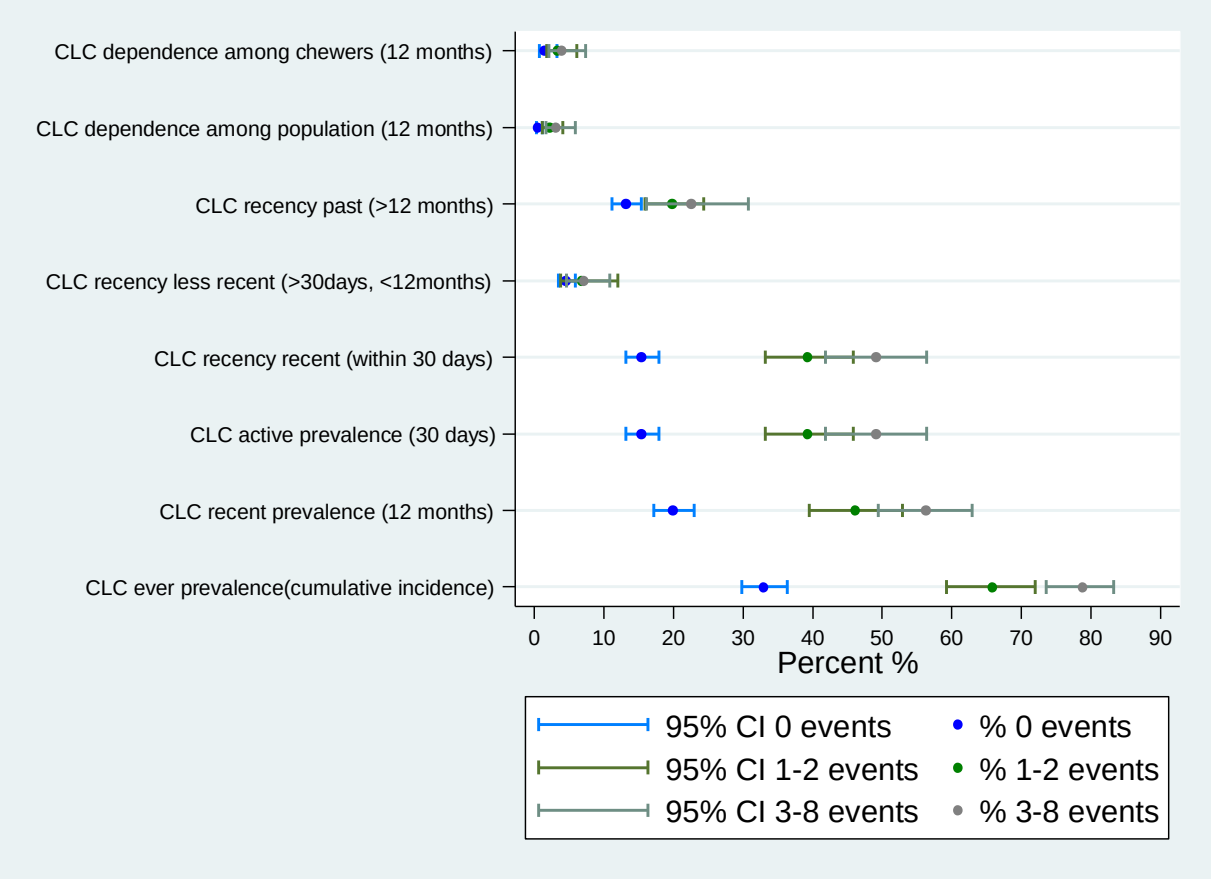
Figure 4.4.5.4.2 Cumulative incidence exposure to the different types of traumatic events associated with political violence and terrorism by the department of residence – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Evidence of the variations of coca leaf chewing use and 12-months dependence syndrome across levels of exposure to traumatic events associated with political violence and terrorism are provided in figure 4.4.5.4.3. These results came from survey contingency table analyses. It shows that cumulative incidence proportion, 12-months prevalence proportion, 30-days prevalence proportion and 30 days recency of coca leaf chewing are statistically significant higher for the rural highlanders with one to two or three to eight traumatic events associated with political violence and terrorism than the rural highlanders who never experience this kind of traumatic events. However, there were no significant differences for 12-months coca leaf

chewing dependence syndrome in relation to the levels of exposure to traumatic events associated with political violence and terrorism.

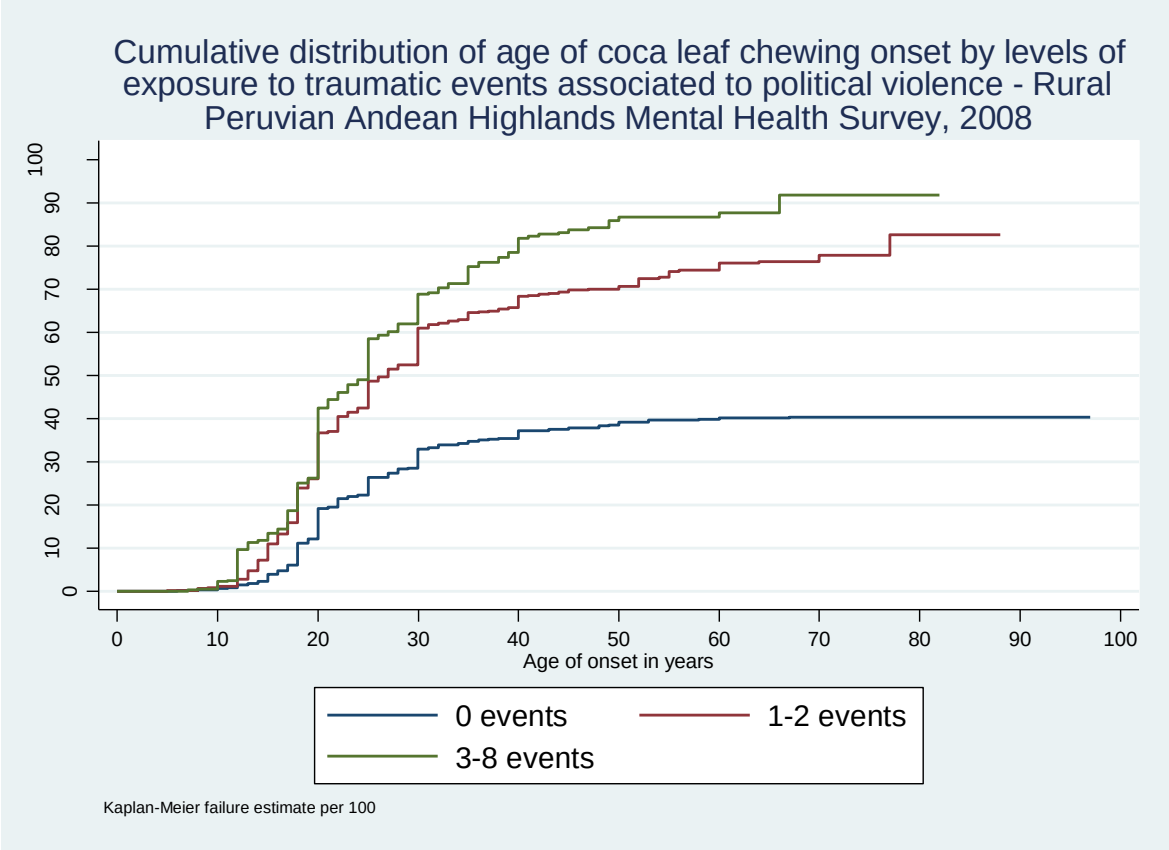
Figure 4.4.5.4.3 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use, and 12-months dependence syndrome by levels of exposure to traumatic events associated with political violence and terrorism – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Estimates of the variations of the age of coca leaf chewing onset across levels of exposure to traumatic events associated with political violence and terrorism are provided in figure 4.4.5.4.4. The cumulative proportions show that the rural highlander with history of exposure to one or more traumatic events associated with political violence and terrorism has

the same likelihood of starting coca leaf chewing for the first time at the age of ten years than the rural highlander without a history of exposure to these traumatic events. However, between ten and thirty years old, the likelihood of start coca leaf chewing for the first time among the rural highlanders with one or more traumatic events increases exponentially. In contrast, this increment among the highlanders without a history of traumatic events is moderate. Around 50 years old, approximately 90% of the rural highlanders with three to eight traumatic events and 70% of the rural highlanders with one to two traumatic events have chewed coca leaf; while among the highlanders without a history of traumatic events, only 40% of them have chewed coca leaf.

Figure 4.4.5.4.4 Cumulative distribution of age of coca leaf chewing onset by levels of exposure to traumatic events associated to political violence - Rural Peruvian Andean Highlands Mental Health Survey, 2008

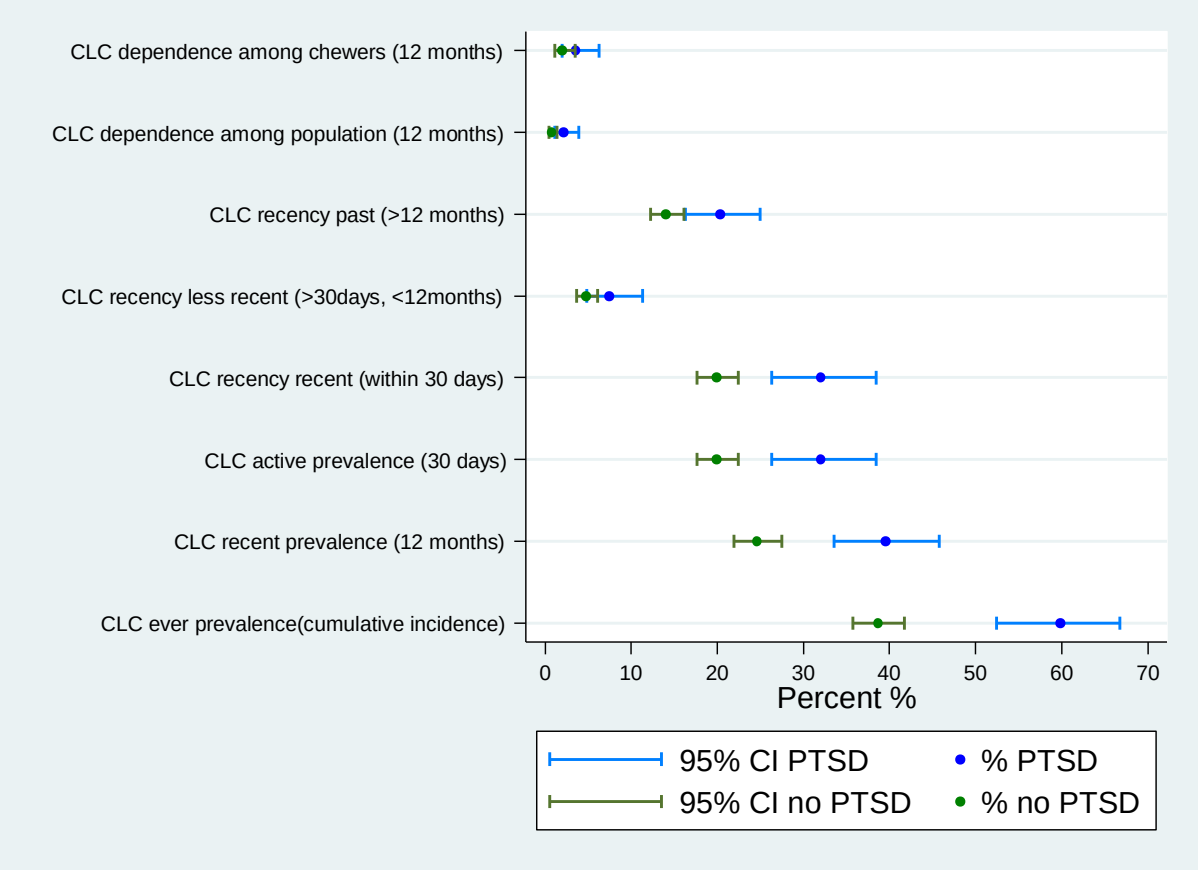


4.4.5.5 Variation Across History of Posttraumatic Stress Disorder (PTSD)

Evidence of the variations of coca leaf chewing use and 12-months dependence syndrome across the history of posttraumatic stress disorder is provided in figure 4.4.5.5.1. These results came from survey contingency table analyses. It shows that cumulative incidence proportion, 12-months prevalence proportion, 30-days prevalence proportion, and 30 days recency of coca leaf chewing are significantly higher among the rural highlanders with a history of posttraumatic stress disorder than the rural highlanders without posttraumatic stress disorder. However, there were no significant differences for the 12-months coca leaf chewing

dependence syndrome of the rural highlanders in function of their history of presence or absence of posttraumatic stress disorder.

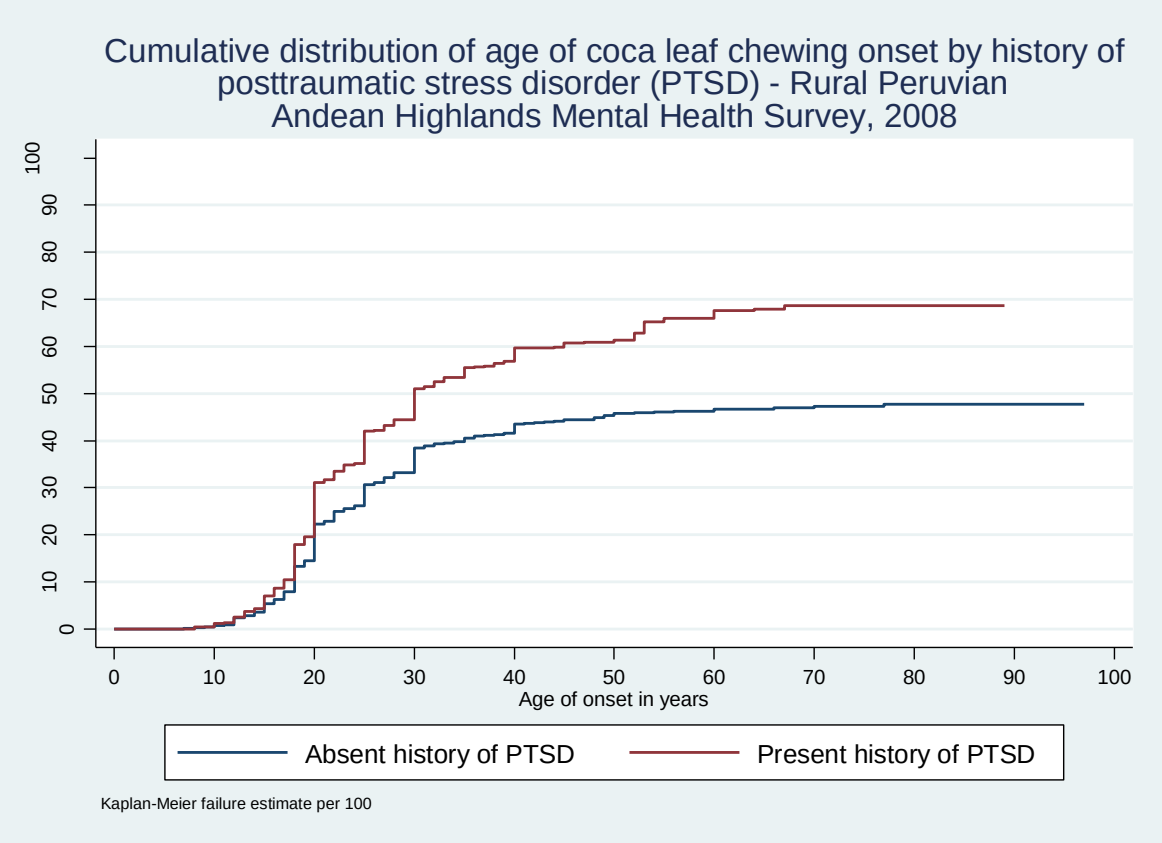
Figure 4.4.5.5.1 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use, and 12-months dependence syndrome by the history of posttraumatic stress disorder (PTSD) – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Estimates of the variation of age of coca leaf chewing onset across the history of posttraumatic stress disorder are provided in figure 4.4.5.5.2. The cumulative proportion shows that regardless of their history of posttraumatic stress disorder, the rural highlanders start chewing coca leaf at the age of ten years. Between ten and twenty years of age, the rural highlanders with and without a history of posttraumatic stress disorder have the same

likelihood of start chewing coca leaf for the first time. After 20 years old, the highlander with a history of posttraumatic stress disorder has a higher possibility of start coca leaf chewing for the first time than the highlander without a history of posttraumatic stress disorder. Around 50 years old, approximately 60% and 45% of the rural highlanders with and without a history of posttraumatic stress disorder have chewed coca leaf, respectively.

Figure 4.4.5.5.2 Cumulative distribution of age of coca leaf chewing onset by the history of posttraumatic stress disorder (PTSD) - Rural Peruvian Andean Highlands Mental Health Survey, 2008



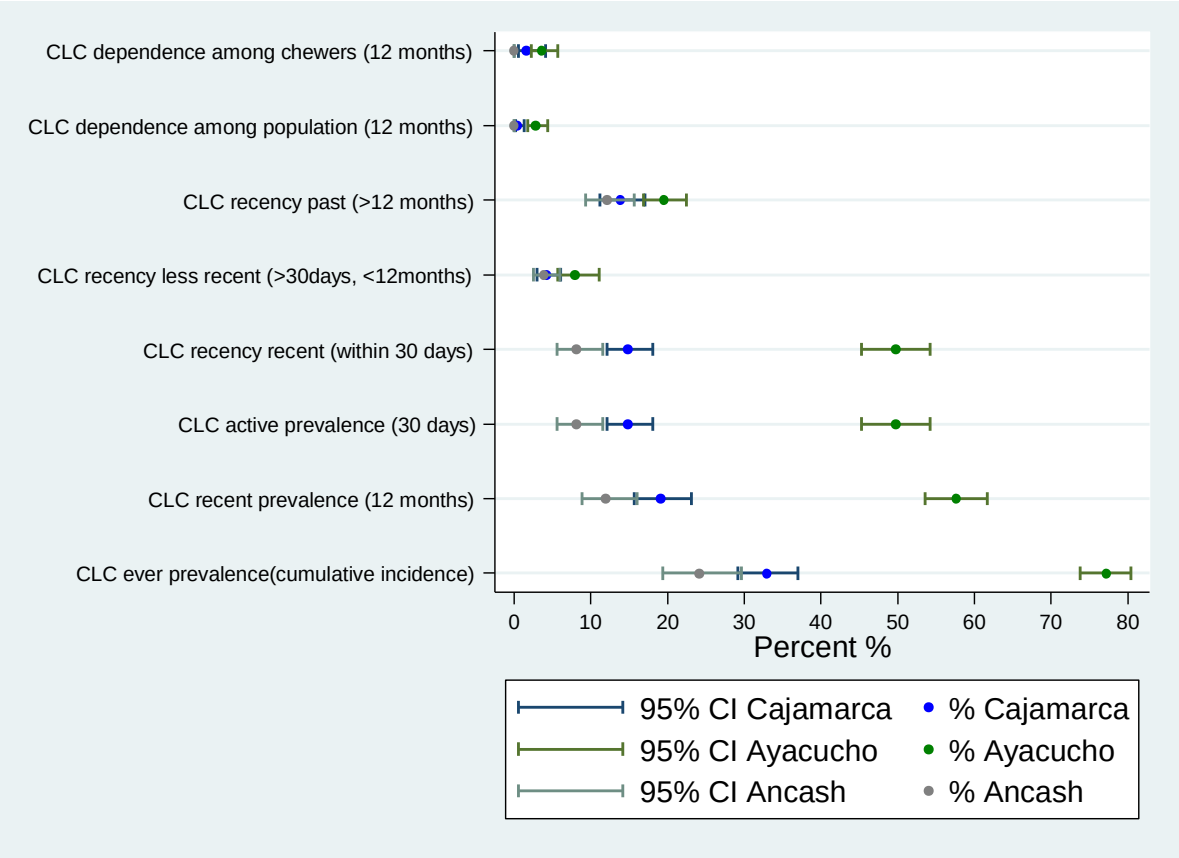
4.4.6 Variations of Coca Leaf Chewing Across Characteristics of Place

Under the variations of coca leaf chewing across characteristics of the place, in section 4.4.6.1, estimations of the variations of coca leaf chewing across region of residence of the Peruvian rural highlanders were done.

4.4.6.1 Variation Across Region of Residence

Evidence of the variations across the region of residence of coca leaf chewing use and 12-months dependence syndrome is provided in figure 4.4.6.1.1. These results came from survey contingency table analyses. It shows that cumulative incidence proportion, 12-months prevalence proportion, 30-days prevalence proportion, and recency within the 30-days of coca leaf chewing were significantly higher among the rural highlanders living in Ayacucho than highlanders living in Cajamarca or Ancash. However, there was a not statistically significant difference in 12-months coca leaf chewing dependence syndrome across the region of residence of the Peruvian rural highlanders.

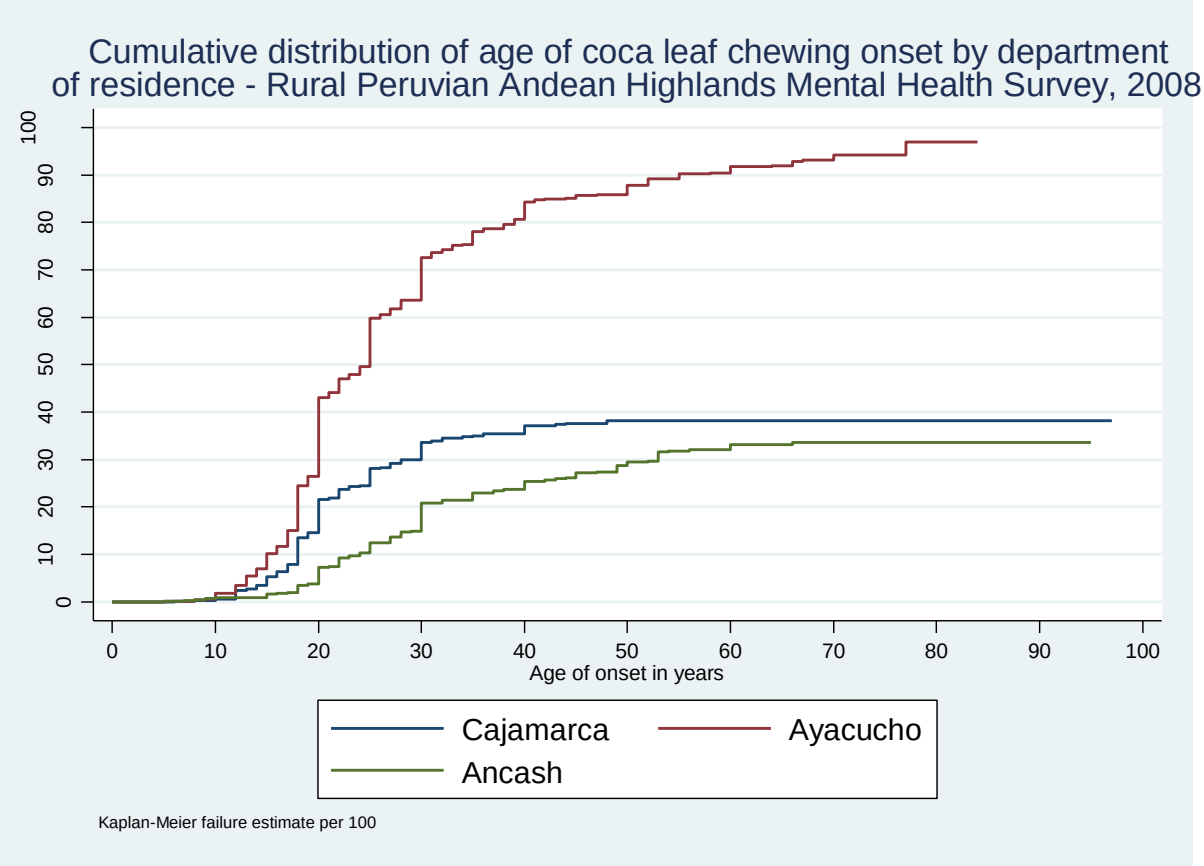
Figure 4.4.6.1.1 Cumulative incidence proportion, recency and prevalence proportions of coca leaf chewing use, and 12-months dependence syndrome by the region of residence – Rural Peruvian Andean Highlands Mental Health Survey, 2008



Estimates of the variations of the age of coca leaf chewing onset across the region of residence of Peruvian rural highlanders are provided in figure 4.4.6.1.2. The cumulative proportions show that regardless of their region of residence, the rural highlanders start chewing coca leaf for the first time at the age of ten years. However, after ten years of age, the highlanders living in Ayacucho has a higher likelihood of start chewing coca leaf for the first time than the highlanders living in Cajamarca or Ancash. By the age of 50 years, approximately 90% of the highlanders living in Ayacucho have chewed coca leaf while among the highlander

living in Cajamarca or Ancash 40% and 30% of them have chewed coca leaf respectively by the age of 50 years.

Figure 4.4.6.1.2 Cumulative distribution of age of coca leaf chewing onset by the region of residence - Rural Peruvian Highlands Mental Health Survey, 2008



4.5 Specific Aim # 3 Results: Epidemiological Rubrics of Causation

Under the specific aim number three, in section 4.5.1, an estimation of the degree to which coca leaf chewing might cause coca leaf chewing dependence syndrome or harmful use according to the International Classification of Diseases 10th edition (ICD-10) was done. Furthermore, in this section, the hypothesis of coca leaf chewing dependence syndrome equal to zero or coca leaf chewing harmful use equal to zero was tested. Finally, in section 4.5.2, an estimation o the degree to which coca leaf chewing or coca leaf chewing dependence syndrome might cause the quality of life impairment was done. Moreover, in this section, evaluation of the hypothesis that the quality of life coca leaf chewers with dependence syndrome is equal to the quality of chewers without dependence syndrome or equal to the quality of life of no chewers was done.

4.5.1 Evidence of coca leaf chewing dependence syndrome among ever chewers

Estimates of the 12-months prevalence of coca leaf chewing dependence syndrome and the 12-months prevalence coca leaf chewing harmful use according to the ICD-10 diagnostic criteria are presented in table 4.5.1.1. Analysis of survey proportion shows a 12-months prevalence of coca leaf chewing dependence syndrome of 0.9% among the general population, and 2.3% among ever coca leaf chewers. However, the 12-months prevalence of coca leaf chewing harmful use among the general population and among ever chewers were almost zero.

Table 4.5.1. 1 Prevalence proportion of coca leaf chewing dependence syndrome and harmful use – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Prevalence	U. No.	W. %	(95% CI)	SE
Coca leaf dependence among the population				
Present (within 12 months)	33	0.9	(0.6, 1.5)	0.2
Absent	2,983	99.1	(98.5, 99.4)	0.2
Coca leaf dependence among chewers (n=1,333)				
Present (within 12 months)	33	2.3	(1.4, 3.5)	0.5
Absent	1,292	97.7	(96.5, 98.6)	0.5
Coca leaf harmful use among the population				
Present (within 12 months)	2	0.0	(0.0, 0.2)	0.0
Absent	3,009	100.0	(99.9, 100.0)	0.0
Coca leaf harmful use among chewers (n=1,333)				
Present (within 12 months)	2	0.1	(0.0, 0.4)	0.1
Absent	1,318	99.9	(99.6, 100.0)	0.1

Abbreviation: CI = confidence interval, SE = standard error, U. No. = Unweighted number, W. % = Weighted percentage

Test hypotheses of the significance of the 12-months prevalence of coca leaf chewing dependence syndrome and the 12-months prevalence of coca leaf chewing harmful use are presented in table 4.5.1.2. Wald test analyses used as a proxy for *survey z proportion test* shows that 12-months prevalence of coca leaf chewing dependence syndrome among the general population and among ever chewers are significantly greater of zero (p-values < 0.0001).

However, the 12-months prevalence of coca leaf chewing harmful use among the general population and among ever chewers were not significantly different from zero (p-values > 0.05).

Table 4.5.1. 2 Testing null hypothesis of prevalence proportion of coca leaf chewing dependence and harmful use by Wald test – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Null hypothesis	Wald tests			
	F statistic	Numerator df*	Denominator df*	Prob > F
Prevalence of coca leaf dependence among the population = 0	19.11	1	207	<0.0001
Prevalence of coca leaf dependence among chewers = 0	19.67	1	202	<0.0001
Prevalence of coca leaf harmful use among the population = 0	2.02	1	207	0.1564
Prevalence of coca leaf harmful use among chewers = 0	2.03	1	202	0.1562

* df = degrees of freedom

4.5.2 Evidence of impairment of quality of life among coca leaf chewers and coca leaf chewing dependents

In this section, an exploratory and estimation analysis of the quality of life of the highlanders were performed. For instance, in the exploratory data analysis, figure 4.5.2.1 presents a scatter-plot of the ten items of the multicultural quality of life index Spanish version (MQLI-Sp). This figure shows an absence of linear distribution of the data of each item of multicultural quality of life index. Figure 4.5.2.2 depicts the scatter-plot of the ten items of the MQLI-Sp for never coca leaf chewers, ever coca leaf chewers, and for the 12-months coca leaf chewing dependents. Similar to figure 4.5.2.1, the figure 4.5.2.2 shows an absence of linear distribution of the scores of the ten items of the MQLI-Sp for never coca leaf chewers, ever coca leaf chewers, and 12-months coca leaf dependents. Figure 4.5.2.3 presents the score profiles of the ten items of the MQLI-Sp for each highlander. The scores of each item of the MQLI Sp go from zero to ten (y-axis). In general, there is no identifiable score profile pattern for the never chewers, ever chewers, or 12-months dependents.

Figure 4.5.2.1 Scatter-plot matrix for the ten items of the Multicultural Quality of Life Index – Rural Peruvian Andean Highlands Mental Health Survey, 2008

Figure 4.5.2.2 Scatter-plot matrix for the ten items of the Multicultural Quality of Life Index by never coca leaf chewing (CLC), ever coca leaf chewing, and 12-months coca leaf chewing dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

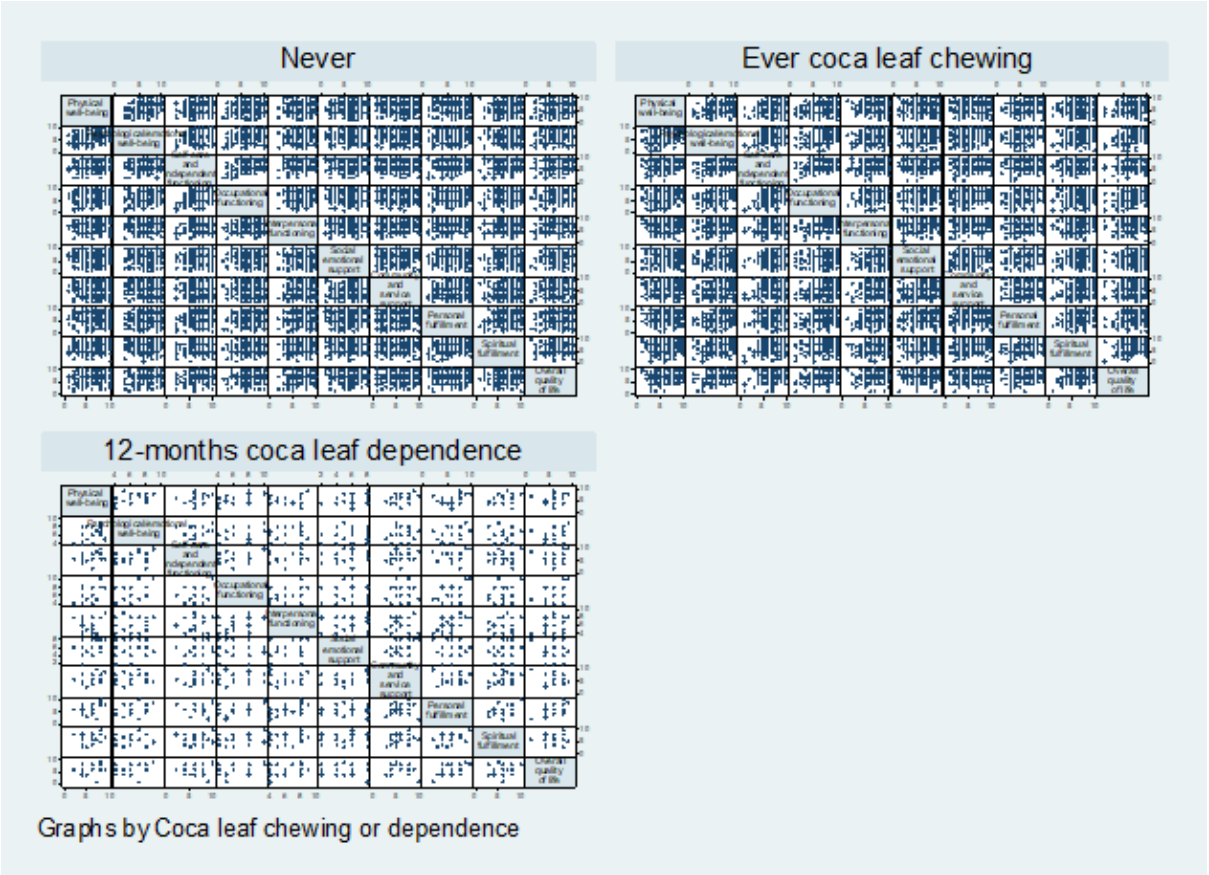


Figure 4.5.2.3 Individual Multicultural Quality of Life Index (MQLI) items scores profiles by never coca leaf chewing, ever coca leaf chewing, and coca leaf chewing dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

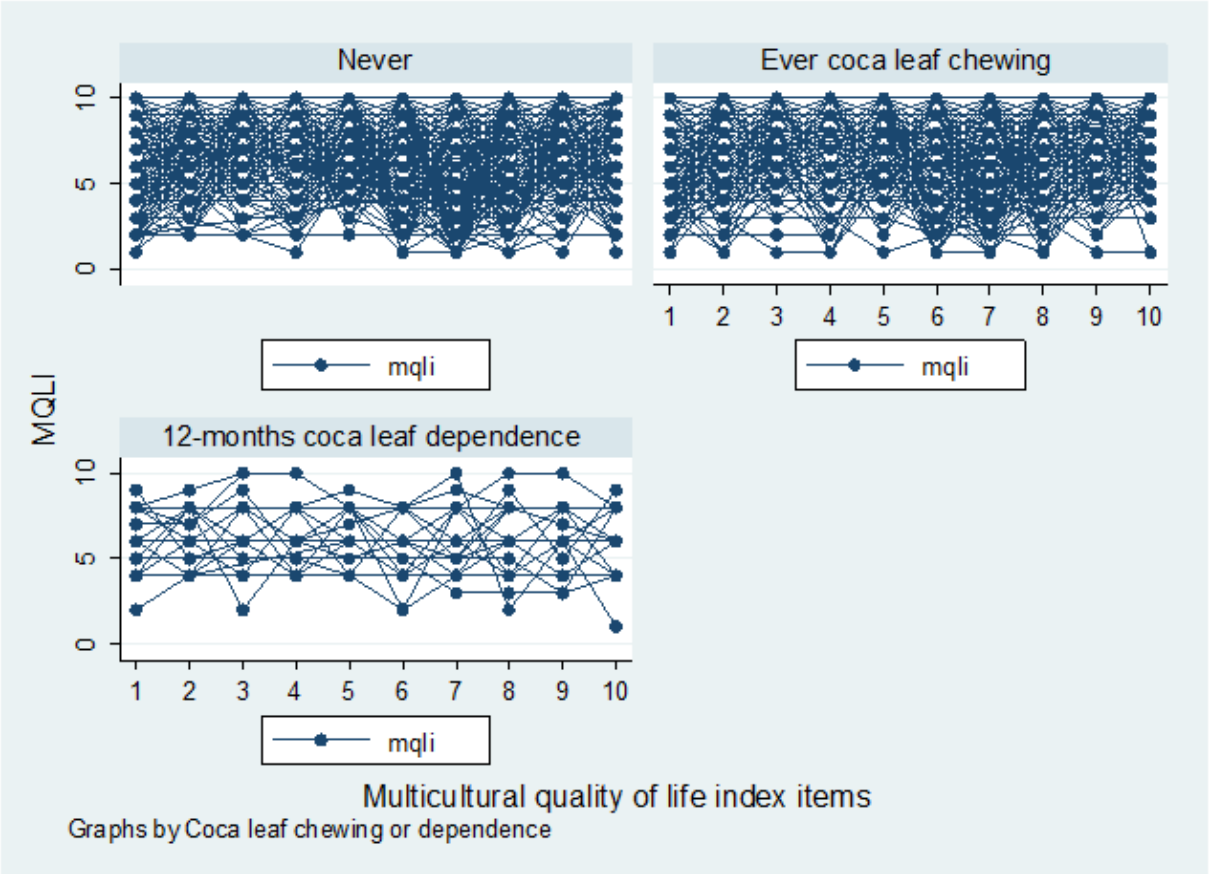


Figure 4.5.2.4 depicts a box plot graphic of each item of the MQLI-Sp for never chewers, ever chewers, and 12-months coca leaf dependents. In general, the mean of each item of the MQLI-Sp for 12-months coca leaf chewing dependents is lower than the mean of each item for never chewers and ever chewers. The means of each item are depicted in the box plot by a red vertical line. Finally, figure 4.5.2.5 presents graphically the mean and its 95% confidence interval of each item of the MQLI-Sp for never chewers, ever chewers, and 12-months coca leaf

dependents. In this picture, the distribution of the means of the MQLI-Sp follows a common pattern for never chewers, ever chewers, and 12-months dependents. Although, the means of MQLI-Sp items for 12-months coca leaf dependents are substantially lower than the means of never and ever chewers. For instance, never and ever chewers have the mean of 'physical well-being' and 'community and service support' below seven; additionally, ever chewers also have the mean of 'social and emotional support' below seven. Contrary, the chewers with coca leaf chewing dependence syndrome have almost all its MQLI-Sp items means below seven. For instance, the means of 'physical well-being,' 'psychological/emotional well-being,' 'social-emotional support,' 'community and service support,' 'personal fulfillment,' and 'overall quality of life' are below seven. Among chewers with coca leaf dependence syndrome, the MQLI-Sp item one 'physical wellbeing' and six 'social-emotional support' have the lowest mean. The mean values of the MQLI-Sp items one and six are below six for chewers with coca leaf dependence syndrome, while for never coca leaf chewers and ever coca leaf chewers without dependence syndrome are above six.

Figure 4.5.2.4 Box plots for the Multicultural Quality of Life Index (MQLI) items scores by never coca leaf chewing (CLC), ever coca leaf chewing, and 12-months coca leaf chewing dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

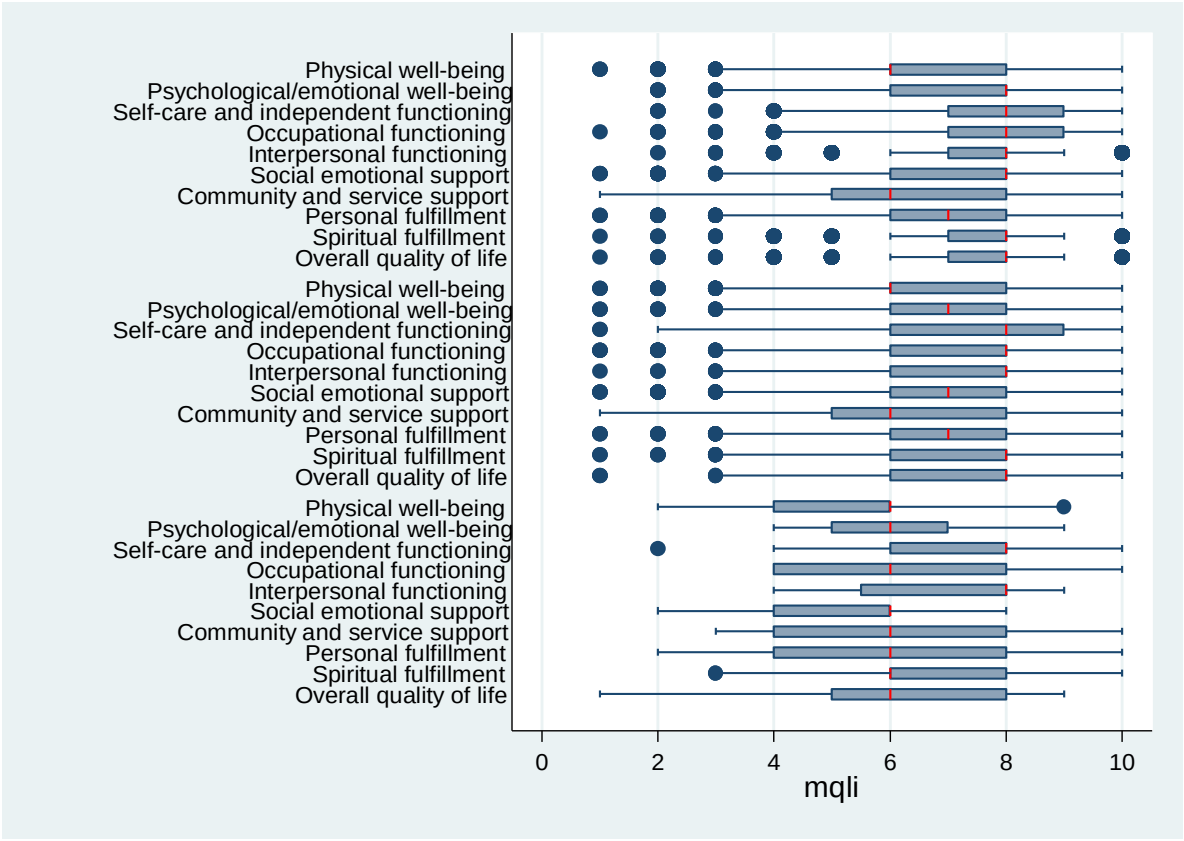
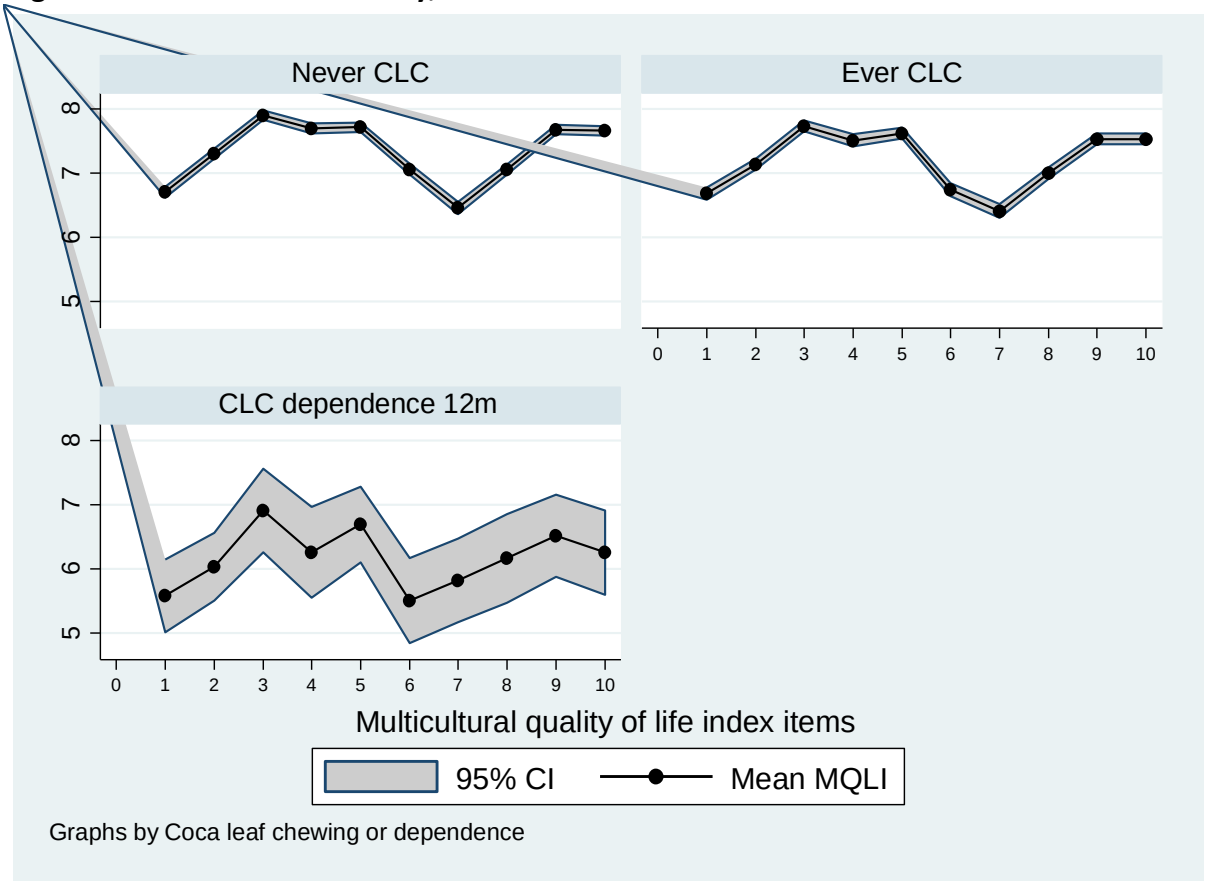


Figure 4.5.2.5 Means and 95% confidence interval (95% CI = mean ± standard error) of the Multicultural Quality of Life Index (MQLI) items scores by never coca leaf chewing (CLC), ever coca leaf chewing, and 12-months coca leaf chewing dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008



In the estimation part of the analysis of MQLI-Sp, the estimated weighted means of the MQLI-Sp average score for never coca leaf chewers, ever coca leaf chewers, and 12-months coca leaf chewing dependents are presented in table 4.5.2.1. This table shows that the mean of the average score of MQLI-Sp of the highlanders with 12-months coca leaf dependence syndrome (mean 6.4, 95% CI 5.9, 6.9) is significantly lower than the mean of the average scores of MQLI-Sp of either never (mean 7.3, 95% CI 7.2, 7.4) and ever coca leaf chewers without coca leaf dependence (mean 7.2, 95% CI 7.1, 7.3). Moreover, in table 4.5.2.2 the t-test confirms that the mean of the average score of MQLI-Sp of coca leaf dependents is significantly lower than the mean of the average score of MQLI-Sp of either never (p-value < 0.001) or ever coca leaf chewers without coca leaf dependence (p-value < 0.001).

Table 4.5.2. 1 Weighted mean estimates of the Multicultural Quality of Life Index average score by history of coca leaf chewing use or dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

`	Weighted MQLI mean	SE	(95% CI)
Never coca leaf chewing	7.3	<0.1	(7.2, 7.4)
Ever coca leaf chewing	7.2	<0.1	(7.1, 7.3)
12 months coca leaf dependence	6.4	0.2	(5.9, 6.9)

Abbreviation: MQLI = Multicultural Quality of Life Index. CI = confidence interval. SE = standard error.

Table 4.5.2. 2 Multiple comparison t-test for the weighted mean estimates of the Multicultural Quality of Life index average score of never coca leaf chewing (CLC), ever coca leaf chewing without coca leaf dependence, and 12-months coca leaf chewing dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

	Contrast	SE	t-test	p_value	(95% CI)
Ever CLC-Never CLC	-0.1	0.1	-1.4	0.156	(-0.2, 0.03)
12 months CLC dependence-Never CLC	-0.9	0.2	-4.0	<0.001	(-1.4, -0.5)
12 months CLC dependence-Ever CLC	-0.8	0.2	-3.6	<0.001	(-1.3, -0.4)

Finally, table 4.5.2.3 presents the results of the regression of the ten items of MQLI-Sp on coca leaf dependence syndrome via generalized linear model/general estimation equation (GLM/GEE). The table 4.5.2.3 shows that in average the mean of MQLI-Sp score of coca leaf dependents is 0.9 lower than the mean of MQLI-Sp of never coca leaf chewers (p-value < 0.001) and 0.8 lower than the mean of MQLI-Sp of ever coca leaf chewers without coca leaf dependence (p-value < 0.001). These differences in MQLI-Sp remain statistically significant after control for the confounding effects of mood/anxiety disorders, poverty and education.

Table 4.5.2. 3 Estimated change of the levels of Multicultural Quality of Life Index scores derived via generalized linear model/general estimation equation (GLM/GEE) by never coca leaf chewing (CLC), ever coca leaf chewing without coca leaf dependence, and 12-months coca leaf chewing dependence – Rural Peruvian Andean Highlands Mental Health Survey, 2008

	Bivariate GLM/GEE regression			Multivariate GLM/GEE regression*		
	U. Coef	(95% CI)	p_value	A. Coef	(95% CI)	p_value
Ever CLC vs Never CLC	-0.1	(-0.2, 0.0)	0.085	-0.1	(-0.2, 0.0)	0.059
12 months CLC dependence vs Never CLC	-0.9	(-1.4, -0.5)	<0.001	-0.8	(-1.2, -0.3)	<0.001
12 months CLC dependence vs Ever CLC	-0.8	(-1.3, -0.4)	<0.001	-0.7	(-1.1, -0.2)	0.002

***** Adjusted for psychiatric disorders (mood/anxiety disorders), poverty, and education. **Abbreviation**: U. Coef = Unadjusted Coefficient, A. Coef = Adjusted Coefficient.

CHAPTER 5 DISCUSSION

5.1 Introduction to chapter 5

The discussion chapter of the thesis research project will be organized into parts, each of which will convey (1) a summary of the main findings of the thesis research project, (2) a critique of the project in terms of limitations as might be improved in future research, and (3) reflection upon the findings in light of previously published research. The contents of this section also will be organized in relation to guidance suggested in Anthony's outline for research articles (http://www.epi.msu.edu/janthony/39%20Sentences.pdf, last accessed 1 July 2015).

5.2 Summary of the main findings

This thesis research, based on a large multistage random sample of the rural population of the Peruvian Andean regions of Ayacucho, Ancash, and Cajamarca, shows that two out of five Andean highlanders have ever chewed coca leaf. One out of four Andean highlanders has recently chewed coca-leaf in the last 12-months. One out of five highlanders has actively chewed coca leaf in the last month. One out of two ever coca leaf chewers has actively chewed coca leaf in the previous month. Furthermore, the likelihood of chewing coca leaf actively in the last month was higher among male, older adults, Quechuas, indigents, Ayacuchans, victims of political violence, and highlanders with a history of posttraumatic stress disorder or mood/anxiety disorders. After control for ethnicity, poverty, education, marital status, posttraumatic stress disorder, mood/anxiety disorders, and exposure to political violence, these

subgroup variations o chewing coca leaf actively in the last month remained only for male, older adults, and Ayacuchans.

Concerning the age of onset of coca leaf chewing, the Andean highlanders start for the first time chewing coca leaf at the age of 10. There is a fast transition from never to ever coca leaf chewing between 10 and 20 years old. Moreover, male, Quechua, Ayacuchans, or Andean highlanders with posttraumatic stress disorder or history of political violence had increased likelihood of start coca leaf chewing for the very first time at an early age.

Finally, two percent of the Andean coca leaf chewers present dependence syndrome according to the International Classification of Diseases Tenth Revision (ICD-10) (World Health Organization, 1993). The Andean coca leaf chewers with ICD-10 coca-leaf dependence syndrome had a mild but statistically significant detriment of the quality of life as compared to the Andean coca leaf chewers without ICD-10 coca leaf dependence syndrome. This detriment of the quality of life remains statistically significant even after control for the confounding effects of mood/anxiety disorders, poverty, and low level of education.

5.3 Limitations

Before a detailed discussion of the results, several of the more significant study limitations that may affect the present research will be presented with careful attention and description of their possible effects.

The cross-sectional design of the present research may not be free of selection bias, such as duration ratio bias (Szklo & Nieto, 2007) or length-biased sampling (Simon, 1980). It is because after the onset of coca leaf chewing, chewers with prolonged survival time have a

higher probability of being included in the study sample than chewers who die soon after the onset of coca leaf chewing. If there is any of this selection bias, its effect size is small because the blood concentration of cocaine after chewing is ten times lower than after intravenous administration of cocaine (Barnett et al., 1981; B. Holmstedt et al., 1979); thus, the potentially toxic effects of low blood concentration of cocaine triggered by coca leaf chewing is not plausible. The other source of selection bias in the present study may be the so-called coverage error (Lavrakas, 2008); it is because members of our target population were excluded from the study sample, which may affect the representativeness of our study population. The sample frame included rural dwelling units just from three Peruvian Andean regions and not from the entire 12 Peruvian Andean regions. Although the random sample size of 3276 highlanders was relatively large data, it did not have enough power to detect cases of ICD-10 dependence syndrome to coca leaf; It detects just 33 cases. Most of these 33 cases of ICD-10 dependence syndrome to coca leaf are among older adults (65+ years), who were also underrepresented in this study. This age group represents just 14 percent of the entire sample size. Fortunately, the effect of the nonresponse error in this study is low because the participation level was higher; we got a participation level of 92 percent.

Concerning the information bias, the present study might not be free of respondent bias or interviewer bias (Szklo & Nieto, 2007). It is because bilingual interviewer using Spanish survey questionaries evaluated the presence of ICD-10 dependence syndrome to coca leaf among illiterate and just Quechua speaker respondents. In the present study, approximately 21 percent of the participants were illiterate and just Quechua speakers. By the way, the conceptual model used in this study for the evaluation of coca leaf chewing dependence

syndrome based upon just in the ICD-10 dependence criteria might not be sufficient for an exhaustive evaluation of coca leaf chewing addiction liability. It is plausible that people chewing coca leaf might develop some clinical features of IDC-10 dependence syndrome. Notwithstanding, if these people do not develop a compulsive and uncontrolled consumption of coca leaf with clear evidence of toxicity to neurons and other cells, we cannot conclude that coca leaf is an addictive substance such as cocaine powder or base (Johanson, 1984).

In the data analysis step, one limitation might be the use of the Wald test for the confidence interval estimation because the standard intervals of the Wald large sample test for binomial distribution are inadequate when the sample proportion of success is near to zero or one. In the present study, the sample proportion of coca leaf chewing dependence syndrome (p) of two percent is close to zero; thus, the possibility to get a misleading result in the evaluation of the null hypothesis (p=0) with the Wald test is plausible (L. D. Brown, Cai, & DasGupta, 2001). The principal limitation of the present study resides in the evaluation of the aim three. The aim three evaluates the addiction plausibility of coca leaf chewing. The revision of the current scientific literature suggests that the prevalence of the suspected coca leaf chewing dependence syndrome is zero or close to zero. However, the sample size of 3,276 participants of this secondary data analysis study has sufficient precision to estimate prevalence as low as 30 percent. Thus, the sample design of the present study does not have enough power to estimate accurately the expected low prevalence of the suspected coca leaf chewing dependence syndrome.

By the way, the secondary data of the present study does not have variables of quantity, frequency, and duration of the habit of coca leaf chewing. These variables joined with the

variable age of onset of coca leaf chewing may allow the construction of a new variable representing the intensity of coca leaf chewing, which could be an essential predictor variable of coca leaf chewing dependence syndrome.

Finally, the study finding of two percent of coca leaf chewing dependence syndrome based upon in the presence of three or more ICD-10 clinical features per se is not sufficient evidence to conclude that coca leaf chewing causes dependence syndrome to cocaine. The second necessary condition for the evaluation of coca leaf chewing addiction liability is the demonstration that coca leaf chewing produces physical harm among chewers (Johanson, 1984). In the present study, the absence of a direct measure of the suspected physical harm produced by coca leaf chewing was another limitation in the secondary data analysis. Nonetheless, the mild impairment in the multicultural quality of life index (Mezzich et al., 2000) score observed among chewers with coca-leaf dependence syndrome might be an expression of the suspected physical harm produced by coca leaf chewing. Especially when our finding suggests that this detriment in the quality of life among coca leaf chewing dependents remains statistically significant even after control for the confounding effects of mood/anxiety disorders and poverty in the generalized linear model/generalized estimation equation regression model. However, there was not possible to control for the confounding effects exerted by physical or medical diseases on the relationship of coca leaf chewing dependence syndrome with quality of life impairment.

Notwithstanding limitations such as these, this is the first study to find ICD-10 dependence syndrome to coca-leaf chewing, although the clinical significance of this finding still

needs to be clarified. The results of this study may have significant implications for the evaluation of the addiction liability of coca-leaf chewing.

5.4 Relating the findings with previous researches

Under the specific aim number one, the rubric of the quantity of coca-leaf chewing, our result of 41% of lifetime prevalence or cumulative incidence proportion of coca-leaf chewing was similar to the findings of previous researches. For instance, in 1950, the United Nations Commission of Enquiry on the Coca Leaf estimated the lifetime prevalence of coca-leaf chewing of 50% among Peruvian Quechuas or Aymaras. Although, this estimation was not based on a survey study (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). The first attempt to measure the prevalence of coca-leaf chewing via a survey study was in 1965, notwithstanding, this research never ends. Caravedo-Carranza and Almeida-Vargas, using this incomplete data, reported a lifetime prevalence of coca-leaf chewing of 50% among the rural population of Peru, aged 14 years old or over (Caravedo-Carranza & Almeida-Vargas, 1972).

Other researchers found the lifetime prevalence of coca-leaf chewing even higher than our results of 41%. In 1965, the lifetime prevalence of coca-leaf chewing in Pusi was 72% (Alfred A. Buck et al., 1968). In 1998, the lifetime prevalence of coca-leaf chewing in Ingavi was 69% (Etty Indriati, 1998). Nevertheless, none of these two previous studies used a random sampling approach for the estimation of coca-leaf chewing prevalence. Thus, the high concentration of the aborigen population in these two regions may explain the high prevalence of coca leaf

chewing observed there. For instance, Pusi has a concentration of Quechua population of 94%; and Ingavi has an Aymara population of approximately 100 percent.

Among the pre-Columbian population, the lifetime prevalence of coca leaf chewing seems to be similar to our results. Thus, researchers found a lifetime prevalence of coca leaf chewing of 47 percent among mommies on the north part of Chile (Cartmell et al., 1991), 45 percent among mommies from the north of Chile and south of Peru (Cartmell et al., 1994), and 41% among mommies of the south coast of Peru (E. Indriati & Buikstra, 2001).

Previous researchers have not yet estimated the 12-months and 30-days prevalence of coca-leaf chewing. Nevertheless, the prevalence of everyday coca-leaf chewing may be a proxy of the 30-days coca-leaf chewing (active coca-leaf chewing). For example, among Aymaras of the south of Bolivia and north of Chile, the prevalence of everyday coca-leaf chewing was 20% (Etty Indriati, 1998). This value was pretty close to the 30-days prevalence of coca-leaf chewing of 21% that we got in the present study.

Under the specific aim number two of the rubric of location of coca-leaf chewing, the current scientific literature has not shown clear male-female differences of coca-leaf chewing yet. Some studies show a higher prevalence of ever coca-leaf chewing among men than women, and other studies show a slightly higher prevalence of ever coca-leaf chewing among women than men. For instance, the United Nations Commission of Enquiry on the Coca Leaf found a lifetime prevalence of coca-leaf chewing of 45% among men and 20% among women in 1950 (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Buck et al. found a lifetime prevalence of coca-leaf chewing of 45% among men and 10% among women in the village of Yacango, and 36% among men, and 22% among women in the

village of Cachicoto (Alfred A. Buck et al., 1968). Contrary, Buck et al. found a lifetime prevalence of coca-leaf chewing of 74% among women and 69% among males in the village of Pusi (Alfred A. Buck et al., 1968). As well as, Indriati found a lifetime prevalence of 70% among women and 67% among men, although this difference was not statistically significant (Etty Indriati, 1998). It is essential to mention that none of these studies used a random sample to estimate the prevalence of coca-leaf chewing. The results of the present survey study show that ever and last 30-days prevalence of coca-leaf chewing is three times greater among men than women; although the persistence of coca-leaf chewing, define as the proportion of ever coca leaf chewers who remain chewing coca leaf actively in the last 30 days, is similar in both sexes.

In the subgroup variation of coca-leaf chewing by age, similar to our results, the literature shows that the prevalence of ever coca-leaf chewing increases with age. For example, among the residents of the village of Cachicoto, the lifetime prevalence of coca-leaf chewing is zero percent in the age group of 0-9 years. It is four percent in the age group of 10-19 years, 20% in the age group of 20-29 years, 30% in the age group of 30-39 years, and 33% in the age group of 40 years or more (A. A. Buck et al., 1968). Moreover, the prevalence of coca-leaf chewing in Aymara communities of Bolivia and Chile is 37 percent among 15-25 years old, and 86 percent among 26-40 years and older than 40 years (Etty Indriati, 1998). In the present survey study, the highlanders almost do not start chewing coca-leaf for the first time before the age of 10 years, and most of them started chewing coca leaf between 15 and 20 years.

Moreover, the present study shows that the cumulative incidence proportion or lifetime prevalence of coca-leaf chewing among the age group of 18-44 years was 37 percent, among 45-64 years was 45 percent, and among over 64 years was 54 percent. The

corresponding active prevalence of coca-leaf chewing within the last 30 days was 18 percent for the age group of 18-44 years, 25 percent for the age group of 45-64 years, and 29 percent for the age group 65+ years. This age gradient of been active chewers remains even after control for other variables such as sex, ethnicity, poverty, education attainment, marital status, the region of residence, posttraumatic stress disorder, mood/anxiety disorders, and exposure to political violence.

Middle age and elder highlanders are significantly more active chewers than the highlanders aged 18-44 years. This difference is not explained by age-by-age differences in the age-specific cumulative incidence rates for the onset of coca-leaf chewing before the age of 45 years because these incidence rates are similar for these three age groups. Furthermore, this difference is not explained either by variations in the rates of been persistent active coca-leaf chewers because one-half persisted in active chewing once chewing started, no matter the age group where they belong. The most plausible explanation of the age-related variation in the prevalence of active coca leaf chewing is the different rates of migration among age groups. Thus, young adults migrate more than old adults from rural to urban regions looking for better educational or labor opportunities in big cities such as Lima.

Similar to the findings of the present study, previous research findings showed that most coca-leaf chewers are South American Indians. For instance, in 1950, researchers found that 90 percent of the Indians of Peru and Bolivia chew coca-leaf (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Another research carried out in 1968 found that the prevalence of coca-leaf chewing increases in Peruvian villages with a high concentration of Indians. For example, Pusi, with a population of Quechuas

of 94 percent, had a lifetime prevalence of coca-leaf chewing of 72 percent. Cachicoto, with a population of Quechuas of 24 percent, had a lifetime prevalence of coca-leaf chewing of 29 percent. Yacango, with a population of Aymaras of 13 percent and Quechuas of four percent, had a lifetime prevalence of coca-leaf chewing of 26 percent. Finally, San Antonio, with a population of Quechuas and Aymaras of 0.2 percent, had a lifetime prevalence of coca-leaf chewing of three percent (Alfred A. Buck et al., 1968). In the present study, we found that the lifetime prevalence of coca leaf chewing among Quechuas is 54 percent, while among mestizos is 33 percent.

Contrary to the findings of previous studies, we found that coca-leaf chewing is not associated with illiteracy. In the 1950s, researchers found between 75 to 90 percent of illiteracy in places with a high prevalence of coca leaf chewing (Carlos Gutierrez-Noriega & Von Hagen, 1951; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950; Zapata-Ortiz, 1952). Notwithstanding, we cannot rule out the confounding effects of ethnicity in this association because those places with a high prevalence of coca leaf chewing also have large concentrations of American Indian population who have the millenary custom of chewing coca leaf; furthermore, there is a high prevalence of illiteracy among the American Indian population of those regions.

Similar to our findings of the high lifetime prevalence of coca-leaf chewing among the inhabitants of the southern Andean region of Ayacucho, previous researchers found a high prevalence of coca-leaf chewing among the inhabitants of the southern highland regions of Peru (Zapata-Ortiz, 1952). Furthermore, other researchers found a direct positive correlation between high altitude and coca-leaf chewing (Alfred A. Buck et al., 1968; Monge, 1952). The

most plausible explanation of the high lifetime prevalence of coca-leaf chewing among the Andean population of Ayacucho found in the present study is the high availability of coca-leaf among this population. There is evidence that from immemorial time, Huanta was the leading center of coca leaf cultivation in Peru due to its favorable location in the high jungle of Ayacucho, which fosters the growing up of coca shrubs (Unanue, 1794). The hypothesis that the hazardous life in high altitude induces the chewing of coca-leaf is less plausible because the South American Indians used to live in large concentrations in this geographic area, and they often chew coca leaf as part of their cultural heritage.

Like a previous study, we found that most of the Andean highlanders start chewing coca-leaf for the first time between the ages of 10 to 30 years. For instance, Indriati found that 75 percent of the Aymara highlanders start chewing coca-leaf for the first time between the ages of 19 to 25 years (Etty Indriati, 1998). Notwithstanding, other researchers found cocaine in the hair of pre-Columbian mommies as early as 0-2 years old 54 percent and 3-14 years old 33 percent. The presence of cocaine in the hair of these children mommies might be explained more by maternal transmission via the placenta, breastfeeding, or ingestion of coca tea than direct ingestion of cocaine via coca leaf chewing (Cartmell et al., 1994; Cartmell et al., 1991).

No previous studies have evaluated the subgroup variation of coca-leaf chewing by a history of exposure to traumatic events. Therefore, this is the first study to find an association between the histories of exposure to traumatic events related to political violence and coca leaf chewing. Political violence caused the death of 69,280 persons in Peru; half of these deaths occurred in Ayacucho, and 75 percents of this deceased were farmers from the Andean highlands whose mother language were Quechua (Laplante & Holguin, 2006; Truth and

Reconciliation Commission of Peru, 2003). Thus, the current finding of three times more prevalence of active coca-leaf chewing during the last 30 days among the Andean highlanders with history of traumatic events as compare to those without (44 percent vs. 15 percent), might reflect the medical use of coca-leaf chewing as a mean of obtaining relief from the psychological and physical negative effects of the traumatic events. It is because neither the traumatic events nor the posttraumatic stress disorder related to political violence was associated with coca-leaf chewing dependence or addiction. These results contradict previous findings that posttraumatic stress disorder increases the odds of developing substance use dependence or addiction (Breslau et al., 2003; Chilcoat & Breslau, 1998a, 1998b).

Concerning the coca-leaf chewing addiction liability, most of the previous studies found that coca-leaf chewing did not trigger tolerance to its stimulant effects (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; Monge, 1952; Negrete, 1978a, 1978b; Negrete & Murphy, 1967; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950; Wolff, 1949, 1952; Zapata-Ortiz, 1952, 1970). Some researches showed that coca leaf chewing produces slight withdrawal symptoms among chewers whose consumption is greater than 100 grams per day (Zapata-Ortiz, 1952, 1970) or among inveterate chewers (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; Wolff, 1949, 1952). Notwithstanding, other studies did not find withdrawal symptoms among coca-leaf chewers (Monge, 1952; Negrete, 1978a, 1978b; Negrete & Murphy, 1967; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Some studies reported slight (Negrete, 1978a, 1978b; Negrete & Murphy, 1967; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950) or strong

(C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; Wolff, 1949, 1952) craving for chewing coca leaf; albeit, other researches did not show craving among coca leaf chewers (Joel M. Hanna, 1971; J M Hanna & Hornick, 1977; Monge, 1952). Most of the researchers agreed that the Andean highlanders chew coca leaf due to its mild stimulant effects (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; Joel M. Hanna, 1971; J M Hanna & Hornick, 1977; Monge, 1952; Negrete, 1978a, 1978b; Negrete & Murphy, 1967; Wolff, 1949, 1952). However, there is not an agreement in the possibility that coca leaf chewing might cause addiction. Most of the researchers think that coca leaf chewing might cause addiction among chronic and inveterate users of high quantities of coca leaf (Negrete, 1978a, 1978b; Negrete & Murphy, 1967; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950; Zapata-Ortiz, 1952, 1970). Three researchers think that coca leaf chewing causes addiction at the quantity that is used to chew in the communities (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; Wolff, 1949, 1952). While other three researchers think that coca leaf chewing is a habit that not cause addiction at the quantities that are used to chew in the communities; nonetheless, they recommend carrying out more researches to disentangle this controversy (Joel M. Hanna, 1971; J M Hanna & Hornick, 1977; Monge, 1952).

Previous studies showed that coca leaf chewing was associated with epilepsy (C. Gutierrez-Noriega & Von Hagen, 1950; Negrete, 1978a, 1978b; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Nowadays, the endemic neurocysticercosis caused by the larva of the Taenia solium explains better the presence of high rates of epilepsy among the Andean coca leaf chewers of those regions than chewing coca leaf

per se (Burneo & Cavazos, 2014). Coca leaf chewing was associated with liver diseases (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951; United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Nonetheless, the concomitant high consumption of alcoholic beverages among coca leaf chewers of those regions may be the real cause of these liver diseases (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). Previous researches showed that coca leaf chewing produces cretinism, grow retardation, and racial degeneration (C. Gutierrez-Noriega & Von Hagen, 1950; Carlos Gutierrez-Noriega & Von Hagen, 1951). Nevertheless, these conditions are better explained by the poor diet of the Andean highlanders characterized by the lack of iodine, proteins, vitamins, and other micronutrients; which triggers malnutrition in almost the entire population of South American Indians (United Nations Commission of Enquiry on the Coca Leaf - Economic and Social Council, 1950). In conclusion, the current evidence suggests that coca leaf chewing does not cause the neurotoxicity and cardiotoxicity observed in the users of cocaine powder or cocaine base.

5.5 Strengths

The strength of the present research lies in its methodology. To our knowledge, this is the first study aiming the estimation of the prevalence of coca-leaf chewing dependence according to the ICD-10 diagnostic criteria via a community mental health survey. While previous studies used the non-probabilistic convenience sampling design, the present study used the multistage random sampling design for the estimation of the magnitude of ICD-10 coca-leaf chewing dependence at the community level. The target population was the rural Andean highlanders

from the Peruvian regions of Ayacucho, Ancash, and Cajamarca. The study population of 3,031 highlanders was randomly selected from the target population. This sampling design decreases the likelihood of commit selection bias in the estimation of the prevalence of ICD-10 coca-leaf chewing dependence because each highlander has the same probability of being included in the study population. As all the previous studies were carried out before the development of the current criteria of substance dependence or addiction stated in the DSM-III-R in 1987 (American Psychiatric Association, 1987) and the ICD-10 in 1992 (World Health Organization, 1992b), this is the first study in using a standardized assessment of coca leaf chewing dependence based upon in the six ICD-10 diagnostic criteria of dependence syndrome. The standardized assessment of ICD-10 coca leaf chewing dependence via the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998) decreases the likelihood of committing information bias at the moment of classifying the participants in having or not having coca leaf chewing dependence. Thus, the decrease in the possibility of committing selection or information bias enhanced the internal validity of the estimation of the prevalence of coca leaf chewing dependence syndrome for our target population. Although the selection of the target population Ayacucho, Ancash, and Cajamarca was non-probabilistic, Ayacucho is a good representative of the southern Peruvian Andean regions; Ancash is a good representative of the central Peruvian Andean regions, and Cajamarca is a good representative of the northern Peruvian Andean regions. Thus, the target population is a representative sample of the external population constituted by the population of all the Peruvian Andean regions increasing in this way the external validity or generalizability of the estimates o coca leaf chewing dependence to the external population.

Finally, to our knowledge, this is the first survey study carried out in the 21st century among the underserved rural Andean population of Peru aiming to disentangle the coca leaf chewing addiction liability controversy.

5.6 Future directions

The present study found a prevalence of two percent of ICD-10 coca leaf chewing dependence syndrome among chewers. Thus, the next step in the study of coca leaf addiction liability may be the identification of patterns of the six ICD-10 clinical features of coca leaf chewing dependence at the population level. From a clinical point of view, it will also be essential to figure out the relative importance of each of the six ICD-10 clinical features of dependence syndrome in the diagnosis of coca leaf chewing dependence at the population level. This analysis of the patterns and importance of the ICD-10 clinical features of coca leaf chewing dependence may be performed via latent class analysis (Collins & Lanza, 2010) or generalized linear model/generalized estimating equation logit analysis (Diggle et al., 1994).

It is also indispensable to study the interaction effects of coca leaf chewing with alcohol ingestion in the generation of addiction to coca leaf because the liver carboxylesterase-1 generates cocaethylene from cocaine and alcohol via transesterification (Dean et al., 1991). Cocaethylene is as active as cocaine inhibiting the reuptake of dopamine at nucleus accumbens (Hearn, Flynn, et al., 1991; Jatlow et al., 1991), which is an essential part of the mechanisms by which cocaine elicit its self-administration (Ritz et al., 1987). Moreover, cocaine toxicity is potentiated with the simultaneous ingestion of alcohol because cocaethylene is even more toxic than cocaine (Hearn, Rose, et al., 1991; Rose, 1994).

The present study shows a mild but significant decrease in the mean score of quality of life of highlanders with coca leaf chewing dependence as compare to chewers without coca leaf dependence. From a clinical point of view, it will be crucial to know which one of the ten Multicultural Quality of Life Index (MQLI) (Mezzich et al., 2000) dimensions gets worse among chewers with coca leaf dependence as compared to those who do not have dependence. These ten dimensions of the MQLI are physical well-being, psychological/emotional well-being, self-care/independent functioning, occupational functioning, interpersonal functioning, social-emotional support, community and service support, personal fulfillment, spiritual fulfillment, and overall quality of life.

In conclusion, the current evidence does not support that coca leaf chewing causes neurotoxicity or cardiotoxicity, similar to those observed among users of cocaine powder or cocaine base. Future studies should evaluate the neuropsychiatric and cardiological effects of coca leaf chewing among inveterate users or chewers with coca leaf chewing dependence.

CHAPTER 6 CONCLUSIONS

The final chapter of this Master of Science thesis research report is organized in three sub-parts, one for each aim, plus a final concluding remark about directions for future research and potential significance of the research findings.

6.1 Conclusions With Respect to Aim #1: Overall Frequency and Occurrence of Coca Leaf Chewing

Under Aim #1, with all the strengths and limitations of cross-sectional data from epidemiological field survey samples, this thesis research project found that active coca leaf chewing is a current behavior for an estimated 21 percent of adult household residents living in rural areas near the three sampled communities of Peru's Andean highlands during 2008 (roughly one in five; 95% confidence interval, CI = 19%, 24%). In contrast with this estimate of the prevalence proportion in the last 30-days, the estimated cumulative incidence proportion or lifetime prevalence for coca leaf chewing now is 41% (95% CI = 38%, 44%). From the survey data, it can be estimated that roughly one-half of the coca leaf chewers living in these rural Andean highlands areas have persisted in chewing and remain active chewers once the coca leaf chewing behavior has started (95% CI = 48%, 56%). Even so, as shown below, there is considerable area-by-area subgroup variation in these estimates.

6.2 Conclusions With Respect to Aim #2: Subgroup Variation in Coca Leaf Chewing

Under Aim #2, subgroup variation in the occurrence of active coca leaf chewing within the last 30 days was investigated in relation to a small set of characteristics and conditions of a place, person, and time. In relation to place, Cajamarca had an intermediate prevalence proportion (15%, 95% CI = 12%, 18%), as compared to a lower prevalence estimate for Ancash (8%; 95% CI = 6%, 12%), and a greater prevalence estimate for Ayacucho (50%, 95% CI= 45% , 54%). The analyses under this aim showed that residence in the rural areas that surround the city of Ayacucho is robustly associated with being an active coca leaf chewer. In contrast, residence in rural areas around Ancash is robustly associated with lower odds of active coca leaf chewing, based on unconditional logistic regression models with and without statistical adjustment for covariate terms such as sex and age. To illustrate, in the comparison of the odds of active coca leaf chewing among residents of rural Ayacucho versus rural Cajamarca, the estimated covariate-adjusted odds ratio was 8.3 (OR = 8.3; 95% CI = 4.9, 14.3; $p < 0.001$). By comparison, the estimated OR prior to covariate adjustment was 5.7 (95% CI = 4.2, 7.6; $p < 0.001$). According to the evidence, the corresponding covariate-unadjusted odds ratio estimate for Ancash (relative to Cajamarca) was 0.5 (95% CI = 0.3, 0.8; $p = 0.004$); this OR estimate was not appreciably attenuated when the model was extended to include covariates (adjusted OR= 0.6; 95% CI=0.3, 1.1; $p = 0.113$). Upon further inspection of the estimates, these variations in active coca leaf chewing prevalence across areas can be traced back to the force of incidence and also to the separable force of persistence of the behavior, once coca leaf chewing starts. As described in Chapter 3, there was a gradient in the cumulative incidence proportion for the lifetime history of coca leaf chewing, with estimates substantially lower than the mean of 41%

in Ancash (24%; 95% CI = 19%, 30%) and substantially higher than the mean in Ayacucho (77%; 95% CI = 74%, 80%). In addition, concerning the persistence of use, an estimated 34% of the ever-chewers in Ancash remained active coca leaf chewers (95% CI = 24%, 43%), whereas the corresponding persistence estimate for Ayacucho was 64% (95% CI = 60%, 69%), and Cajamarca had an intermediate persistence estimate (45%; 95% CI = 38%, 52%).

With respect to characteristics of the person, I discovered robust male-female differences in the frequency of active coca leaf chewing during the last 30 days, as well as robust differences across age strata. To illustrate, in the unadjusted model, the odds of coca leaf chewing was substantially greater for male adult residents of the rural Andean highlands as compared to the female residents (OR = 3.8; 95% CI =3.0, 4.8; $p < 0.001$). The corresponding estimate from the covariate-adjusted model showed a somewhat stronger male-female variation, independent of the associations with other covariates (OR = 7.2; 95% CI =5.4, 9.5; $p < 0.001$). As described in Chapter 3, the 18-44-year-old rural highlands residents were robustly less likely to be active coca leaf chewers as compared to the middle-aged and elderly rural residents ($p < 0.05$). According to my life table analysis, this subgroup variation apparently is not due to age-by-age differences in the age-specific cumulative incidence rates for starting to chew coca leaf before age 45 years, which were roughly equivalent for all three age strata. Furthermore, among area residents, roughly one-half persisted in active chewing once chewing started, no matter which age stratum was examined. The observed age-related variation might be a limitation pertinent to differential survivorship rates as well as age-specific variation in residential mobility (e.g., differential movement from the rural areas into the cities).

It came as somewhat of a surprise that the covariate adjustments under the regression model did not disclose subgroup variations in active coca leaf chewing in relation to many characteristics of place, person, and time that were found to be associated in the estimates of bivariate associations. For example, being exposed to political violence and the occurrence of PTSD was associated with active coca leaf chewing in the estimates of bivariate associations ($p < 0.05$). Even so, these associations were not statistically independent of the other associations under study and became statistically fragile once the models were re-specified to include terms for covariates such as sex, age, and area of residence.

6.3 Conclusions With Respect to Aim #3: Dependence on the Coca Leaf

Aim #3 is especially novel because no one previously has produced an epidemiological estimate for a drug dependence syndrome attributed to coca leaf chewing, although there is a clinical description of the syndrome. As explained in previous chapters, when the ICD-10 diagnostic criteria for drug dependence clinical features have been formed into items about the experiences of active coca leaf chewers in this sample, there are statistically significant associations among the items, indicating greater than chance co-occurrence of these experiences as is required when epidemiological evidence favors the existence of a syndrome. As gauged by the ICD-10 research diagnostic criteria (3 or more criteria met), an estimated 0.9 percent of the rural adults in these Andean highlands areas qualify for a recently active coca leaf dependence syndrome (95% CI = 0.6%, 1.5%). Among the adults with a lifetime history of coca leaf chewing, an estimated 2.3 percent qualified as cases of the coca leaf dependence syndrome (95% CI = 1.4, 3.5). Only 33 cases were discovered in the study sample, large enough

for estimation of these proportions, but not large enough for statistically powerful or precise tests of hypotheses about multiple associations and subgroup variations in the occurrence of this dependence syndrome. Even so, it was possible to make a basic comparison between the following subgroups in relation to the Multicultural Quality of Life index, based on the Aim #3 hypothesis that the subgroup with active coca leaf dependence might have lower MQLI mean scores as compared to those with no lifetime history of coca leaf chewing, and that these cases also might have lower MQLI mean scores as compared to adults with a lifetime history of coca leaf chewing without dependence to coca leaf. In the overall multiple comparison t-test analysis without adjustment for covariates, and in exploratory multiple regression analyses, the coca leaf dependence cases had lower MQLI scores as compared to these contrasted subgroups ($p < 0.05$), even with exploratory statistical adjustment for the presence of other psychiatric disturbances, education, and poverty.

6.4 Concluding Remarks

This Master of Science thesis research report offers a wealth of new epidemiological findings on the practice of coca leaf chewing among adults living in rural areas surrounding three of Peru's Andean highland cities. Of most substantial clinical and public health significance is the finding of the coca leaf dependence syndrome; this apparently rather rare neuropsychiatric and behavioral syndrome in the general community population affects only about two percent of those with a history of coca leaf chewing. Nonetheless, the study estimates on coca leaf dependence and quality of life seem to indicate coca leaf-associated disruptions in the quality

of life are occurring, even when individual-level characteristics such as poverty level, educational level, and comorbid psychiatric disturbances are taken into account.

Prior clinical research on coca leaf chewing in the Andes generally has suggested no major physical health hazards, with the several exceptions noted in the preceding chapters of this thesis report. Here, we have some compelling new evidence of a coca leaf dependence syndrome, with concomitant disruption of quality of life, which deserves additional study -- perhaps with larger sample surveys in the Ayacucho area in order to help clarify the situation in that part of Peru, where coca leaf chewing has been found to have noteworthy prevalence.

The potential clinical and public health implications of this epidemiological study are limited. It would be premature to call for screening programs to detect coca leaf chewing or the coca leaf dependence syndrome for a variety of reasons. Even if the coca leaf dependence syndrome were not so rare, it is not clear that we have a large enough evidence base to claim that this syndrome, without intervention, is a major burden on the individual's health or public health. Nor do we have any evidence base on what might be an effective intervention program if and when the screening result indicates the presence of a case. It is clear that a more substantial evidence base will be needed before strong statements about clinical or public health implications can be made.

APPENDICES

APPENDIX A:

Rubric of Mechanisms

In this section, a description of the pharmacokinetics and pharmacodynamics of coca-leaf chewing will be provided. In pharmacokinetics a description of the absorption of cocaine after chewing coca leaves will be shown, as well as its bioavailability, distribution, metabolism (biotransformation), and excretion from the body. In pharmacodynamics, a description of the biochemical and physiological effects of coca-leaf chewing, and their biological mechanisms is going to be depicted.

7.1 Pharmacokinetics of Coca Leaf Chewing

In general, the pharmacokinetics of coca-leaf chewing is similar to the pharmacokinetics of oral cocaine use. Although this affirmation should be taken with caution because just one study has directly investigated the pharmacokinetics of coca-leaf chewing in humans (B. Holmstedt, Lindgren, Rivier, & Plowman, 1979). The other studies have investigated the pharmacokinetics of cocaine powder (the salt cocaine hydrochloride) administered orally (Jufer, Walsh, & Cone, 1998; Jufer, Wstadik, Walsh, Levine, & Cone, 2000; Van Dyke, Jatlow, Ungerer, Barash, & Byck, 1978; Walsh, Stoops, Moody, Lin, & Bigelow, 2009; Wilkinson, Van Dyke, Jatlow, Barash, & Byck, 1980).

7.1.1 Absorption

Cocaine is rapidly absorbed after chew coca leaves via buccal and oral administration. Oral administration because after extensive chewing on average, 86 percent of coca leaves is swallowed, and the rest throw away (Zapata-Ortiz, 1952, 1970). Moreover, buccal administration because the coca leaf quid is kept between the gums and cheek and periodically rechewed (Joel M. Hanna, 1974). The absorption through the oral mucosa is faster because it has thin epithelium and rich vascularity; however, the contact is relative brief for significant absorption (Merck Sharp & Dohme Corp., 2013).

Measurable quantities of cocaine on plasma were detected as soon as 5 minutes after started chewing 4.4 or 6.4 gm of sun-dried coca leaves (Erythroxylum coca Lamarck) with "llipta" (quinoa ashes). The person who chewed 4.4 gm of coca leaves ingested cocaine at doses of 0.34 mg/kg of body weight. Furthermore, the person who chewed 6.4 gm of coca leaves ingested cocaine at doses of 0.41 mg/kg of weight. The ***half-life of absorption*** or the time needed to absorb 50 percent of the cocaine via chewing coca leaves was 36 and 25 minutes for doses of 0.34 and 0.41 mg/kg, respectively (B. Holmstedt et al., 1979). As Holsmstedt did not use intravenous administration of cocaine for comparison, other researchers corrected these values of the half-life of absorption to 73 and 112 minutes for the doses of 0.34 and 0.41 mg/kg, respectively (Barnett, Hawks, & Resnick, 1981). The average absorption half-life time is 92 minutes.

The ***peak plasma concentration*** of cocaine after chewed coca leaves was 149, and 78 ng/ml reached at one and two hours, respectively. The higher peak plasma concentration corresponded to a dose of 0.34 mg/kg, and the lower peak plasma concentration corresponded

to a dose of 0.41 mg/kg (B. Holmstedt et al., 1979). The average peak plasma concentration of cocaine after chewed 5.4 g of coca leaves was 114 ng/ml, and it was reached in 90 minutes.

In contrast, after the administration of cocaine hydrochloride in a gelatin capsule at doses of two mg/kg, cocaine was detected on plasma no before 30 minutes after the ingestion of it. This delayed absorption of cocaine administered orally is not explained by the time needed to dissolve the gelatin capsule, because this capsule dissolves easily in two or three minutes in contact with the acid medium of the stomach. A most reliable explanation of this delayed absorption is the absence of assimilation of cocaine hydrochloride through the oral mucosa because the gelatin capsule prevents the release of it. Moreover, there is no absorption of cocaine hydrochloride in the stomach because cocaine, a weak base, in contact with hydrochloric acid gets transform in its ionized form (hydrophilic), which cannot pass through the non-polar part of the cell membrane. This transformation of cocaine to its ionized form or conjugate acid is explained by the cocaine's dissociation constant (pKa) of 8.6, which is higher than the acidity (pH) of the stomach solution of 1.5 to 3.5. It is important to mention if the acidity of a solution (pH) is lower than the pKa (acid dissociation constant) of a base, then the base will exist in its ionized form or conjugate acid. Reversely, if the pH of a solution is higher than the pKa of a base, then the substance will exist as freebase (un-ionized form). "The pKa is the pH at which concentrations of ionized and un-ionized forms are equal" (Merck Sharp & Dohme Corp., 2013).

In consequence, cocaine as a week base with pKa of 8.6 exists in its ionized form or conjugated acid in the stomach and its un-ionized form or freebase in the small intestine. The pH in the duodenum is four to five, and it increases more and more until it reaches eight in the

ileum (Merck Sharp & Dohme Corp., 2013). Thus, cocaine as conjugated acid (hydrophilic) is hardly absorbed in the stomach and cocaine as the free base (lipophilic) is extensively absorbed in the small intestine (Schwartz-Bloom & Halpin, 2003; Wilkinson et al., 1980). Furthermore, independently of its ionized or un-ionized form, most of absorption happens in the small intestine because its absorption surface area is vast, and its cell membranes are more permeable (Merck Sharp & Dohme Corp., 2013).

After given capsules of cocaine hydrochloride at doses five-fold higher than the dose studied by Holmstedt (B. Holmstedt et al., 1979) among coca leaf chewers, Van Dyke got maximum concentrations of plasmatic cocaine only two-fold higher than the maximum concentration obtained via chewing 4.4 to 6.4 g of coca leaves (Van Dyke et al., 1978). This fact is clear evidence that coca leaf chewing has buccal absorption of cocaine, which does not experience the first-pass metabolism in the liver. Albeit, the buccal absorption of cocaine from coca leaves through the oral mucosa is not considerable, due to either the low concentrations of cocaine on the coca leaves (0.63 to 0.73 percent of cocaine), and the limited capacity of the oral cavity to hold huge quantities of coca leaves. For this reason, Barnett consider that the average consumption of 30 g of coca leaves by chewers in the Andean mountains barely would reach the plasmatic concentrations of cocaine of 1000 ng/ml observed after the administration of intravenous cocaine hydrochloride (Barnett et al., 1981; Rerat et al., 1997). The peak plasma concentration of cocaine after administered it via intravenous or smoking appears to be between 500 and 1000 ng/ml (Jatlow, 1988; Paly, Jatlow, Van Dyke, Jeri, & Byck, 1982).

7.1. 2 Bioavailability

The only study measuring cocaine in the blood of coca-leaf chewers did not estimate bioavailability parameters because it was not a pharmacokinetic research per se (B. Holmstedt et al., 1979). However, the fraction of dose absorbed, after oral administration of cocaine hydrochloride at doses of 2 mg/kg, might be used as a proxy for a fraction of dose absorbed after chewing coca leaves. For instance, Barnett found a bioavailability of 30 percent of oral cocaine; it means that 30 percent of the oral doses of 2 mg/kg of cocaine hydrochloride administered via capsules were absorbed into the systemic circulation (Barnett et al., 1981). This low rate of absorption of oral cocaine might be explained by the effect of the first-pass metabolism in the intestinal wall and liver (Merck Sharp & Dohme Corp., 2013; Pond & Tozer, 1984). Although, other researchers found a bioavailability of 60 percent after the oral administration of capsules of cocaine hydrochloride at doses of 2 mg/kg (Wilkinson et al., 1980), and a bioavailability of 80 percent after nasal insufflation of cocaine hydrochloride (snorting) (Jeffcoat, Perez-Reyes, Hill, Sadler, & Cook, 1989).

7.1.3 Distribution

Currently, there are no studies about the distribution of cocaine to the body's tissues after chewed coca leaves. Thus, pharmacokinetic results from studies of intravenous administration of cocaine hydrochloride were used as a proxy for the estimation of the volume distribution of cocaine. The volume distribution is the theoretical volume at which cocaine has to be diluted to get the usual plasma concentration of cocaine (Merck Sharp & Dohme Corp., 2013). For instance, Barnett et al. found a range of volume distribution of intravenous cocaine

hydrochloride from 84 to 179 liters. This volume distribution is larger than the total body's water of approximately 40 liters. In consequence, the larger volume of distribution, higher than the total body's water, indicates that there is a significant binding of cocaine to the extravascular tissues (Barnett et al., 1981).

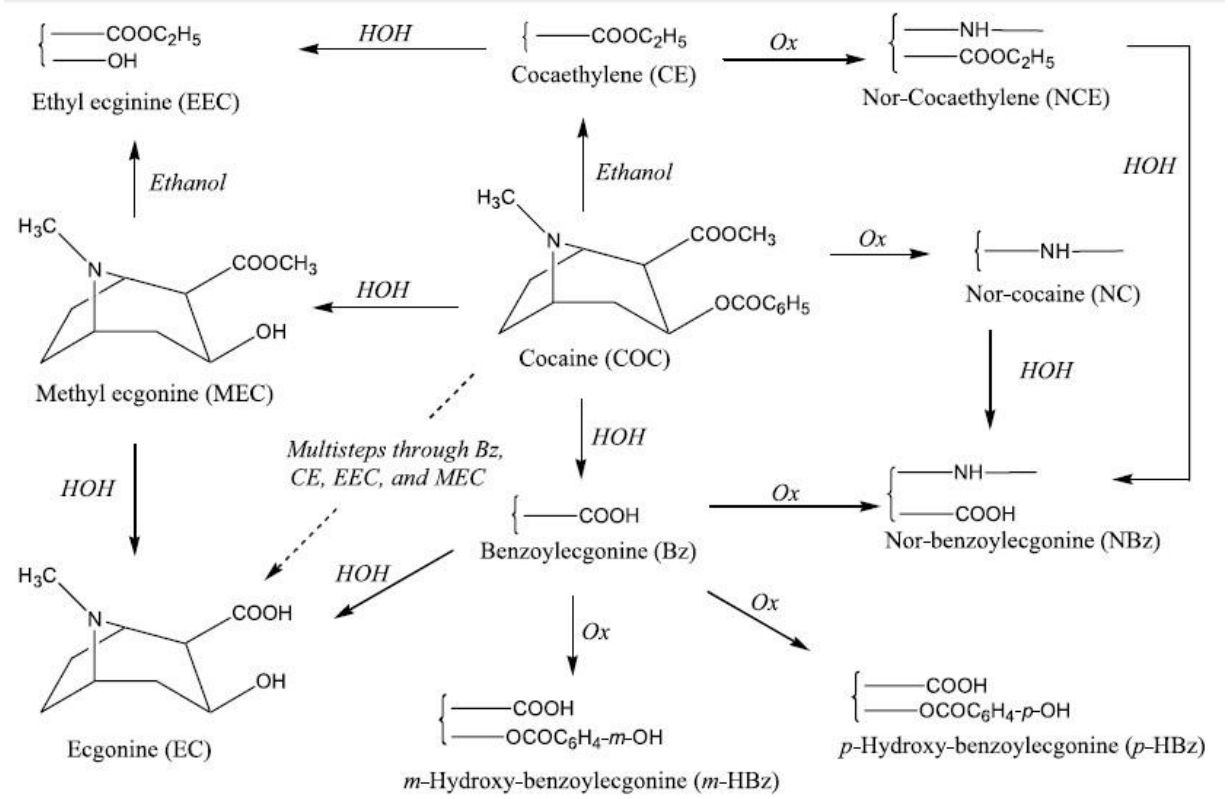
Moreover, different organ's tissues bind cocaine, such as the tissue of the brain (Fowler et al., 1989), lung, heart, liver, and adrenals (N D Volkow et al., 1992). From them, the brain and adrenals have the highest and similar uptake rate of cocaine, following for the liver and the heart. The uptake of the lung's tissue is almost inexistent (N D Volkow et al., 1992). After the administration of intravenous cocaine hydrochloride, the peak concentration of cocaine in the brain occurs between 4 and 10 minutes. Furthermore, the uptake rate of cocaine is 0.006 percent of the injected dose per cc of the whole brain and 0.01 percent of the injected dose per cc of the striatum. In consequence, the corpus striatum, a region with the highest concentration o monoamine transporters (Scherman, Boschi, Rips, & Henry, 1986), has the highest uptake rate of cocaine in the human body (Fowler et al., 1989).

7.1.4 Metabolism

Cocaine in the human body is extensively metabolized via two pathways, the hydrolytic and oxidative pathways. While the hydrolytic pathway is responsible for 90 percent of the cocaine biotransformation, the oxidative pathways are responsible for 10 percent of it (Kloss, Rosen, & Rauckman, 1984). The hydrolytic pathway is responsible for the generation of the following principal metabolites: benzoylecgonine, ecgonine methyl ester (methyl ecgonine), ecgonine, and cocaethylene (ethylcocaine). The oxidative pathway is responsible for the generation of the

following principal metabolites, norcocaine, norcocaethylene, and norbenzoylecgonine (figure 7.1.4.1).

Figure 7.1.4.1 Cocaine metabolism after hydrolysis (HOH), oxidation (Ox), and ethanol transesterification (ethanol) in human



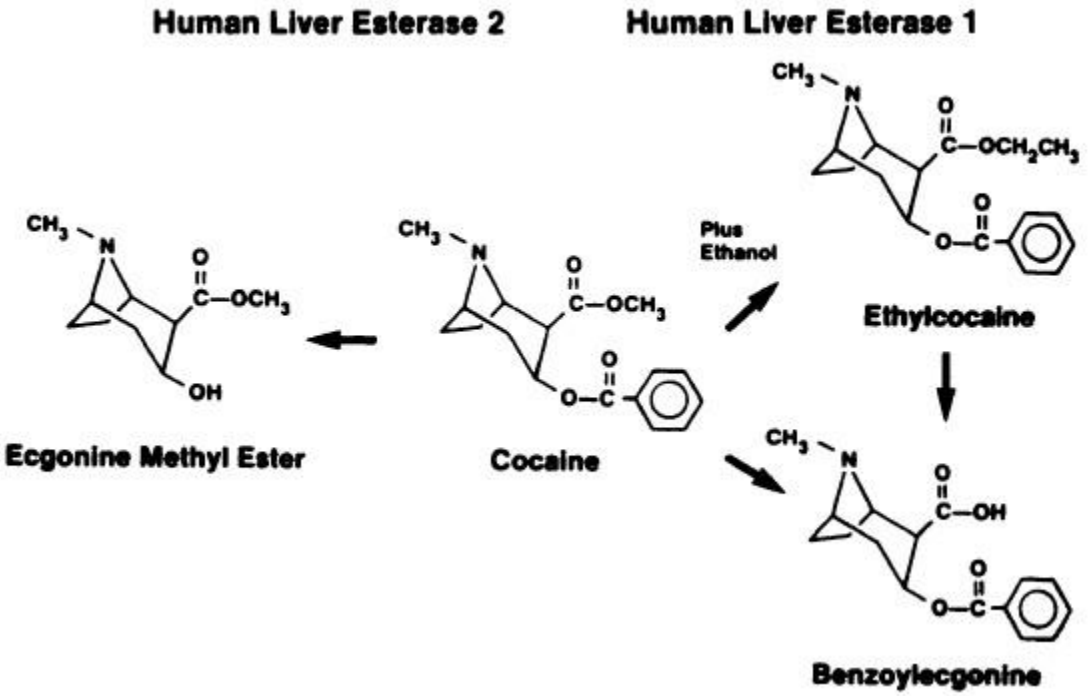
Source: Paul BD, Lalani S, Bosy T, Jacobs AJ, Huestis MA. Concentration profiles of cocaine, pyrolytic methylecgonidine, and thirteen metabolites in human blood and urine: determination by gas chromatography-mass spectrometry. Biomedical chromatography: BMC. Nov 2005;19(9):677-688.

7.1.4.1 Hydrolytic Metabolism

Cocaine on blood has a short ***half-life*** of approximately 1 hour (Jufer et al., 1998; Warner & Norman, 2000) because it is extensively hydrolyzed into its major metabolites benzoylecgonine, ecgonine methyl ester (methyl ecgonine) and ecgonine (Brzezinski, Abraham, Stone, Dean, &

Bosron, 1994). These three principal cocaine metabolites are pharmacologically inactive (Dean, Christian, Sample, & Bosron, 1991; Misra, Nayak, Bloch, & Mule, 1975; Spealman, Madras, & Bergman, 1989). While together, the benzoylecgonine and the ecgonine methyl ester represent the 80 to 90 percent of the cocaine dose eliminated in the urine (Jatlow, 1988), the ecgonine represents the two to eight percent of the cocaine dose eliminated in the urine (Fish & Wilson, 1969). The human liver carboxylesterase-1 (hCE-1) and 2 (hCE-2) hydrolyzes the cocaine in the liver. The hCE-1 is also called esterase 1, and the hCE-2 is called esterase 2 (Brzezinski et al., 1997). The hCE-1 hydrolyzes the methyl ester of cocaine, generating benzoylecgonine. In the presence of ethanol, hCE-1 catalyzes the ethyl transesterification of cocaine to cocaethylene or ethylcocaine; then, the hCE-1 hydrolyzes the ethylcocaine to get Benzoylecgonine. The hCE-2 hydrolyzes the benzoyl ester of cocaine, generating ecgonine methyl ester (Dean et al., 1991) (figure 7.1.4.1.1).

Figure 7.1.4.1.1 Pathways of cocaine metabolism in the human liver



Source: Dean RA, Christian CD, Sample RH, Bosron WF. Human liver cocaine esterases: ethanol-mediated formation of ethylcocaine. FASEB journal: official publication of the Federation of American Societies for Experimental Biology. Sep 1991;5(12):2735-2739.

In general, benzoylecgonine is considered the major metabolite of cocaine (Stewart, Inaba, Lucassen, & Kalow, 1979), with roughly 35 to 50 percent of the total cocaine doses been metabolized into benzoylecgonine in vivo (Fish & Wilson, 1969; Warner & Norman, 2000). Initial studies showed that benzoylecgonine was generated in the blood via nonenzymatic mechanisms or spontaneous hydrolysis at its physiological pH of 7.4 (Stewart et al., 1979). Nonetheless, current evidence suggests that 80 percent of the benzoylecgonine is formed by methylesterase activity and only 20 percent by spontaneous alkaline hydrolysis at a pH of 7.4 (Warner & Norman, 2000). The major methylesterase responsible for the hydrolysis of cocaine to benzoylecgonine is the hCE-1 (Brzezinski et al., 1994).

The other major cocaine metabolite is the ecgonine methyl ester, which accounts for 32 to 49 percent of the cocaine metabolites in urine (Inaba, Stewart, & Kalow, 1978; Stewart et al., 1979). Plasma cholinesterase and the human liver carboxylesterase-2 (hCE-2) hydrolyzes cocaine to ecgonine methyl ester (Stewart et al., 1979; Stewart, Inaba, Tang, & Kalow, 1977).

Ecgonine, the other major cocaine metabolite, accounts for two to eight percent of its metabolites (Fish & Wilson, 1969; Stewart et al., 1979). Ecgonine is generated via hydrolysis of benzoylecgonine and ecgonine methyl ester (B. D. Paul, Lalani, Bosy, Jacobs, & Huestis, 2005; Stewart et al., 1979).

Another principal cocaine metabolite, named cocaethylene, has been identified in the urine of simultaneous cocaine and alcohol users (Rafla & Epstein, 1979; Smith, 1984). The human liver carboxylesterase-1 (hCE-1) generates cocaethylene from cocaine and alcohol via transesterification (Dean et al., 1991). Cocaethylene is crucial because it is as active as cocaine blocking the dopamine reuptake in the nucleus accumbens (Hearn, Flynn, et al., 1991; Jatlow et al., 1991), which seems to be responsible for the self-administration of cocaine (Ritz, Lamb, Goldberg, & Kuhar, 1987). Furthermore, the toxicity of cocaine is potentiated with the concomitant use of alcohol, because cocaethylene is more toxic than cocaine (Hearn, Rose, Wagner, Ciarleglio, & Mash, 1991; Rose, 1994).

7.1.4.2 Oxidative Metabolism

The principal cocaine metabolite of the oxidative pathway is norcocaine. Approximately 2.6 to 6.2 percent of cocaine is metabolized to norcocaine in humans (Inaba et al., 1978). In the oxidative pathway, the liver microsomal cytochrome P-450 3A4 (CYP3A4) demethylases cocaine

to form norcocaine (Inaba, 1989; Jufer et al., 1998). Roughly 80 percent of this demethylation takes place in the liver (Stewart et al., 1979). Pharmacologically, norcocaine is an active metabolite with almost the same psychomotor properties as cocaine (Inaba, 1989; Inaba et al., 1978).

Moreover, norcocaine and its further metabolites such as norbenzoylecgonine are the primary inductors of cocaine hepatotoxicity. Specially individuals with diminished plasma cholinesterase activity are particularly vulnerable to the hepatotoxic effects of cocaine. It is because the low cholinesterase will not allow to hydrolyzed cocaine to ecgonine methyl ester at the expected rate. Then, the liver CYP3A4 will transform the excess of cocaine into its hepatotoxic metabolite norcocaine (Brzezinski et al., 1997; Kloss et al., 1984). It is essential to mention that that cocaine is hydrolyzed in the serum and liver at comparable rates (Stewart et al., 1979).

7.1.5 Excretion

Cocaine is almost entirely excreted in the form of metabolites (Ambre, 1985; Ambre, Fischman, & Ruo, 1984; Ambre, Ruo, Nelson, & Belknap, 1988; Fish & Wilson, 1969; Inaba et al., 1978). For instance, one to three percent of the intravenously administered cocaine is excreted in the urine as cocaine (Ambre et al., 1988). Nonetheless, 10-20 percent of the oral cocaine dose is excreted as cocaine in the urine after chewing coca leaf (Cruz-Sanchez & Guillen, 1949). Moreover, 13-15 percent of the intranasal dose of cocaine is excreted as cocaine in the urine (Ambre et al., 1984). Benzoylecgonine and ecgonine methyl ester are the major cocaine metabolites excreted in the urine. While, Benzoylecgonine represents 35 to 54 percent of the

cocaine metabolites excreted in the urine (Fish & Wilson, 1969), ecgonine methyl ester represents the 26 to 60 percent of the cocaine metabolites excreted in the urine. Furthermore, the half-life of benzoylecgonine and ecgonine methyl ester elimination are 5.1-7.5 and 3.6-4.2 hours respectively (Ambre, 1985; Ambre et al., 1984). Cocaine is metabolized to benzoylecgonine and ecgonine methyl ester almost in the same quantity, and the slower urinary excretion of benzoylecgonine explains its longer half-life (Ambre, 1985). By the way, two to eight percent of the intravenous cocaine dose is transformed in ecgonine (Fish & Wilson, 1969), and only 2.6 to 6.2 percent of the oral cocaine dose is converted in norcocaine (Inaba et al., 1978).

After oral administration of cocaine, the maximum urine concentration of cocaine is 324 ng/ml, for benzoylecgonine 6,142 ng/ml, for ecgonine methyl ester 3,555 ng/ml, for ecgonine 308 ng/ml, and 369 ng/ml for norbenzoylecgonine. The time to maximum urine concentration of cocaine is 4.5 hours, for benzoylecgonine 6.0 hours, for ecgonine methyl ester 4.5 hours, for ecgonine 13.3 hours, and 7.5 hours for norbenzoylecgonine.

Finally, cocaine follows first-order kinetics over a broad range of doses (Ambre, 1985). Its ***clearance*** is inversely correlated with the doses of cocaine (Pearson correlation r=-0.973). For instance, at the cocaine dose of 1 mg/kg, the plasma clearance of cocaine is 1.8 liters/kg/hour, while at the cocaine dose of 3 mg/kg, the clearance is 0.5 liters/kg/hour (Barnett et al., 1981). After chewing coca leaf at the cocaine dose of 0.34 to 0.41 mg/kg, the ***elimination half-life*** of cocaine was 25 to 36 minutes (Barnett et al., 1981; B. Holmstedt et al., 1979).

7.2 Pharmacodynamics of Coca Leaf Chewing

This section is going to describe the neurobiological effects of acute and chronic cocaine consumption. This description will be done in the framework of the so-called addiction cycle proposed by Koob and Le-Moal (G. F. Koob & Le Moal, 1997). The acute effects and the transition from voluntary to habitual and compulsive cocaine use will be described in the binge/intoxication stage. The chronic effects o cocaine will be described in the withdrawal/negative affect and preoccupation/anticipation stages. The withdrawal/negative affect stage is related to the abstinence syndrome, and the preoccupation/anticipation stage is related to craving and relapse. Finally, a brief description of the biological mechanisms of the toxic cocaine effects will be presented.

7.2.1 Binge/intoxication stage

Cocaine is an inhibitor of dopamine, norepinephrine, and serotonin reuptake receptors (Korpi et al., 2015). It is also a blocker of sodium (Crumb & Clarkson, 1990), potassium (Zhang et al., 2001), and calcium channels (Tsushima, Kelly, & Wasserstrom, 1996). This stage will provide a description of the rewarding, incentive salience, and compulsiveness of cocaine use.

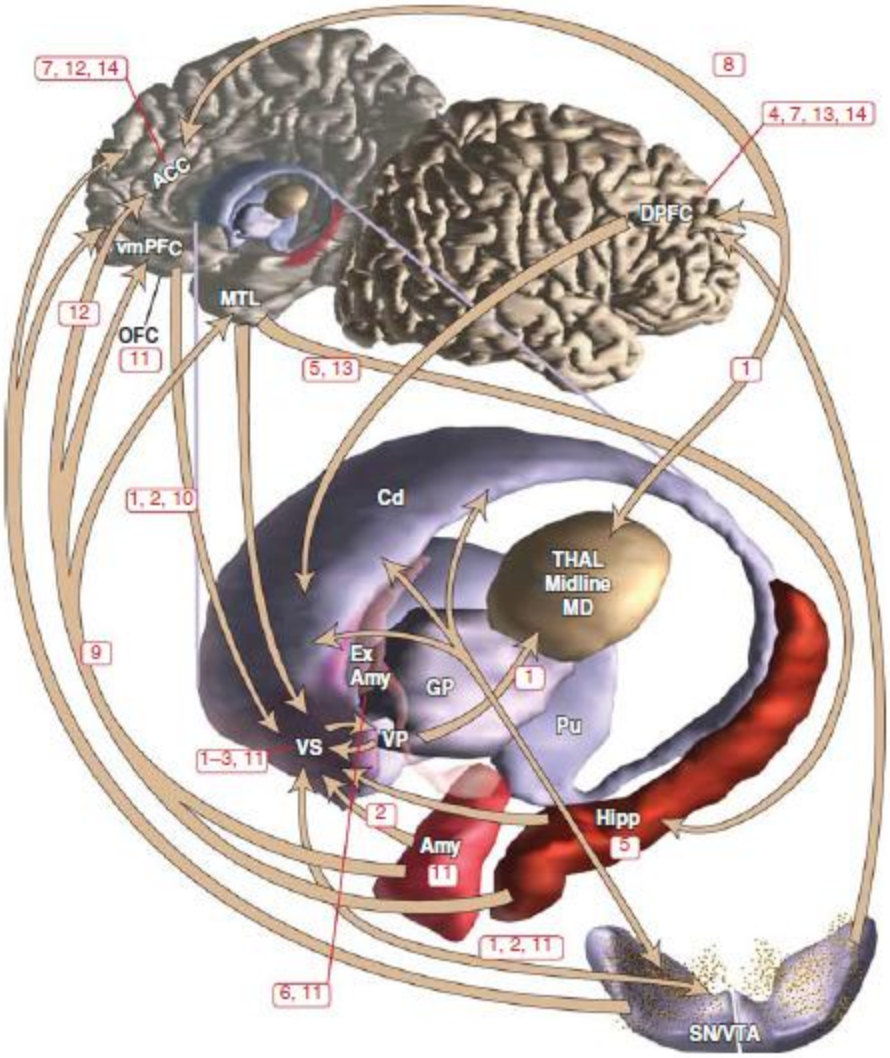
7.2.1.1 Cocaine reward

Cocaine as almost all the others addictive drugs produces an increment of dopamine in the synaptic cleft of nucleus accumbens shell and olfactory tubercle which is believed to be the principal part of the mechanism of its rewarding effects (Di Chiara & Imperato, 1988; Everitt et al., 2008; Pettit & Justice, 1989). Furthermore, the olfactory tubercle seems to be more

rewarding to cocaine than the nucleus accumbens (Ikemoto, 2003). A reward is whatever experience that increases the odds of a response via a hedonic mechanism (G. F. Koob & Volkow, 2016). Cocaine exerts this reinforcing effects by binding and inhibiting the dopamine uptake receptor located in the nucleus accumbens shell and olfactory tubercle (G. F. Koob, Sanna, & Bloom, 1998; Pierce & Kumaresan, 2006; Reith, 1988; Ritz et al., 1987; Wise, 2004). These two structures receive dopamine afferents from the ventral tegmental area, which is called the mesolimbic dopamine system (Wise, 2009).

Furthermore, nearly all the addictive drugs directly or indirectly activate the mesolimbic dopaminergic transmission to the nucleus accumbens; cocaine and amphetamine act directly while opiates and alcohol indirectly (Nestler, 2005). This phasic or sudden increase of dopamine in the nucleus accumbens shell and the olfactory tubercle is associated with the so-called "high," "rush," or "euphoric" experience (Nora D. Volkow, Fowler, & Wang, 2003). Figure 7.2.1.1.1 shows the brain structures and pathways involved in addictive disorders.

Figure 7.2.1.1.1 Brain structures and pathways involved in addictive disorders



Arrows illustrate projections; numbers refer to chapters in which those structures or pathways are discussed. Amy, amygdala; ACC, anterior cingulate cortex; Cd, caudate nucleus; DPFC, dorsal prefrontal cortex; GP, globus pallidus; Ex Amy, extended amygdala; Hipp, hippocampus; MD, medial dorsal nucleus of the thalamus; MTL, medialtemporal lobe; OFC, orbital frontal cortex; Pu, Putamen (dorsal striatum consist of Cd and Pu); SN, substantia nigra; yellow dots, dopamine neurons; Thal, thalamus; vmPFC, ventral medialprefrontal cortex; VP, ventral pallidum; VS, ventral striatum (VS consist of nucleus accumbens and olfactory tubercle); VTA, ventral tegmental area.
Source: Haber, S. N., & Rauch, S. L. (2010). Neurocircuitry: A Window into the Networks Underlying Neuropsychiatric Disease. Neuropsychopharmacology, 35(1), 1-3.

At the molecular level, the phasic or abrupt increase of dopamine triggered by cocaine activates the low-affinity dopamine D1 receptors (D1R), which is believed to be necessary for the rewarding/psychomotor effects of cocaine (Caine et al., 2007; Drago, Gerfen, Westphal, & Steiner, 1996; Gingrich & Caron, 1993; G. F. Koob & Volkow, 2016; Moratalla, Xu, Tonegawa, & Graybiel, 1996) and the classical conditioning learning of environmental cues associated to cocaine use (Zweifel et al., 2009). The D1 is the most abundant dopamine receptor of the brain, expressed in almost all the brain regions innervated by dopamine neurons; being the striatum (caudate, putamen, nucleus accumbens, and olfactory tubercle) the brain region with the highest concentration of D1 receptors (Gingrich & Caron, 1993; Herve, 2011; Jaber, Robinson, Missale, & Caron, 1996; Missale, Nash, Robinson, Jaber, & Caron, 1998). The D1R couples with Gαolf or Gαs G-proteins. The prefrontal cortex neurons express high levels of Gαs and low levels of Gαolf; conversely, the striatum (caudate, putamen, nucleus accumbens, and olfactory tubercle) medium spine neurons (MSN) express high levels of Gαolf and low levels of Gαs (Herve, 2011; Missale et al., 1998). Moreover, cocaine increases the concentration of dopamine in the striatum; subsequently, dopamine joining the D1R activates the Gαolf G protein to exert psychomotor stimulation and c-fos gene induction (Corvol et al., 2007; Zhuang, Belluscio, & Hen, 2000). Eliciting the replacement of GDP by GTP in the Gαolf subunit activates the Gαolf/β2/γ7 heterotrimer; subsequently, the activated Gαolf subunit activates the transmembrane-bound enzyme adenylyl cyclase, which catalyzes the conversion of ATP to the second messenger cyclic-3',5'-adenosine monophosphate (cAMP) (Herve, 2011). The striatum medium spine neurons have high concentrations of adenylyl cyclase 5 (AC5), which is responsible for 80% of basal adenylyl cyclase activity in the striatum (Herve, 2011). It seems

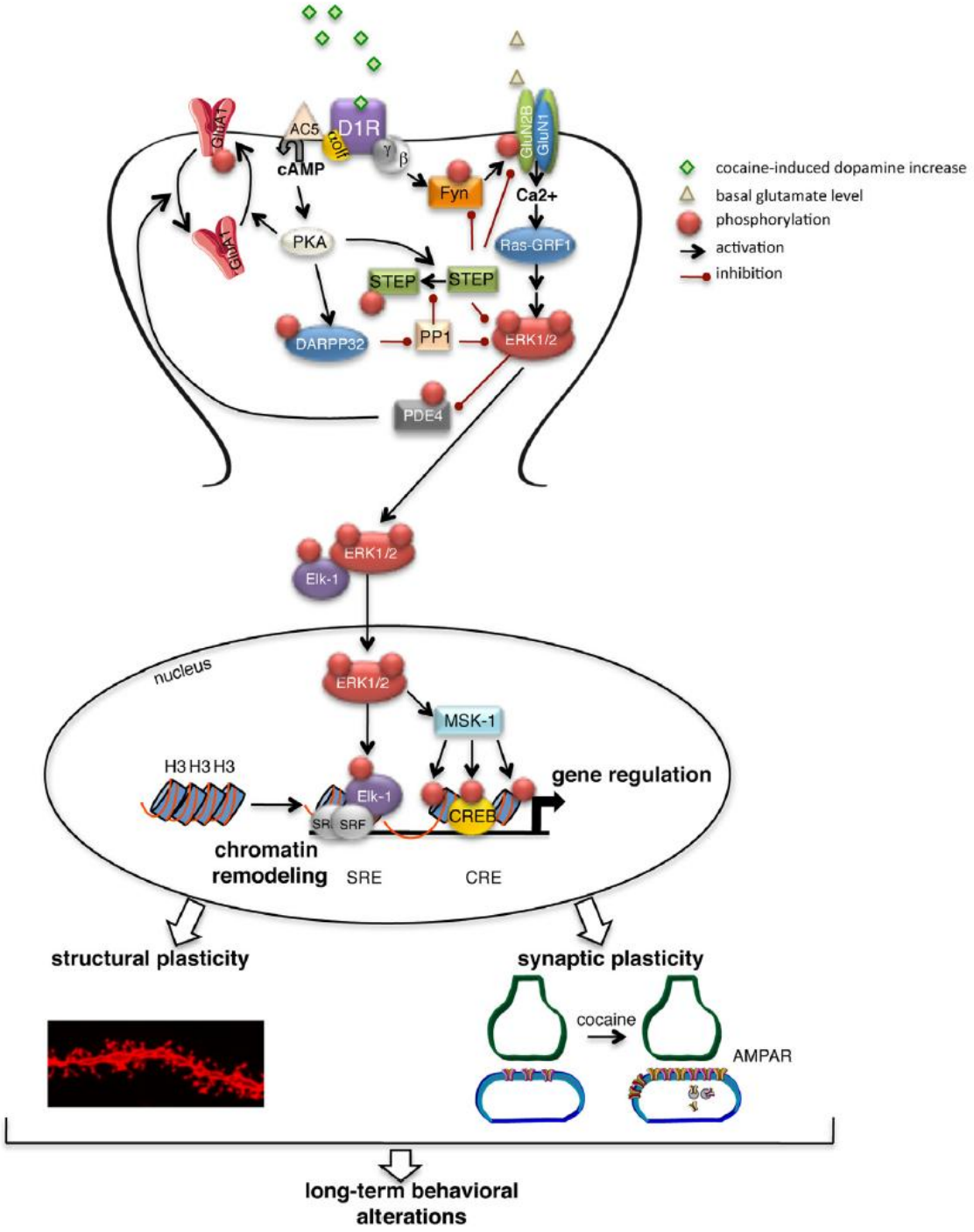
that the metabotropic D1 and D2 receptors exert their physiological effects in the striatum through activation and inhibition of AC5, respectively (Iwamoto et al., 2003; Lee et al., 2002). Then, the second messenger cAMP activates the protein kinase A (PKA); subsequently, the PKA inactivates the striatal-enriched protein phosphatase (STEP) via phosphorylation. Thus, the inactive STEP cannot inhibit the extracellular signal-regulated kinase one (ERK1) and two (ERK2) via dephosphorylation. Furthermore, the PKA activates the dopamine and cAMP-regulated phosphoprotein (DARPP-32) via phosphorylation; then, the activated DARPP32 inhibits potently the protein phosphatase 1 (PP1). The inhibition of PP1 stimulates the inactivation of STEP because the PP1 promotes the activation of STEP via dephosphorylation. Thus, the net result of the activation of PKA and the inhibition of PP1 is the inactivation of STEP; then, the inactive STEP cannot inactivate the ERK1 and ERK2 via dephosphorylation.

In summary, the dopamine activation of D1R cannot directly activate ERK1 and ERK2 via phosphorylation; instead, it indirectly stimulates the activation of them via the inactivation of STEP (Pascoli, Cahill, Bellivier, Caboche, & Vanhoutte, 2014; S. Paul et al., 2000). Moreover, the D1R activation of ERK1 and ERK2 requires the stimulation of N-methyl-D-aspartate receptor (NMDAR) by the endogenous or tonic glutamate. As cocaine does not increase the concentration of glutamate in the striatum, the cocaine increase of dopamine acting in D1R facilitates the activation of NMDAR by the endogenous glutamate. The dopamine stimulation of D1R activates the βγ subunits of G-protein couple to D1R; the βγ subunits of G-protein activates the tyrosine kinase Fyn (Fyn) via phosphorylation. The Fyn is a member of the Src-family kinase (SFKs). Subsequently, the activated Fyn activates the NMDAR via phosphorylation of glutamate NMDA receptor subunit type 2B (GluN2B) at tyrosine 1472. The activated STEP inhibits the

activation of NMDAR by Fyn. The glutamate release is typically transient, leading to rapid activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid glutamate receptor (AMPAR) and depolarization of the neuron. Conversely, NMDAR is usually inactive due to the block exerted by magnesium ion. Thus, NMDAR gets active only after sufficient depolarization exerted by AMPAR activation and D1R facilitation of NMDAR activation. Notwithstanding, once active, NMDAR has long-lasting permeability to calcium ion. Therefore, NMDAR permits prolonged neuronal stimulation by allowing the influx of calcium into the medium spine neuron cytoplasm. The increase of calcium concentration activates the small guanosine triphosphate-binding protein GRF1 (Ras-GRF1). The activated Ras-GRF1 activates the mitogen-activated protein kinase ERK-kinase (MEK) via phosphorylation. Subsequently, the activated MEK activates the ERK1 and ERK2 via phosphorylation. Furthermore, the D1R-dependent tyrosine phosphorylation of GluN2B residues by Fin increases NMDAR synaptic expression (Hopf, 2017; Pascoli et al., 2011; Pascoli et al., 2014). After activation, the ERK1 and ERK2 proteins translocate to the cell nucleus, where they activate the transcriptional factor Elk-1 and MSK-1 via phosphorylation. The dendrite to nucleus trafficking of activated ERK is achieved via endocytosis of a molecular complex, including ERK, clathrin proteins, and AMPAR. Thus, the AMPAR activation of NMDAR triggers the internalization of AMPAR via calcium activation of the small GTPases Rap, which is essential for long-term depression synaptic plasticity. The AMPAR insertion at the membrane via the activation of the small GTPases Ras is related to long-term potentiation synaptic plasticity. The NMDAR influx of calcium activates the calcium-sensitive enzyme CaMKII, which subsequently activates the Ras via phosphorylation. Moreover, the membrane insertion of AMPAR requires the PKA phosphorylation of the AMPAR's GluA1

subunit, which will be amplified by the stimulation of D1R. Besides, the activated ERK1 and ERK2 indirectly favor the membrane insertion of AMPAR via inhibition of the phosphodiesterase 4 (PDE4), which promotes the internalization of AMPAR via dephosphorylation of GuA1 subunit of AMPAR. In the nucleus, the activated Elk-1 binds the serum response element (SRE) present in the promoter of specific genes, including c-Fos, Egr-1, and FosB. In this way, the activated Elk-1 induces the expression of c-Fos, Egr-1, and FosB. The activated MSK-1 bears the CRE sites in their gene promoters of c-Fos, dynorphin, and FosB; thus, the activated MSK-1 induces the expression of c-Fos, dynorphin, and FosB via the phosphorylation of cAMP-responsive element-binding (CREB) (Beattie et al., 2000; Levine et al., 2005; Pascoli et al., 2014; Trifilieff et al., 2009; E. Valjent et al., 2000; J. J. Zhu, Qin, Zhao, Van Aelst, & Malinow, 2002). Furthermore, MSK-1 triggers chromatin remodeling via histone H3 phosphorylation (Brami-Cherrier, Betuing, Caboche, Roze, & Girault, 2009). The rewarding effects of cocaine require the presence of Egr-1, also called Zif268; contrasting with c-Fos, chromatin remodeling at the promoter Egr-1 is independent on MSK-1 and H3 phosphorylation (Brami-Cherrier et al., 2009; Emmanuel Valjent, Aubier, & Corbillé, 2006). In addition to the synaptic plasticity described above, chronic cocaine use induces structural plasticity in D1R medium spine neuron of nucleus accumbens characterized by increases in the dendritic spine density. This structural plasticity depends on D1R, NMDAR, ERK1, ERK2, and MEF2 activation; the MEF2 is the transcription factor myocyte enhancer factor 2. Furthermore, the activation of NMDAR is achieved by phosphorylation of the GluN1 subunit of NMDAR (Pascoli et al., 2014) (Figure 7.2.1.1.2).

Figure 7.2.1.1.2 Cocaine-induced ERK 1 and 2 activation and associated long-term neuronal adaptations

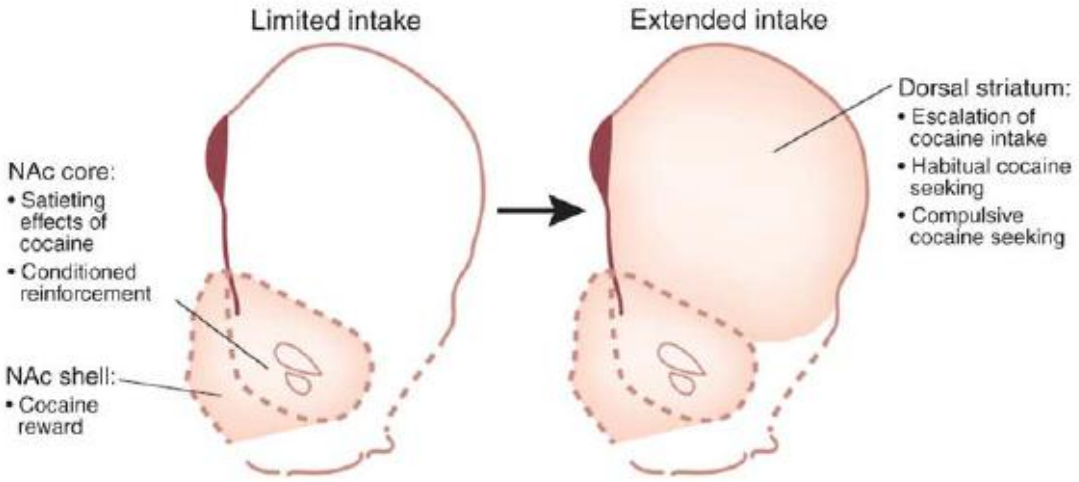


Source: Pascoli, V. et al. (2014). Extracellular signal-regulated protein kinases 1 and 2 activations by addictive drugs: a signal toward pathological adaptation. Biol Psychiatry, 76(12), 917-926

7.2.1.2 Incentive salience

Incentive salience is the motivation or inclination to generate organized activity to get rewards. The internal physiological state and the previously learned association about the reward cue produce the incentive salience, which is mediated by the mesocorticolimbic dopamine system. The learning about the reward cue associated with cocaine use is reached via conditioned reinforcement by which previously neutral environmental stimulus associated with the rewarding effects of cocaine acquires the property to be a conditioned stimulus or reinforcer in its own right (G. F. Koob & Volkow, 2010, 2016). The neurobiological studies related to incentive salience show that the phasic activation of the mesocorticolimbic- and nigrostriatal-dopamine neurons coming from the ventral tegmental area and the substantia nigra pars compacta respectively mediate the cocaine reward (Wise, 2009). Thus, a novel-and-single exposure to cocaine triggers long-term potentiation of AMPAR at excitatory synapses of dopamine neurons of the ventral tegmental area, which induces the phasic release of dopamine on nucleus accumbens (Ungless, Whistler, Malenka, & Bonci, 2001). The increase of dopamine concentrations in the nucleus accumbens shell facilitates the rewarding effects of cocaine, while the increase of dopamine concentrations in the nucleus accumbens core facilitates the conditioned reinforcement (figure 7.2.1.2.1) (Jonkman & Kenny, 2013). The conditioned reinforcement is achieved via classic or Pavlovian conditioning (Everitt, Dickinson, & Robbins, 2001). Initially, the mesolimbic dopamine system fires in response to a novel reward. After repeated exposure, the mesolimbic dopamine system stops firing during the reward delivery and instead fired in the presence of the conditioned stimuli that predict the reward (Schultz, Dayan, & Montague, 1997).

Figure 7.2.1.2.1 Subregions of the rodent anterior striatum involved in cocaine self-administration



At the beginning of cocaine self-administration, the nucleus accumbens (NAc) shell mediates the rewarding effects of cocaine, while the nucleus accumbens core mediates the satiating effect of cocaine and the classical conditioned effect cocaine-paired stimuli. After chronic cocaine self-administration, the NAc still mediates the self-administration of cocaine, but the dorsal striatum comes to control the intensification of cocaine intake and the habitual/compulsive cocaine-seeking even under concomitant foot-shock punishment.

Source: Jonkman, S., & Kenny, P. J. (2013). Molecular, cellular, and structural mechanisms of cocaine addiction: a key role for microRNAs. Neuropsychopharmacology, 38(1), 198-211.

Moreover, cocaine-seeking behavior endures more than cocaine-taking. Whereas conditioned environmental stimuli associated with cocaine consumption profoundly influence cocaine-seeking behavior, the primary reinforcing effects of cocaine mediate cocaine-taking behavior (Everitt et al., 2008; Everitt et al., 2001). It seems that the nucleus accumbens core (Ito, Robbins, & Everitt, 2004) and its afferents from the basolateral amygdala (Everitt & Robbins, 2000; Whitelaw, Markou, Robbins, & Everitt, 1996) mediate the acquisition of cocaine-seeking behavior. In humans, cue-induced cocaine craving activates limbic regions such as the amygdala and anterior cingulate cortex (Childress et al., 1999), as well as other prefrontal

regions associated with memory formation such as the dorsolateral prefrontal cortex and the medial orbitofrontal cortex. While the medial orbitofrontal cortex mediates the formation of explicit episodic memory (conscious remind of experiences such as the rewarding effect of reinforcers), the dorsolateral prefrontal cortex mediates the formation of working memory (short-term memory useful for task processing and decision making) (S. Grant et al., 1996).

7.2.1.3 Compulsive cocaine use

Cocaine addiction can be viewed as a transitional phenomenon, going from voluntary to habitual to compulsive use, being the last two stages the expression of the loss of control of cocaine use (Everitt et al., 2008).

In the beginning, cocaine-taking and cocaine-seeking is a voluntary or goal-directed activity. Moreover, this voluntary cocaine-taking and cocaine-seeking seem to be mediated by the learning of response-outcome associations via the instrumental conditioning process (Olmstead, Lafond, Everitt, & Dickinson, 2001). The medial prefrontal cortex mediates the acquisition of response-outcome associations in instrumental conditioning, especially the prelimbic area of the medial prefrontal cortex. Notwithstanding, the medial prefrontal cortex is not involved in the permanent storage or expression of the response-outcome association. Moreover, as the basolateral amygdala share mutual connections with the medial prefrontal cortex, thus, the basolateral amygdala seems to mediate the acquisition (consolidation and reconsolidation) of reward representations in the response-outcome learning of instrumental conditioning.

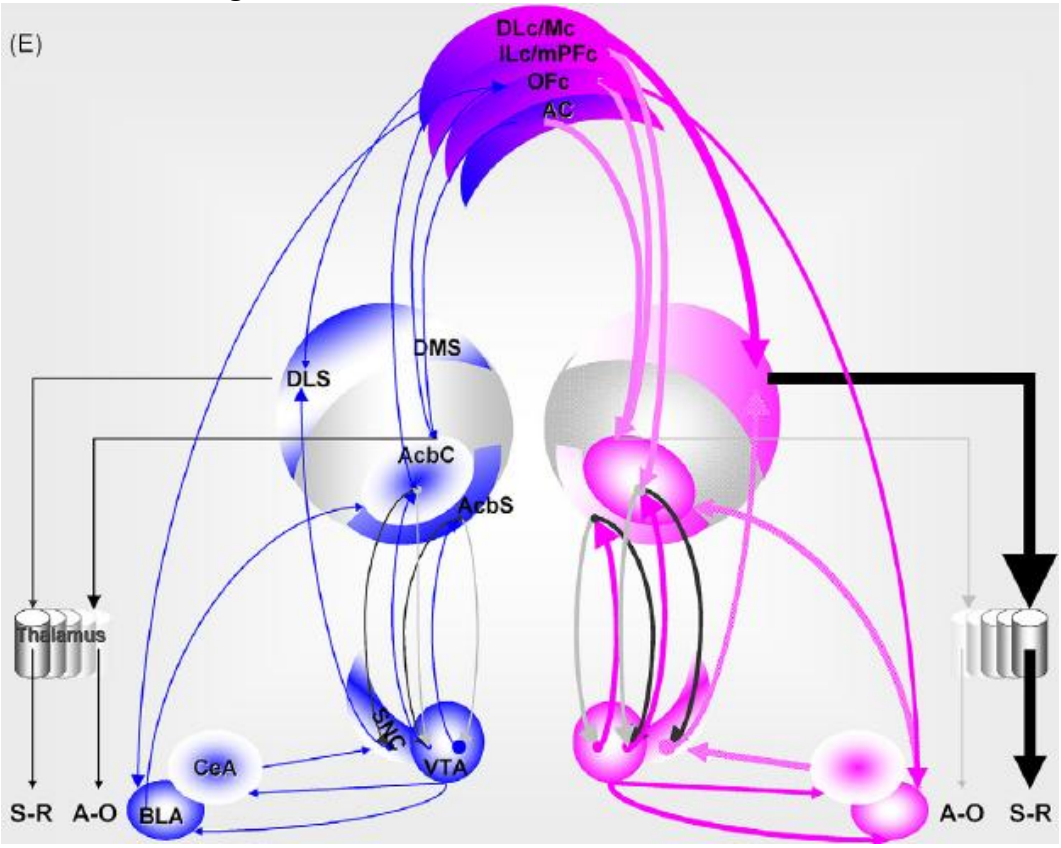
Furthermore, the medial prefrontal cortex sends efferent to the dorsomedial striatum and the ventral striatum, especially to the nucleus accumbens core. This medial prefrontal cortex projection to the striatum overlaps with the amygdalostriatal projections from the basolateral amygdala. Thus, the dorsomedial striatum and the nucleus accumbens core seem to integrate the response-outcome information coming from the medial prefrontal cortex with the information about reward value coming from the basolateral amygdala. Therefore, these structures contribute to goal-directed action. For instance, the nucleus accumbens core seems to modulate the goal-directed action based upon in the reward-related information (incentive value) of the expected outcomes, and the posterior dorsomedial striatum seems to play a relative long-lasting role in the expression of response-outcome learning as well as in the acquisition of instrumental response. It seems that goal-directed instrumental learning needs feedback from dorsomedial striatum to prefrontal cortex via the mediodorsal thalamus (Balleine & Killcross, 2006; Ito et al., 2004; Ostlund & Balleine, 2005; Yin, Ostlund, Knowlton, & Balleine, 2005). Overall, as at the beginning, cocaine-taking and cocaine-seeking is a subject of devaluation, researchers hypothesized that the comprehension of the relationship between cocaine-seeking response and its corresponding outcome mediate cocaine-seeking at early stages of acquirement and execution (Everitt et al., 2008; Olmstead et al., 2001)Harlan & de Wet, 1973.

As was pointed out previously, cocaine-seeking is mediated by the ventral striatum during the early stage of the acquisition period. In this stage, cocaine-taking triggers the release of dopamine in the nucleus accumbens shell, nucleus accumbens core, olfactory tubercle, caudate nucleus (dorsomedial striatum in rats), and putamen (dorsolateral striatum in rats).

Additionally, the unexpected presence of the cocaine-associated conditioned stimulus increases the release of dopamine just in the nucleus accumbens core (Ito, Dalley, Howes, Robbins, & Everitt, 2000). Albeit, after the prolonged manifestation of cocaine-seeking, the contingent presentation of the cocaine-associated conditioned stimulus release dopamine just in the dorsal striatum (Ito, Dalley, Robbins, & Everitt, 2002). Thus, the instrumental behavior of cocaine-seeking at the beginning is under control of the response-outcome association, and this initial goal-directed behavior is under control of the limbic striatal region (ventral striatum) and the associative striatal region (dorsomedial striatum in rats or caudate nucleus in primates). Subsequently, after extensive cocaine-taking, cocaine-seeking becomes a habit, which is inflexible and resistant to a devaluation of the outcome. Furthermore, the cocaine-seeking habit seems to be under the control of the stimulus-response associations mediated by the sensorimotor striatal region (dorsolateral striatum in rats or putamen in primates) (Faure, Haberland, Conde, & El Massioui, 2005; Yin, Knowlton, & Balleine, 2004). Other brain regions, such as the orbitofrontal cortex (Ostlund & Balleine, 2007) and the basolateral amygdala (Balleine & Killcross, 2006), seem to mediate the stimulus-response associations or pavlovian learning. Thus, the shift of associative encoding of cue-evoked cocaine-seeking from ventral to dorsal striatum observed in animals (Takahashi, Roesch, Stalnaker, & Schoenbaum, 2007) was also observed in human cocaine users (Garavan et al., 2000; N. D. Volkow et al., 2006). The neuroanatomical basis of this shift of cocaine-seeking might be the "intrastriatal dopamine-dependent spiraling circuitry," functionally linking the ventral with the dorsal striatum. Therefore, the nucleus accumbens shell innervates the dopamine neurons of the ventral tegmental area, which subsequently innervates the nucleus accumbens shell, and the nucleus

accumbens core. Then, the nucleus accumbens core innervates the dopamine neurons of the substantia nigra pars compacta, which subsequently innervates the nucleus accumbens core, the dorsomedial striatum (caudate nucleus) and finally the dorsolateral striatum (putamen) (Belin & Everitt, 2008; Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009; Haber, Fudge, & McFarland, 2000; Ikemoto, 2007). See figure 7.2.1.3.1 for more details.

Figure 7.2.1.3.1 Schematic representation of the neural networks underpinning Pavlovian and instrumental learning mechanisms involved in the control of behavior for natural rewards and addictive drugs



Schematic representation of the development of incentive habits and addiction. Left: The neural circuitries involved in the control of voluntary behavior are organized in parallel segregated cortico-striatal loops or integrative mechanisms dependent upon the AcbC. Right: Drugs of abuse enhance dopamine transmission in the limbic cortico-striatal systems, alter the processing of the dorsal striatum, impair top-down executive control from the prefrontal cortex and recruit intra-striatal dopamine-dependent ascending circuitry linking the ventral to the dorsal striatum. Thus drugs of abuse facilitate the direct link between Pavlovian mechanisms dependent upon the amygdala and S-R mechanisms dependent upon the dorsolateral striatum through their connection with the AcbC. The resulting incentive habits may be important mechanisms underlying the development of drug addiction. Nucleus accumbens core (AcbC), nucleus accumbens shell (AcbS), the posterior dorsomedial striatum (DMS), dorsolateral striatum (DLS), basolateral nucleus of the amygdala (BLA), ventral tegmental area (VTA), substantia nigra compacta (SNc), central nucleus of the amygdala (CeA), anterior cingulate cortex (AC), orbitofrontal cortex (OFc), medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLc), goal-directed behaviour (A-O), stimulus-response behavior (S-R).
Source: Belin, D., Jonkman, S., Dickinson, A., Robbins, T. W., & Everitt, B. J. (2009). Parallel and interactive learning processes within the basal ganglia: Relevance for the understanding of addiction. Behav Brain Res, 199(1), 89-102.

By the way, the current evidence suggests that impulsivity predicts the propensity to escalate cocaine consumption (Everitt et al., 2008). Animal models have shown that low availability of dopamine D2 and D3 receptors in the ventral striatum correlated with high trait impulsivity and high tendency to escalate intravenous cocaine self-administration (Dalley et al., 2007). Notwithstanding, studies carried out in humans have found contradictory results; some of them reporting low availability of dopamine D2 and D3 receptors in the ventral striatum of healthy impulsive humans (Caravaggio et al., 2016), and others reporting high availability of dopamine D2 and D3 receptors in the ventral striatum of healthy non-planning impulsive humans (Reeves et al., 2012). Notwithstanding, impulsive humans have a higher risk of using illicit drugs, although the unique effect of impulsivity was small, suggesting that impulsivity is not a sufficient cause of drug use (Nigg et al., 2006). The current evidence suggests that high impulsivity is the consequences of drug use; nonetheless, some studies reveal that high impulsivity precedes the onset of drug use (J. E. Grant & Chamberlain, 2014). Furthermore, predating impulsivity seems to increase the susceptibility to relapse after cocaine abstinence (Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009; Pattij & De Vries, 2013).

7.2.2 Withdrawal/negative affect stage

Motivational symptoms such as anhedonia or loss of motivation for natural rewards, anergia, decreased activation, amotivation, intense boredom, and anxiety characterize the withdrawal/negative affect stage of cocaine addiction (Gawin & Kleber, 1986, 1988). The neurobiological mechanism of this loss of motivation for natural rewards seems to be explained by the elevations in reward thresholds observed in animal models of cocaine withdrawal stage

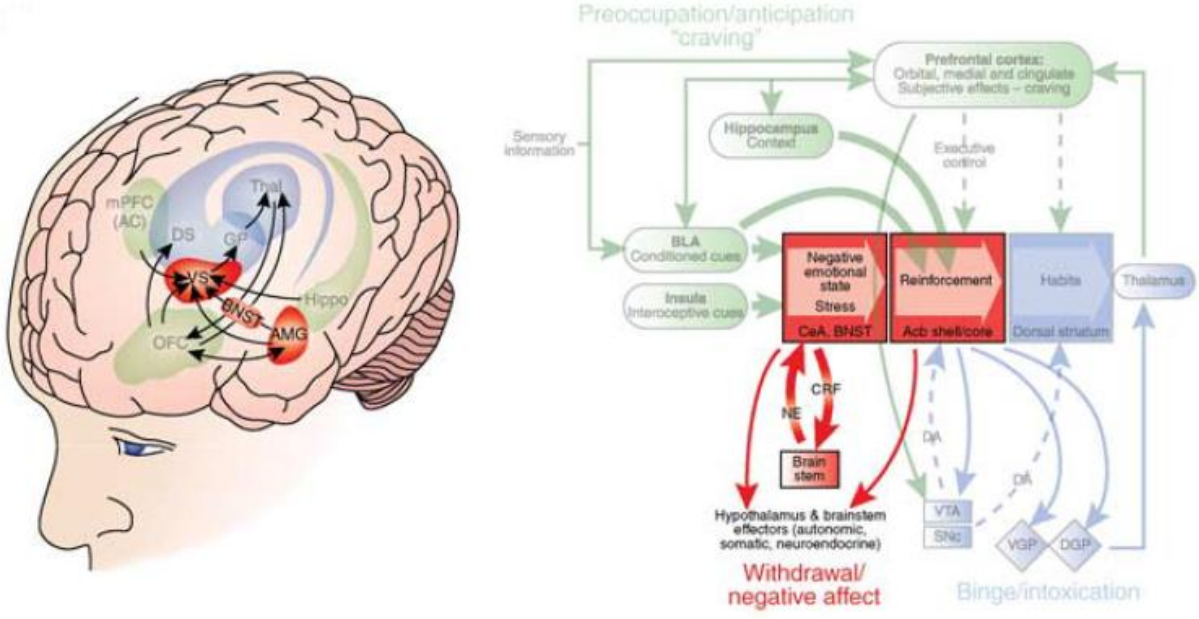
(Markou & Koob, 1991; Stoker & Markou, 2011). Furthermore, human brain functional magnetic resonance imaging study showed an attenuated response to normal rewarding stimuli among cocaine users in the withdrawal stage (Garavan et al., 2000). Chronic drug use triggers the **within-system neuroadaptations** of the neurochemical systems implicated in acute drug reward; when these neuroadaptations to neutralize the drug effects continue after the drug disappears produces the withdrawal syndrome (G. F. Koob & Bloom, 1988; G. F. Koob & Volkow, 2016). For instance, animal models showed a decrease in the extracellular levels of dopamine (Weiss, Markou, Lorang, & Koob, 1992) and serotonin (Parsons, Koob, & Weiss, 1996) in the nucleus accumbens during withdrawal from cocaine self-administration. Moreover, Human studies showed a blunted response of amphetamine-induced dopamine release in the nucleus accumbens and lower self-report of cocaine rewarding effects among cocaine-dependent subjects during the withdrawal phase (Martinez et al., 2007; N. D. Volkow et al., 2014; N. D. Volkow et al., 1997). Other within-system neuroadaptations to chronic cocaine use are the increment of the mu-opioid receptor density in the nucleus accumbens, caudate, putamen, and cingulate cortex (Schroeder, Niculescu, & Unterwald, 2003), although the increment of the mu opioid receptor density in the nucleus accumbens was just transient (Azaryan, Clock, Rosenberger, & Cox, 1998). The activation of the mu opioid receptor in nucleus accumbens was associated with an increase in the mesolimbic dopamine release (Spanagel, Herz, & Shippenberg, 1990). Furthermore, human studies showed that chronic cocaine use is associated with an increase in mu-opioid receptors binding in the frontal, lateral temporal, and anterior cingulate cortex, which was positively correlated with self-reported cocaine craving (Gorelick et al., 2005) and cocaine relapse (Gorelick et al., 2008).

Chronic activation of the reward system also triggers the **between-system neuroadaptations** of systems not related with reward such as the hypothalamic-pituitary-adrenal (HPA) axis and brain stress system (G. F. Koob & Bloom, 1988; G. F. Koob & Volkow, 2016) both systems acts via a dysregulated corticotrophin-releasing factor (CRF). The main constituent of the brain stress system is the extended amygdala conformed of the central nucleus of the amygdala, bed nucleus of the stria terminalis, and a transition zone of the medial nucleus accumbens shell (G. F. Koob & Volkow, 2010). Cocaine withdrawal triggered the extracellular release of CRF in the central nucleus of the amygdala (Richter & Weiss, 1999), which subsequently activates the hypothalamic-pituitary-adrenal axis and the brain stress system. The CRF via the portal vein reaches the anterior pituitary, where it acts in the CRF receptor one (CRF_1) on corticotrophic cells favoring the release of adrenocorticotrophic hormone (ACTH) and β-endorphin into the peripheral blood circulation. ACTH in the adrenal cortex stimulates the synthesis and secretion of glucocorticoids such as cortisol in humans and corticosterone in rodents (A. J. Dunn & Swiergiel, 2008). In physiological circumstances, the HPA axis is negatively feedback regulated by the hippocampus and the paraventricular nucleus of the hypothalamus when the circulating glucocorticoids contact these places (E. S. Brown, Rush, & McEwen, 1999; Jankord & Herman, 2008).

Furthermore, the CRF released by the central nucleus of the amygdala, bed nucleus of the stria terminalis, and paraventricular nucleus stimulates the release of norepinephrine on the locus coeruleus, which subsequently stimulates the release of CRF on the central nucleus of the amygdala, bed nucleus of the stria terminalis, and paraventricular nucleus (G. Koob & Kreek, 2007; G. F. Koob, 1999). The CRF release from the central nucleus of the amygdala

produces stress-induced anxiety by increasing the tonic production of norepinephrine in the locus coeruleus (McCall et al., 2015). Moreover, the chronic glucocorticoid elevation in the hippocampus triggered the stress-induced hyperactivity of the HPA axis (L. J. Zhu et al., 2014), hypertrophy of the amygdala and hypotrophy of the hippocampus (Pagliaccio et al., 2014). Chronic stress disinhibits the amygdala by inactivating its tonic inhibition through the GABA A receptors currents (Liu et al., 2014). Thus, decreases in the release of dopamine in the nucleus accumbens, and increases in the activity of CRF in the amygdala contribute to the negative emotional state observed in cocaine withdrawal (G. F. Koob & Volkow, 2016). Chronic cocaine use increases the transcription of dynorphin in the nucleus accumbens neurons; the subsequent increased release of dynorphin acting in the k-opioid receptors of the ventral tegmental area dopaminergic neurons decreases the dopamine release in the nucleus accumbens (Carlezon, Nestler, & Neve, 2000). Observe figure 7.2.2.1 for more details.

Figure 7.2.2.1 Neurocircuitry associated with withdrawal/negative affect stage of the addiction cycle



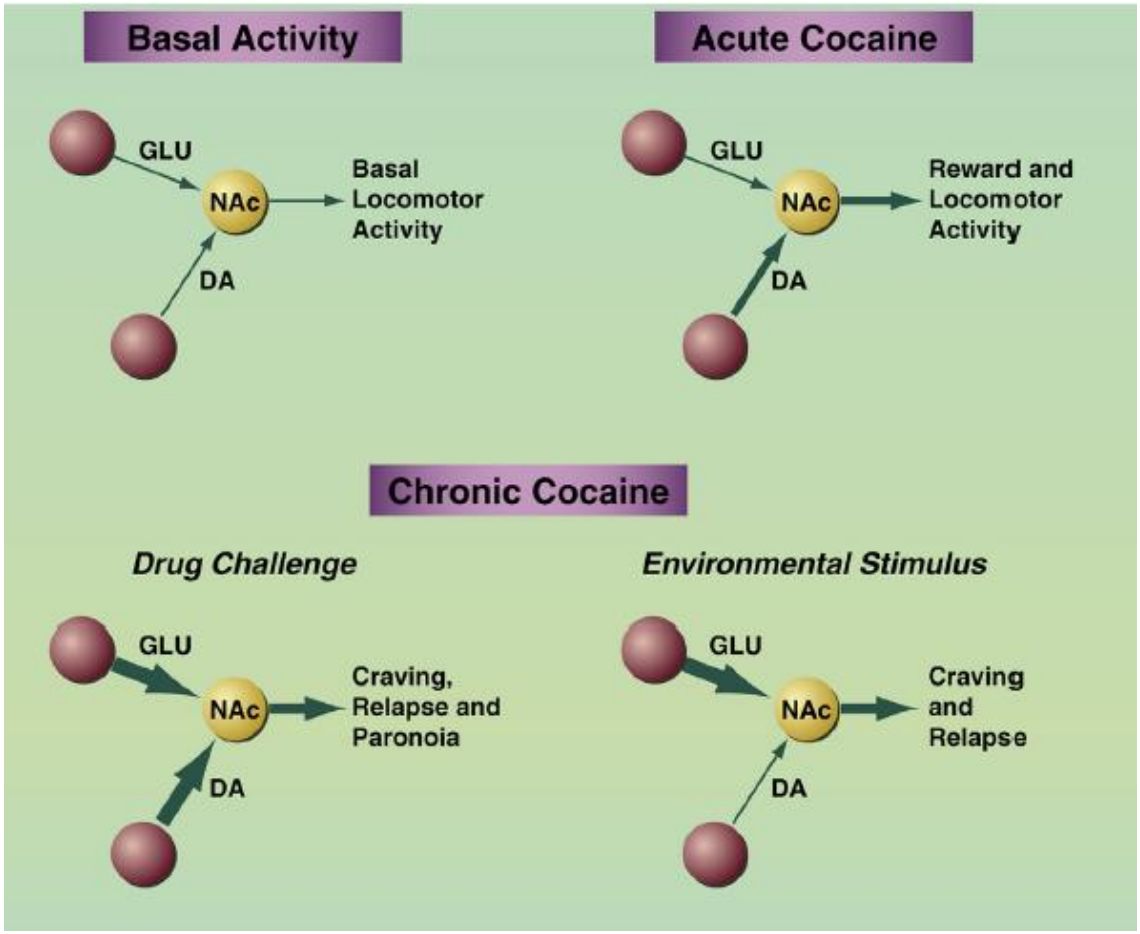
The negative emotional state of withdrawal may engage the activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition zone in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala hypothesized to have a function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. Major projections of the extended amygdala are to the hypothalamus and brainstem.
Source: Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. Neuropsychopharmacology, 35(1), 217-238.

7.2.3 Preoccupation/anticipation (craving) stage

One of the prominent features of cocaine addiction is an intense desire or need to obtain the drug even after months or years of last using it (Kalivas & McFarland, 2003); thus, the current scientific literature suggests three types of neurobiological mechanisms of cocaine relapse: (1) drug-induced reinstatement, (2) cue-induced reinstatement, and (3) stress-induced reinstatement (Shaham, Shalev, Lu, de Wit, & Stewart, 2003).

The nucleus accumbens mediates the drug-induced cocaine reinstatement. Thus, the ingestion of amphetamine or other drugs that mimic the cocaine effects elicits an enhanced dopamine and glutamate transmission in the nucleus accumbens of chronic cocaine users. While the dopamine enhanced transmission comes from the ventral tegmental area, the enhanced glutamate transmission comes from the medial prefrontal cortex (anterior cingulate cortex or prelimbic cortex). These enhanced dopaminergic and glutamatergic transmission in the nucleus accumbens triggers the cocaine craving and relapse via the activation of dopamine D2 receptors which is believed to be the direct consequence of the activation of internal cues associated to cocaine taking (G. F. Koob, Arends, & Le Moal, 2014; Shaham et al., 2003). Look at figure 7.2.3.1 for more details.

Figure 7.2.3.1 The role of glutamate (GLU) and dopamine (DA) transmission in the relapse to drug-seeking behavior



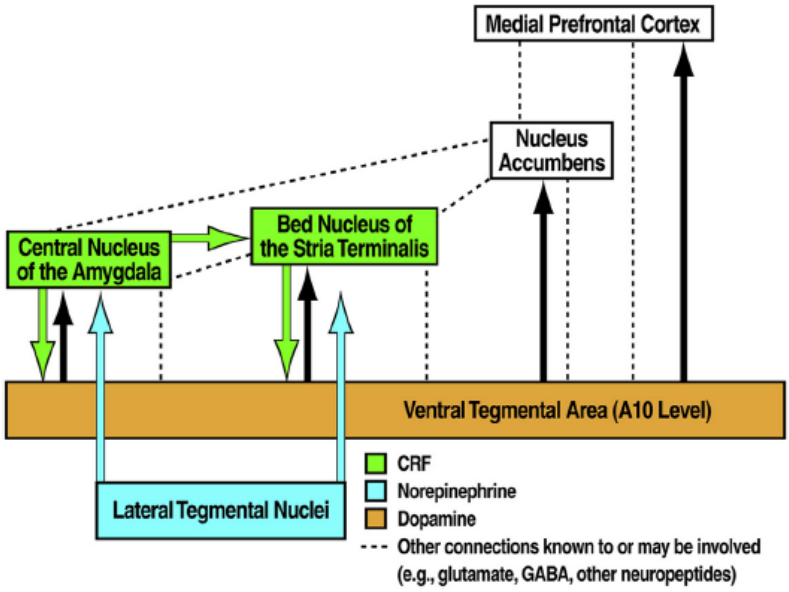
During baseline neurotransmission, tonic dopamine and glutamate transmission equally modulate the output of the nucleus accumbens (NAc) to allow normal locomotor activity. Following acute cocaine administration, dopamine levels in the nucleus accumbens are elevated, with little effect on glutamatergic tone, to increase locomotor activity and stimulate reward processes. After withdrawal from chronic drug intake, a single cocaine administration may induce relapse to drug taking or paranoia through increased dopamine release associated with and dependent on increased glutamate transmission which may be a consequence of interoceptive cues (that is, internal cues within the body or brain) associated with drug taking. However, in the absence of cocaine administration, an environmental cue may induce craving and relapse through enhanced glutamate transmission with little dopamine involvement. Source: Cornish JL, Kalivas PW. (2001). Cocaine sensitization and craving: differing roles for dopamine and glutamate in the nucleus accumbens. Journal of Addictive Diseases, 20(3), 43–54.

The basolateral amygdala mediates the cue-induced cocaine reinstatement. In the absence of cocaine self-administration, an environmental cue may induce craving and relapse to cocaine consumption via the increased release of glutamate in nucleus accumbens core coming from the prelimbic cortex (anterior cingulate cortex); this enhanced glutamatergic stimulus in the nucleus accumbens core correlates with the magnitude of cocaine reinstatement response. This release of glutamate is dopamine-dependent from the projections of the ventral tegmental area to the prelimbic cortex (McGlinchey, James, Mahler, Pantazis, & Aston-Jones, 2016). Furthermore, the environmental cue associated with cocaine taking activates the orbitofrontal cortex to basolateral amygdala subcircuit to promote cue-induced cocaine reinstatement; the dopaminergic inputs from ventral tegmental area acting in D1 receptors of the orbitofrontal cortex regulates this subcircuit (Lasseter et al., 2014). For learning the association of the environmental cue with cocaine consumption via long-term potentiation, it seems to be necessary the dopamine activation of D1 receptors of the basolateral amygdala; studies showed that the activation of the D1 receptor of the basolateral amygdala is a crucial modulator of cue-induced cocaine-seeking (See, Kruzich, & Grimm, 2001). Look at figure 7.2.3.1 for more details.

The central nucleus of the amygdala and the bed nucleus of the stria terminalis mediates the stress-induced cocaine reinstatement. The stressful event activates the norepinephrine neurons from the lateral tegmental nuclei, which subsequently activates the corticotropin-releasing factor projection neurons from the central nucleus of the amygdala to the bed nucleus of the stria terminalis. Then, the corticotropin-releasing factor projection neurons from the bed nucleus of the stria terminalis to the ventral tegmental area activate the

dopamine projection neurons from the ventral tegmental area to the nucleus accumbens and medial prefrontal cortex. Finally, the dopamine activation of the nucleus accumbens and medial prefrontal cortex initiates the approach behavior related to stress-induced reinstatement of cocaine-seeking (G. F. Koob et al., 2014). See figure 7.2.3.2 for more details.

Figure 7.2.3.2 Overview of the circuitry that comprises and integrates the extended amygdala and mesocorticolimbic systems and that forms the basis for a neuroanatomical model of stress-induced reinstatement of cocaine seeking

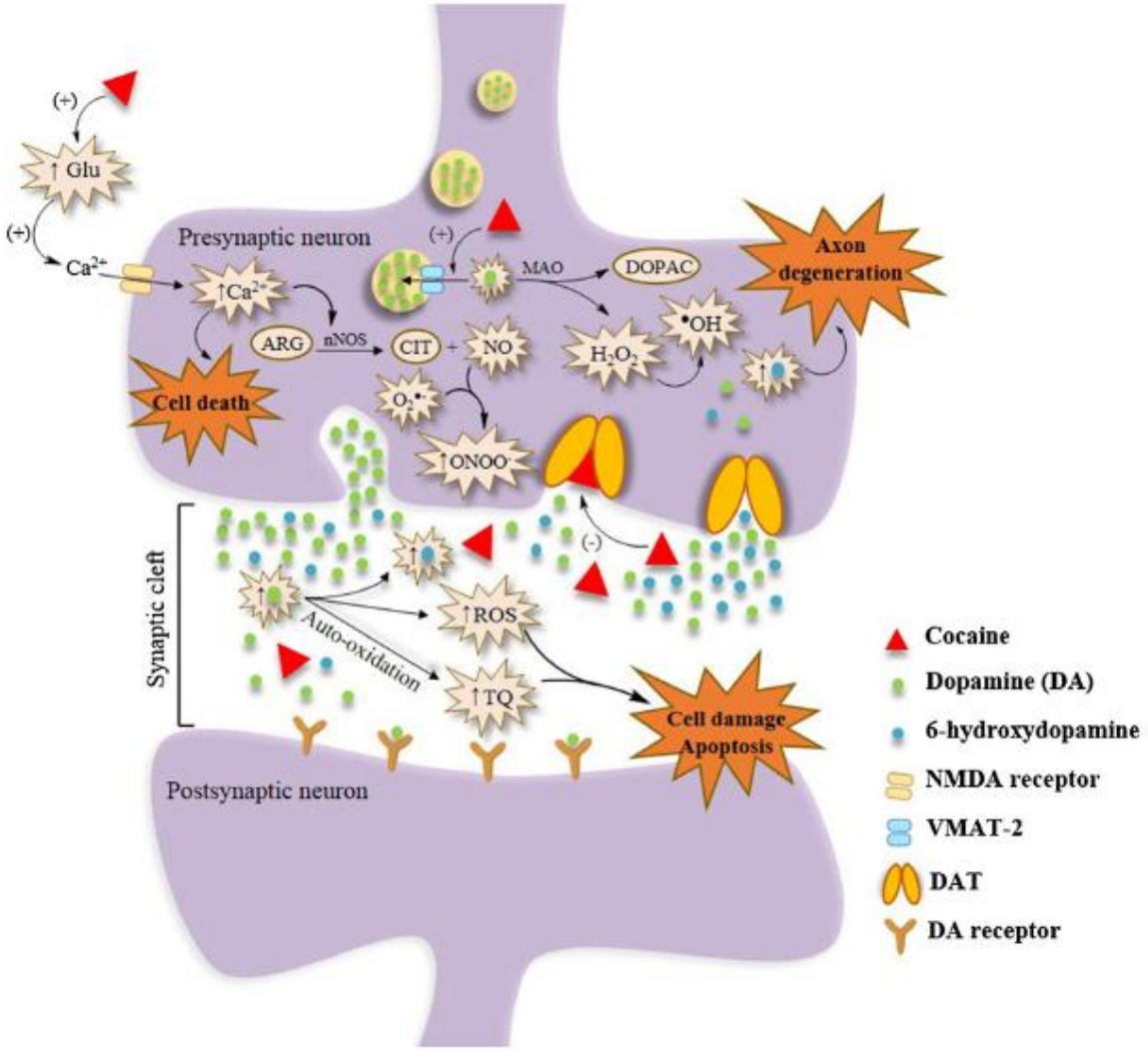


"The extended amygdala circuitry extends from a transition area in the shell of the nucleus accumbens to the bed nucleus of the stria terminalis and central nucleus of the amygdala. The mesocorticolimbic dopamine system originates in the ventral tegmental area and comprises a system of dopamine neurons that provide projections between the ventral tegmental area, nucleus accumbens, and prefrontal cortex. The bed nucleus of the stria terminalis and central nucleus of the amygdala receive major noradrenergic (that is, norepinephrine) innervation from neurons of the lateral tegmental nuclei, which give rise to the ventral norepinephrine pathway. Although the extended amygdala is also innervated by the dorsal noradrenergic pathway originating in the locus coeruleus, it is the ventral pathway that has been specifically implicated in the effects of norepinephrine on stress-induced reinstatement of drug seeking and the aversive effects of opiate withdrawal. The central nucleus of the amygdala and bed nucleus of the stria terminalis are also innervated by dopamine neurons originating in regions of the midbrain, including the ventral tegmental area. Both norepinephrine and dopamine neurons synapse with, or in close proximity to, corticotropin-releasing factor (CRF) neurons in the central nucleus of the amygdala and bed nucleus of the stria terminalis. CRF neurons in the central nucleus of the amygdala are hypothesized to project to the bed nucleus of the stria terminalis and ventral tegmental area, and CRF neurons in the bed nucleus of the stria terminalis provide a local source of CRF and also project to the ventral tegmental area. CRF in the ventral tegmental area may initially have an excitatory effect on dopamine and glutamate transmission in the region."
Source: Erb, S. (2010). Evaluation of the relationship between anxiety during withdrawal and stress-induced reinstatement of cocaine seeking. Prog Neuropsychopharmacol Biol Psychiatry, 34(5), 798-807.

7.2.4 Mechanisms of cocaine toxic effects

Cocaine cause neurological complications such as ischemic or hemorrhagic stroke, subarachnoid or intracerebral hemorrhages, transient ischemic attack, seizures, movement disorders, migraine, headache, transient loss of consciousness, cerebrospinal fluid rhinorrhea, fungal cerebritis, and vasculitis (Buttner et al., 2003; Fessler et al., 1997; Goldfrank & Hoffman, 1991; Lowenstein et al., 1987; Spivey & Euerle, 1990). Furthermore, cocaine is causally associated with many psychiatric complications such as agitation, anxiety, depression, psychosis, paranoia, suicidal ideation, suicide attempt, and suicide (Lowenstein et al., 1987). One explanation of these neuropsychiatric complications is the dysregulation of the dopaminergic system exerted by chronic cocaine use. Cocaine acting on the vesicular monoamine transporter 2 (VMAT-2) increases the quantity of dopamine storage in the vesicles. Thus, in the next depolarizing stimulus, the presynaptic neurons release higher quantities of dopamine to the synaptic cleft. The subsequent metabolism of dopamine via auto-oxidation or monoamine oxidase (MAO) catalyzes produce toxic reactive oxygen species (ROS) such as hydroxyl radical and superoxide, as well as other toxic substances such as quinones, and peroxynitrite. These toxic substances are responsible for the axon degeneration and ultimate for the neuron death (apoptosis) (Pereira, Andrade, & Valentao, 2015). See figure 7.2.4.1 for more details.

Figure 7.2.4.1 Mechanism by which cocaine induces oxidative stress, altering the levels of extracellular dopamine

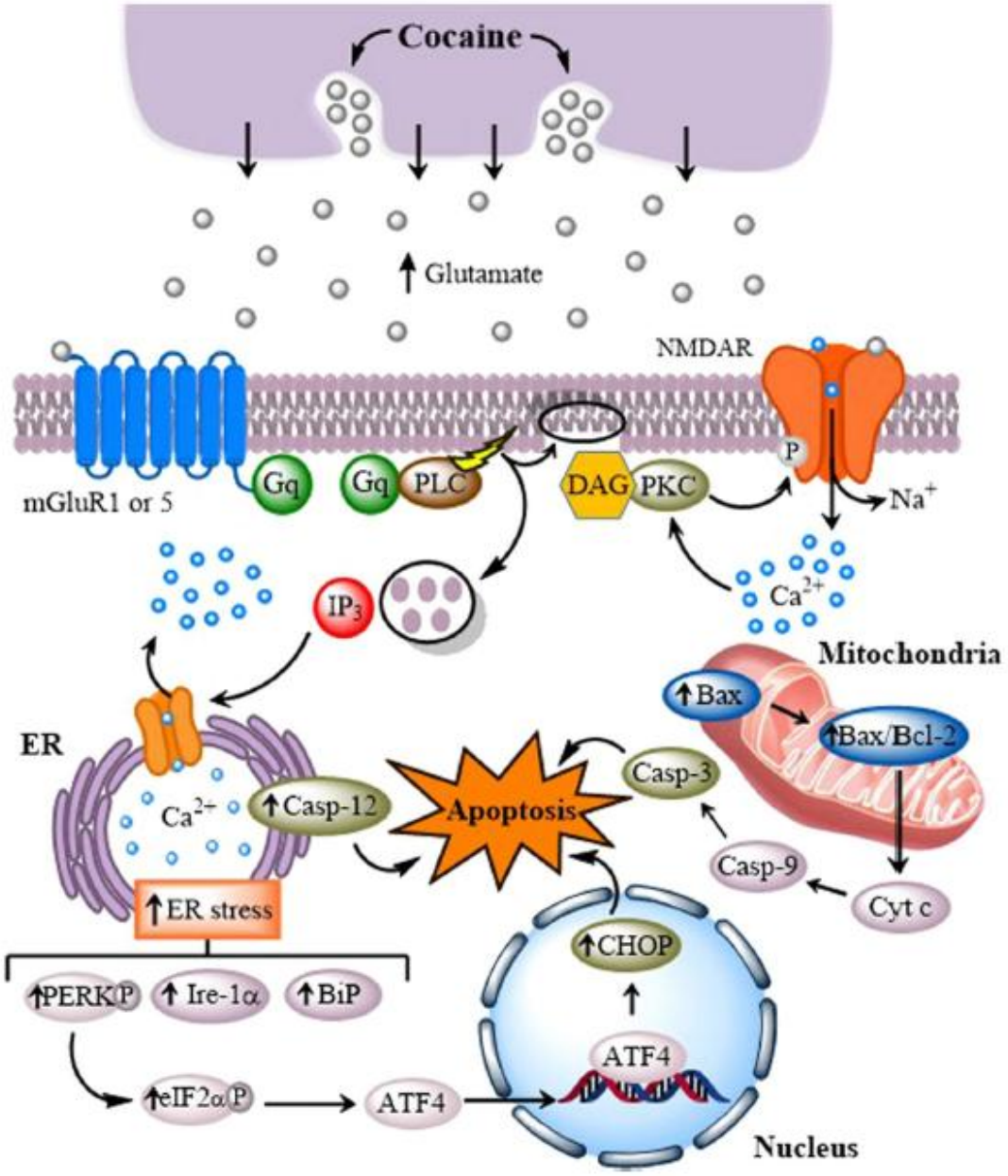


Glutamate (Glu), arginine (ARG), citrulline (CIT), and toxic quinones
Source: Pereira, R. B., Andrade, P. B., & Valentao, P. (2015). A Comprehensive View of the Neurotoxicity Mechanisms of Cocaine and Ethanol. *Neurotox Res, 28*(3), 253-267.

The other mechanism of cocaine neurotoxicity is via the induction of endoplasmic reticulum stress. Cocaine consumption increases the extracellular concentration of glutamate in the dorsal striatum. Subsequently, the excess of glutamate profusely activates the glutamate N-

methyl-D-aspartate receptors, and the group I glutamate metabotropic receptors (I mGluRs) such as the mGluR1 and the mGluR5. This over-activation of the glutamate receptors triggers the over-excitation of neurons via the increase in the concentration of intracellular calcium. This increase of the intracellular calcium activates a series of enzymes from the endoplasmic reticulum known as the unfolded protein response (UPR). Finally, the induction of the UPR generates C/EBP-homologous protein (CHOP), caspase-12, and caspase-3, which subsequently causes the neuron apoptosis (Pereira et al., 2015). See figure 7.2.4.2 for more details. Moreover, via the release of dopamine, cocaine activates the sympathetic nervous system triggering a massive release of catecholamines. Thus, the increases in catecholamines induce high blood pressure and vasoconstriction, which subsequently might cause a stroke (Pereira et al., 2015).

Figure 7.2.4.2 Mechanism by which cocaine induces endoplasmic reticulum (ER) stress and mitochondrial dysfunction, leading cell to apoptosis

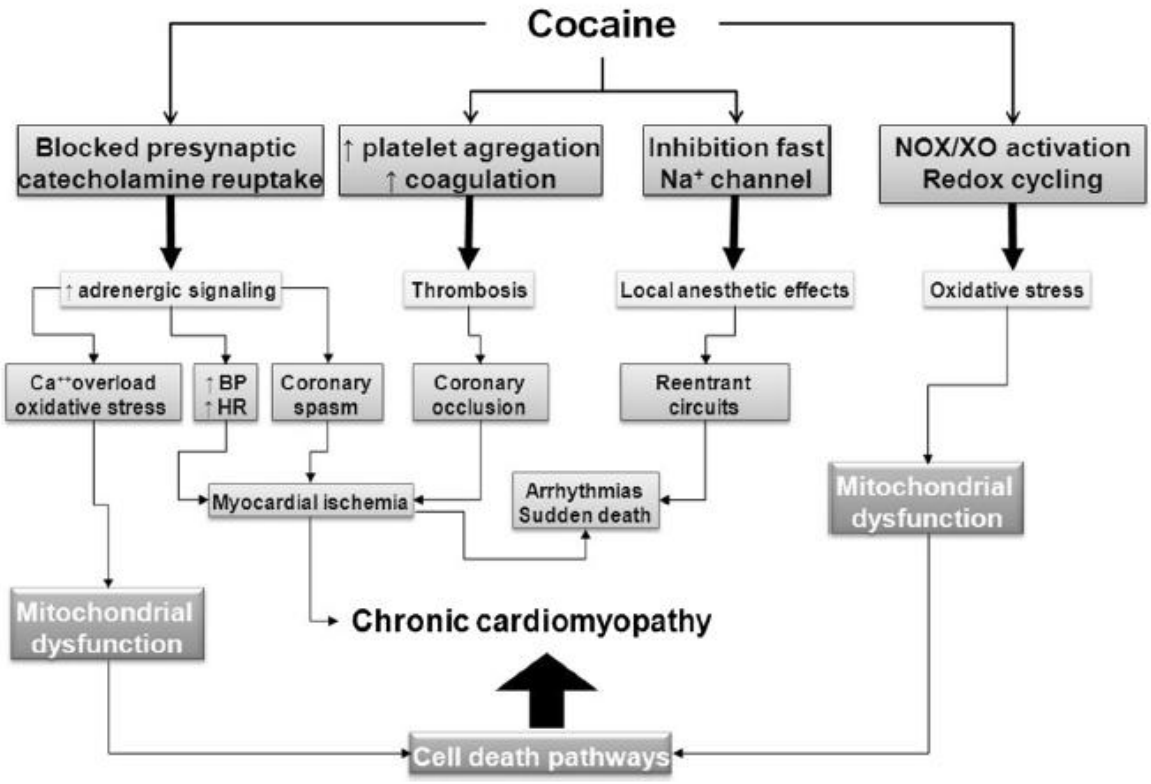


Source: Pereira, R. B., Andrade, P. B., & Valentao, P. (2015). A Comprehensive View of the Neurotoxicity Mechanisms of Cocaine and Ethanol. *Neurotox Res, 28*(3), 253-267.

Cocaine also triggers cardiac complications such as acute myocardial infarction, myocardial ischemia, coronary vasospasm, cardiac arrhythmias, cardiomyopathies, ventricular hypertrophy, tachycardia, blood hypertension, and rupture of the Ascending Aorta (Cregler & Mark, 1986; Goldfrank & Hoffman, 1991; Schindler, 1996). The cocaine marked sympathomimetic effects produce intense stimulation of α_1 and β_1 adrenergic receptors. While the α_1-adrenergic stimulation provokes arterial vasoconstriction with subsequent high blood pressure and reduced microvascular blood flows, the β_1-adrenergic stimulation increases the heart rate and the myocardial contractility. Thus, the activation of the α_1 and β_1 adrenergic receptors causes an imbalance in the demand and supply of oxygen, leading to myocardial ischemia or myocardial infarction. The cocaine increase of blood pressure via α1-adrenergic stimulation causes cerebral hemorrhage and aortic dissection.

Furthermore, cocaine promotes atherosclerosis and endothelial dysfunction via the activation of platelets and coagulation, which subsequently cause myocardial infarction and ischemic stroke. Cocaine also induces the myocardial oxidative stress and mitochondrial dysfunction via the formation of reactive oxygen species (ROS), which subsequently triggers the cocaine-induced cardiomyopathy. Finally, cocaine produces major arrhythmias and sudden cardiac death via its sympathomimetic effects and its blocking effects of sodium channels, which prolongs the QRS duration and the QT interval (Liaudet, Calderari, & Pacher, 2014). See figure 7.2.4.3 for more details.

Figure 7.2.4.3 Major mechanisms of cocaine toxicity in the cardiovascular system



Blood pressure (BP), heart rate (HR), NADPH oxidase (NOX), and xanthine oxidase (XO).
Source: Liaudet, L., Calderari, B., & Pacher, P. (2014). Pathophysiological mechanisms of catecholamine and cocaine-mediated cardiotoxicity. *Heart Fail Rev, 19*(6), 815-824.

APPENDIX B:

Research Questionnaires

8.1 Questions about coca leaf chewing dependence in Spanish

ENTREVISTADOR(A): ENCIERRE EN UN CÍRCULO LAS LETRAS CORRESPONDIENTES A LAS RESPUESTAS POSITIVAS **TARJETA 25**	TABACO (CIGARRILLO, MAPACHO)	TRANQUILIZANTES	PASTILLAS PARA DORMIR	PASTILLAS PARA EL DOLOR DE CABEZA	JARABE PARA LA TOS	ESTIMULANTES (PARA ADELGAZAR)	ÉXTASIS	MARIHUANA	CLORH. COCAÍNA	PASTA BÁSICA (PBC)	HEROÍNA	ALUCINÓGENOS (LSD) TRIP	HOJA DE COCA	INHALANTES	OTROS
1. ¿CUÁL DE ESTAS SUSTANCIAS HA PROBADO EN SU VIDA YA SEA POR CURIOSIDAD, PLACER, O PORQUE LE PRESIONARON A HACERLO (NO POR INDICACIÓN MÉDICA)? ENTREVISTADOR(A): SI NO HA CODIFICADO NINGUNA, PASE A P76	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
2. ¿A QUE EDAD CONSUMIÓ POR PRIMERA VEZ...?															
3. ¿CUANDO FUE LA ÚLTIMA VEZ QUE CONSUMIÓ?															
a. En los últimos 30 días	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
b. Hace más de un mes pero menos de un año	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
c. Ha consumido hace más de un año	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
4. ¿ALGUNA VEZ HA PENSADO O LE HAN DICHO QUE CONSUME (CONSUMÍA MUCHO(A)...	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
55. ¿HA QUERIDO (O QUISIERA) DEJAR DE CONSUMIRLA....? *SI = 1*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NO = 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56. ¿ALGUNA VEZ INTENTÓ DEJAR DE CONSUMIRLA..... PERO NO PUDO? SI = *1*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NO = 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57. ¿HA ESTADO EN TRATAMIENTO PARA DEJAR DE CONSUMIRLA....?	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
ENTREVISTADOR(A): SI P53C ES POSITIVA PASE A P76. CONTINÚE SÓLO SI P58 ES POSITIVA EN LAS SUSTANCIAS RESPECTIVAS, SINO PASE A P69															
58. EN LOS ÚLTIMOS 12 MESES, HA USADO .....MAS DE UNA VEZ PARA ESTAR MUY ALEGRE *SI = 1* O "ENTONADO(A)", SENTIRSE MEJOR O MODIFICAR SU ESTADO DE ÁNIMO? *NO = 0*	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
59. ¿HA LLEGADO A TENER TAL NECESIDAD O DESEO DE CONSUMIR...., QUE NO PODÍA RESISTIR?	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
60. ¿HA LLEGADO A INTENTAR NO CONSUMIR..... PERO SIN CONSEGUIRLO O AL ESTAR USÁNDOLA NO HA PODIDO DETENERSE SINO HASTA HABERSE SENTIDO MUY ALEGRE, EUFÓRICO(A) O	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O

	DESCONECTADO(A)?															
61.	**a. ¿CUÁNDO USABA MENOS ..... O DEJABA DE USARLA, TENÍA MOLESTIAS COMO SENSACIÓN DE INQUIETUD, ANSIEDAD, IRRITABILIDAD O DEPRESIÓN, DOLORES, TEMBLORES, FIEBRE, DEBILIDAD, DIARREA, NÁUSEAS, SUDORACIÓN, ACELERACIÓN DEL CORAZÓN O DIFICULTADES PARA DORMIR?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
	b. ¿HA UTILIZADO ..... U OTRA SUSTANCIA PARA EVITAR ESTAS MOLESTIAS O PARA SENTIRSE MEJOR? (considere la P61 positivo en algunas de las dos preguntas)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
62.	**¿HA USADO MÁS CANTIDAD DE .....PARA CONSEGUIR LOS MISMOS EFECTOS QUE ANTES?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
63.	**¿HA REDUCIDO SUS ACTIVIDADES HABITUALES (DE TRABAJO, ESTUDIO, DEPORTE) POR CAUSA DE ESTA SUSTANCIA?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
64.	**¿SABE USTED SI .....PUEDE CAUSAR PROBLEMAS DE SALUD? SI ES NO PASE A P66** ***SI = 1*** ***NO = 0***	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**
65.	**¿HA CONTINUADO USANDO ..... INCLUSO A PESAR DE QUE LE PODÍA CAUSAR PROBLEMAS?** ***SI = 1*** ***NO = 0***	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**	**1** **0**
66.	**DURANTE LOS ÚLTIMOS DOCE MESES EL CONSUMO DE..... ¿LE HA CAUSADO PROBLEMAS DE SALUD COMO POR EJEMPLO INTOXICACIÓN POR SOBREDOSIS ACCIDENTAL, TOS PERSISTENTE, UNA CRISIS CONVULSIVA, UNA INFECCIÓN, UNA HEPATITIS O UNA HERIDA?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
67.	**DESDE QUE CONSUME...., ¿TIENE PROBLEMAS COMO NO INTERESARSE POR NADA, SENTIRSE TRISTE, DESCONFIAR DE OTROS O SENTIRSE PERSEGUIDO(A), O MÁS AÚN, TENER IDEAS EXTRAÑAS?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
68.	**COMO CONSECUENCIA DEL CONSUMO DE ....., ¿HA TENIDO PROBLEMAS EN EL TRABAJO , CON SU FAMILIA O AMIGOS?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**

8.2 English translation of the Spanish questions about coca leaf chewing dependence

INTERVIEWER: CIRCLE THE LETTERS CORRESPONDING TO THE POSITIVE RESPONSES **CARD 25**	TABACO (CIGARETTE, MAPACHO)	TRANQUILIZERS	SLEEPING PILLS	PILLS FOR HEADACHES	COUGH SYRUP	STIMULANTS (TO LOSE WEIGHT)	ÉXTASIS	MARIHUANA	COCAÍNE CHLORHYD.	PASTA BÁSICA (PBC)	HEROÍNE	HALLUCINOGENS (LSD) TRIP	COCA LEAF	INHALANTS	OTHERS
1. WHICH OS THESE SUBSTANCES HAVE YOU TRIED IN YOUR LIFETIME, EITHER FOR CURIOSITY, PLEASURE OR BECAUSE OF PEER PRESSURE (NOT FOR MEDICAL INDICATION)? INTERVIEWER: IF YOU HAVE NOT CODED ANY ANSWER, GO TO Q76	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
2. AT WHAT AGE DID YOU CONSUME FOR THE FIRST TIME?															
3. WHEN WAS THE LAST TIME YOU CONSUMED?															
a. In the last 30 days	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
b. More than one month but less than a year	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
c. More than one year	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
4. HAVE YOU EVER THOUGH, OR SOMEONE SAID TO YOU, THAT YOU CONSUME TOO MUCH?	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
55. HAVE YOU EVER WANTED (OR DO YOU WANT) TO STOP CONSUMING? *YES = 1*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NO = 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56. HAVE YOU EVER TRIED TO STOP CONSUMING BUT YOU COULDN'T? *YES = 1*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NO = 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57. HAVE YOU EVER BEEN IN TREATMENT TO STOP CONSUMING?	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
INTERVIEWER: IF Q53C IS POSITIVE PASS TO Q76. CONTINÚE ONLY IF Q58 IS POSITIVE IN THE RESPECTIVE SUBSTANCES, OTHERWISE PASS TO Q69															
58. IN THE LAST 2 MONTHS, HAVE YOU EVER USED……., MORE THAN ONE TIME, TO FEEL CHEERFUL OR STIMULATED, FEEL BETTER OR MODIFY YOUR MOOD? *YES = 1*	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
NO = 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
59. HAVE YOU EVER HAD THE NECESSITY TO CONSUME THAT YOU COULD NOT RESIST?	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
60. HAVE YOU EVER TRIED NOT TO CONSUME WITHOUT SUCCEEDING, OR WHEN USING IT, NOT BEING ABLE TO STOP UNTIL YOU'VE BEEN TOO HAPPY, CHEERFUL OR DISCONNECTED?	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
61. a. WHEN DID YOU USE LESS ..... OR YOU STOP USING IT; YOU HAD ANY DISCOMFORT, SUCH AS FEELING OF RESTLESSNESS, ANXIETY, IRRITABILITY OR DEPRESSION, PAIN, TREMORS, FEVER, WEAKNESS, DIAHRREA, NAUSEA, SWEATING, HEART BEATING TOO	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O

	FAST OR SLEEPING DIFFICULTIES? **b. HAVE YOU USED ..... OR ANOTHER SUBSTANCE TO AVOID THESE DISCOMFORT OR TOO FEEL BETTER? (consider P61 positive in either of the two questions)**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
62.	**HAVE YOU USED MORE .....TO GET THE SAME EFFECTS AS BEFORE?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
63.	**HAVE YOU REDUCED YOUR HABITUAL ACTIVITIES (WORK, STUDY, SPORTS) BECAUSE OF THIS SUBSTANCE?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
64.	**DO YOU KNOW IF..... CAN CAUSE HEALTH PROBLEMS? IF NO PASS TO Q66** ***YES = 1***	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	NO = 0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
65.	**HAVE YOU CONTINUED USING .....EVEN THOUGH IT CAN CAUSE YOU PROBLEMS?** ***SI = 1***	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
	NO = 0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
66.	**DURING THE LAST 12 MONTHS OF CONSUMING..... HAS IT CAUSED YOU HEALTH PROBLEMS, SUCH AS INTOXICATION BECAUSE OF ACCIDENTAL OVERDOSE, PERSISTENT COUGH, CONVULSIVE CRISIS, AN INFECTION, HEPATITIS OR A WOUND?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
67.	**SINCE YOU CONSUME...., DO YOU HAVE PROBLEMS SUCH AS NOT INTERESTING IN ANYTHING, FEEL SAD, DISTRUST OTHERS OR FEELING LIKE BEING PERSECUTED OR HAVING WEIRD THOUGHTS?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
68.	**AS A CONSEQUENCE OF CONSUMING ....., HAVE YOU HAD PROBLEMS AT WORK, WITH YOUR FAMILY OR FRIENDS?**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**

8.3 Multicultural quality of life index in Spanish

AHORA LE HARÉ ALGUNAS PREGUNTAS ACERCA DE SU CALIDAD DE VIDA

POR FAVOR OBSERVE LA TARJETA No. 17 Y CALIFIQUE DE 1 A 10 CADA ÁREA DE SU VIDA, SEGÚN CORRESPONDA

ENTREVISTADOR(A): MARQUE 99 SI NO RESPONDE

72. **BIENESTAR FÍSICO** **ES DECIR, SENTIRSE CON ENERGÍA, SIN DOLORES, NI PROBLEMAS FÍSICOS** ☐

73. **BIENESTAR PSICOLÓGICO O EMOCIONAL** **ES DECIR, SENTIRSE BIEN Y SATISFECHO(A) CONSIGO MISMO(A)** ☐

74. **AUTOCUIDADO Y FUNCIONAMIENTO INDEPENDIENTE** **ES DECIR, CUIDAR BIEN DE SU PERSONA (POR EJEMPLO PODER ALIMENTARSE Y ASEARSE SOLO(A)), TOMAR SUS PROPIAS DECISIONES** ☐

75. **FUNCIONAMIENTO OCUPACIONAL** **ES DECIR, SER CAPAZ DE REALIZAR UN TRABAJO REMUNERADO, ACTIVIDADES DE ESTUDIO Y/O ACTIVIDADES DEL HOGAR** ☐

76. **FUNCIONAMIENTO INTERPERSONAL** **ES DECIR, SER CAPAZ DE RESPONDER Y RELACIONARSE BIEN CON SU FAMILIA, AMIGOS Y GRUPOS** ☐

77. **APOYO SOCIAL – EMOCIONAL** **ES DECIR, TENER PERSONAS EN QUIENES CONFIAR Y QUE LE PROPORCIONEN AYUDA Y APOYO EMOCIONAL** ☐

78. **APOYO COMUNITARIO Y DE SERVICIOS** **ES DECIR CONTAR CON BUENOS VECINOS, DISPONER DE AYUDA ECONÓMICA O FINANCIERA Y DE OTROS SERVICIOS COMO POR EJEMPLO: AYUDARSE EN SITUACIONES DIFICILES CON POLLADAS, COLECTAS, ETC.** ☐

79. **PLENITUD PERSONAL** **ES DECIR, ESTE CUMPLIENDO CON LO QUE TE HAS PROPUESTO EN TU VIDA. SENTIDO DE REALIZACIÓN PERSONAL Y DE ESTAR CUMPLIENDO CON SUS METAS MÁS IMPORTANTES** ☐

80. **SATISFACCIÓN ESPIRITUAL** **ES DECIR, HABER DESARROLLADO UNA ACTITUD ESPIRITUAL HACIA LA VIDA MÁS ALLÁ DE LO MATERIAL Y ESTAR EN PAZ INTERIOR CONSIGO MISMO(A) Y CON LAS DEMÁS PERSONAS** ☐

81. **CALIDAD DE VIDA GLOBAL** **ES DECIR, SENTIRSE SATISFECHO(A), (CONTENTO) Y FELIZ CON SU VIDA EN GENERAL** ☐

8.4 English translation of the Peruvian Spanish Multicultural Quality of Life Index

NOW I WILL ASK YOU SOME QUESTIONS ABOUT YOUR QUALITY OF LIFE

PLEASE SEE CARD No. 17 AND SCORE FROM 1 TO 10 EACH AREA OF YOUR LIFE, AS IT BETTER FITS YOU

INTERVIEWER: MARK 99 IF HE/SHE DOES NOT RESPOND

72. PHYSICAL WELL-BEING FEELING ENERGETIC, WITHOUT PAIN AND PHYSICAL PROBLEMS ☐

73. PSYCHOLOGIC OR EMOTIONAL WELL-BEING FEELING GOOD AND COMFORTABLE WITH YOURSELF ☐

74. SELF-CARE AND INDEPENDENT FUNCTIONING CARE ABOUT YOURSELF (FOR EXAMPLE, BEING ABLE TO FEED AND CLEAN UP YOURSELF), MAKING YOUR OWN DECISIONS ☐

75. OCCUPATIONAL FUNCTIONING, ABLE TO CARRY OUT A PAID WORK, STUDY ACTIVITIES AND/OR HOME ACTIVITIES ☐

76. INTERPERSONAL FUNCTIONING, ABLE TO RESPOND AND RELATE WELL TO FAMILY, FRIENDS AND GROUPS ☐

77. SOCIAL-EMOTIONAL SUPPORT, AVAILABILITY OF PEOPLE YOU CAN TRUST AND WHO CAN OFFER HELP AND EMOTIONAL SUPPORT ☐

78. COMMUNITY AND SERVICES SUPPORT, HAVING GOOD NEIGHBORS THAT CAN HELP YOU, ACCESS TO ECONOMIC OR FINANCIAL SUPPORT, OR OTHER SERVICES ☐

79. PERSONAL FULFILLMENT, FULFILLING WITH WHAT YOU HAVE PROPOSED YOURSELF IN LIFE, FEELING OF PERSONAL REALIZATION AND FULFILLING YOUR MOST IMPORTANT GOALS. ☐

80. SPIRITUAL FULFILLMENT, HAVING A SPIRITUAL ATTITUDE TOWARDS LIFE BEYOND THE MATERIAL THINGS AND BEING IN INNER PEACE WITH YOURSELF AND OTHER PEOPLE ☐

81. GLOBAL PERCEPTION OF QUALITY OF LIFE, FEELING SATISFIED AND HAPPY WITH YOUR LIFE IN GENERAL ☐

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