ALTITUDE AND MOOD DISTURBANCES: PERU

By

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ABSTRACT

My research examines the association between the altitude of the participant's residence and the presence of an actively depressed mood, explicitly examining whether individuals experienced a depressed mood during the four weeks before an interview assessment during a population-based epidemiological survey. I explore this association at the community and individual levels. Additionally, I investigated whether using coca leaves might moderate the observed relationship between altitude and depressed mood.

In this dissertation, my epidemiological estimates are from nine yearly cross-sectional epidemiological studies conducted in Peru. These studies encompassed 15 regions in Peru and included community residents in areas situated at different altitudes above sea level.

The main results of my dissertation can be summarized as follows:

Study 1: At the community level (i.e., district level), those populations located at higher altitudes also had higher estimated prevalence proportions of depressed mood. These estimates are from a comparison of direct estimates of survey data analysis, using standardized estimates (i.e., with direct adjustment for age and sex), and finally using estimators corresponding to the Small Area Estimation methodology (i.e., Fay-Herriot model).

Study 2: Estimated at the individual level, an association between altitude and depressed mood was found and remained stable after logistic regression models adjusted for other covariates of interest (i.e., age, sex, mother tongue, marital status, and length of residency). By stratifying the analysis according to the length of stay in the current community, the findings suggested a causal possibility. The estimated effect of high altitude on a person's mood may be more pronounced after a minimum of two years of residing at such heights.

Study 3: In assessing coca-leaf consumption as a moderator of the altitude-depression association, I found an absence of evidence that coca-leaf product use in the month before the survey modifies the relationship between altitude and depressed mood. In fact, if anything, individuals who use coca might be more likely to experience active depressive moods, even at higher altitudes. However, the study's cross-sectional nature prevents the evaluation of the temporal aspect of this association.

As for limitations, the cross-sectional character of the data, with no specification of the age of onset of depressed mood relative to the time of residency at the altitude of the current dwelling, is a crucial limitation. Also, this study did not evaluate other community characteristics that might be covarying with the altitude-depression relationship.

This new evidence on the altitude-depression association draws attention to a need for more research along these lines. The research might gain increased importance during the 21st century intervals of global warming and associated climate change. Given that an estimated 500 million individuals reside in high-altitude regions around the globe, the association that links altitude and the occurrence of depressed mood deserves continuing attention in our epidemiological research projects.

I dedicate this dissertation to Manuel and Aus, my beloved parents.

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LIST OF ABBREVIATIONS

BC – Before Christ

DM – Depressed Mood

CLC – Coca Leaf Chewing

SaO2 – Arterial Oxygen Saturation

HAPE – High-altitude Pulmonary Edema

AMS – Acute Mountain Sickness

HACE – High-Altitude Cerebral Edema

CMS – Chronic Mountain Sickness

PH – Pulmonary Hypertension

MDE – Major Depressive Episode

MDD – Major Depressive Disorder

DSM – Diagnostic and Statistical Manual of Mental Disorders

ICD – International Classification of Diseases

ATP – Adenosine Triphosphate

REM – Rapid Eye Movement

PHQ-9 – Patient Health Questionnaire-9

ENDES – Demographic and Family Health Survey

US – United States

HADS – Hospital Anxiety and Depression Scale

WHO – World Health Organization

SAE – Small Area Estimation

IRB – Institutional Review Board

CEPLAN – Peruvian National Center for Strategic Planning

SRQ – Self Reporting Questionnaire

MINI – Mini-International Neuropsychiatric Interview

EBLUP – Empirical Best Linear Unbiased Prediction

FH – Fay-Herriot

SDG – Sustainable Development Goal

INEI – Peruvian National Institute of Statistics and Informatics

CEPLAN – Peruvian National Center for Strategic Planning

HDI – Human Development Index

TSL – Taylor Series Linearization

GoF – Goodness of fit statistics

GLM – Generalized Linear Models

RCT – Randomized Clinical Trials

DHS – Demographic and Health Surveys

DIF – Differential Item Functioning

MIMIC – Multiple Indicators Multiple Causes

CHAPTER 1: INTRODUCTION, SPECIFIC AIMS, AND HYPOTHESES

1.1 Introduction

Climate and the characteristics of the territory in which populations live have been believed to influence the characteristics and personalities of people since Hippocrates' time (5th century BC)(1). Among Peruvians, Hipólito Unanue, in 1806, reflected on the relationship between climate and mood, describing a melancholy mood as the dominant mood throughout the history of this country (2).

An interesting fact about altitude and mental health occurred in 1842 when Johann J. Guggenbühl hypothesized that intellectually disabled children could be treated and cured at higher altitudes. Guggenbühl opened the Abendberg School 1,200 meters above sea level for children with intellectual disabilities (3). (Other studies on altitude are mentioned later in this report.)

More recently, studies conducted in the 21st century suggest a potential association between the altitude of a residential area and the risk of experiencing depression (4,5) and suicide behavior (6–9). Most epidemiological studies on this topic have been conducted on populations in North America, specifically at elevations not exceeding 1500 meters above sea level.

The Peruvian Andes region includes several cities and towns that reach altitudes of nearly 5,000 meters. Consequently, the Peruvian Andes provide an opportunity to investigate the potential relationship between altitude and depression in a broader context.

Additionally, the Peruvian population traditionally consumes coca leaf, particularly in the Andean region (10,11). Chewing coca leaves allows the consumption of very small doses of fourteen different alkaloids, cocaine being the most significant (12). For this reason, it is postulated that coca leaves might modulate the mood of those who consume them (13–15).

In this context, the present research aims to analyze the relationship between altitude and the prevalence of depressed mood in the Peruvian population and evaluate the possible moderating effect of chewing coca leaf on this association. The secondary analysis of epidemiological survey databases from the "Honorio Delgado - Hideyo Noguchi" National Institute of Mental Health - "Noguchi Surveys" is conducted in this research. These 22 regional surveys include locations on the coast, highlands, and jungle. They were completed sequentially between 2003 and 2013. They were all implemented with a similar methodology that addresses sociodemographic variables, mental disorders, alcohol and other drug use (e.g., coca leaf consumption), intimate violence, and other mental health-related topics.

In this dissertation, after describing relevant concepts and background in Chapter 2, I will describe three studies. First, in Chapter 3, a study at the community level of analysis will analyze the relationship between districts' altitude and the prevalence proportion of depressed mood (DM). In Chapter 4, the second study addresses the relationship between altitude of residence and other relevant covariates with the presence of DM at the individual level of analysis. In Chapter 5, I will explore the possible moderator effect of coca-leaf consumption in the relationship between altitude and DM, also at the individual level of analysis. Chapter 6 is offered as a description of the conclusions of this dissertation and future research that is needed.

1.2 Objective

1. Based on data from Peru's "Noguchi Surveys," this dissertation research project aims to contribute to new epidemiological evidence on the association between the altitude of residence and depressed mood and the possible moderator effect of coca leaf use on that suggested relationship. I will examine the association between altitude and mood at the community (district) and individual levels.

1.3 Specific Aims

1. Via my novel analyses of data from Peru's "Noguchi Surveys," I will estimate active depression prevalence proportions (depression at the time of the interview assessment) with the community district level as the unit of analysis, with hypoxia theory-based expectations that the proportions would be greater in communities at higher altitudes and smaller in communities at lower altitudes (e.g., by tertiles). After initial cross-tabular analyses, I will adjust for age and sex with stratified analyses and direct standardization methods.
2. Extending this initial work with data from Peru's "Noguchi Surveys" and focusing on individuals as the unit of analysis data rather than district-level data, I will estimate the relationship between altitude in the community district and the occurrence of active depression (at the time of the interview). According to hypoxia theory, there might be a lower asymptote for the prevalence proportion (or odds), an upward-turning slope, and then an upper asymptote. I will estimate this altitude-depression locational association using a generalized linear model (e.g., with a logit link), considering a possible need for

more than one slope, and with these covariates: participant's sex, age, and mother tongue.

3. Via my novel analyses of individual-level data from Peru's “Noguchi Surveys,” I will study whether the association between altitude and depression might be subject to modification by a participant's recent history of coca leaf chewing (CLC). Evidence on this question can be addressed with a model fit index approach, comparing model fit statistics before and after adding altitude*CLC product-term(s) to the model and with consideration of slope estimates.

1.4 Hypotheses

Under Specific Aim number 1, the hypothesis can be stated in the null form:

Depressed mood prevalence proportions (i.e., feeling sadness “always” or “almost always” in the last four weeks, as indicated by subjective report at the time of the interview assessment) at the community district level do not vary significantly among communities at different altitude levels (i.e., by deciles), before or after direct standardization methods to adjust for age and sex.

The alternative hypothesis, with hypoxia theory-based expectations, is that the Depressed Mood prevalence proportion would be greater in communities at higher altitudes and lower in communities at lower altitudes.

Under Specific Aim number 2, the hypothesis can be stated in the null form:

Focusing on individual data, there is no association between altitude levels of residence and depressed mood at the time of the interview assessment and after adjusting for relevant covariates (i.e., participant's sex, age, and mother tongue). The odds of having a depressed mood do not vary across different altitude levels (i.e., tertiles).

The alternative hypothesis states that there is a relationship between altitude quantiles and depression (i.e., feels sad “always” or “almost always” in the last four weeks). According to hypoxia theory, the odds of having an active depressed mood could be higher at elevated altitudes of residence.

Under Specific Aim number 3, the hypothesis can be stated in the null form:

There is no evidence suggestive of a moderator effect of coca-leaf use (i.e., “last month's use") on the association between altitude and active depressed mood.

The alternative hypothesis states that the association between altitude and depressed mood might be subject to modification by a participant's recent history of coca leaf chewing (CLC).

CHAPTER 2: OVERVIEW OF CONCEPTS AND BACKGROUND

2.1 Introduction to Chapter Two

In this chapter's four parts, I provide a framework of relevant research and concepts regarding the relationship between altitude and health problems. First, the altitude research and health from Hippocrates to the present will be addressed, considering notions of hypobaric hypoxia. Then, concepts about affective psychopathology and depressed mood pertinent to this dissertation will be reviewed. The third section will address background research, especially the Hypoxia Theory regarding depressive symptoms. Then, background research of epidemiological studies on the altitude/depression association will be addressed.

2.2 Concepts

2.2.1 Altitude Research from Hippocrates to Nowadays

Diseases have been linked to climate, environmental conditions, and health since ancient times. A notable work on this subject was the book attributed to Hippocrates called "Of Airs, Waters, and Places" (5th century BC), considered by some scholars to be a collection of essay fragments and essays from multiple authors.

Whether one person or many, the Greek physician Hippocrates is regarded as the father of Western medicine, and his extensive writings on medicine and health date back to the 5th century BC. In "Of Airs, Waters, and Places," Hippocrates argues that the environment in which a person lives significantly impacts their health. He argued that a region's climate, water quality, and air quality could influence the prevalence of diseases and illnesses (16).

Although Hippocrates didn't mention altitude specifically, the Hippocratic essays introduced a mainstream theory of disease causation known as the "miasma theory" (17). In particular, it was observed that elevations higher than low-lying swamps and marshes might be conducive to a reduced disease occurrence. Consequently, populations living high above miasmas might be less susceptible to diseases associated with them.

Three centuries later, the influential physician Galen extended the work of Hippocrates. Galen's medical approach also conceived the environment as one of the most significant factors for health (18). These ideas and the miasma theory were carried forward by many medical authorities for thousands of years. Even in the 19th century, the miasma theory and other environmental factors were addressed by William Farr. In 1843, in his Fifth Annual Report, he described how rurality was related to health outcomes. With a numerical approach, he described how population density was associated with higher mortality. He extended further, proposing an equation calculating mortality rates according to population density (19).

Farr also endorsed the miasmatic theory of the disease. He found that cholera deaths were more frequent in places at low altitude levels. Contradictory evidence came from John Snow, who argued that water was the source of cholera. For many historians of epidemiology, Snow's work qualifies him as the European father of modern environmental epidemiology (20,21).

Another milestone in studying health-related environmental factors was the Great Smog of London in 1952. Thousands of deaths followed this combination of smoke and fog, finally leading to changes in the British legislation designed to reduce air contamination (20).

During the 20th century and early 21st century, the epidemiological study of the environment and its effects on health has become increasingly intensive. Central themes in this research include a growing interest in the harmful effects of living in large cities, changing lifestyles, and especially in the environmental changes caused by man (22).

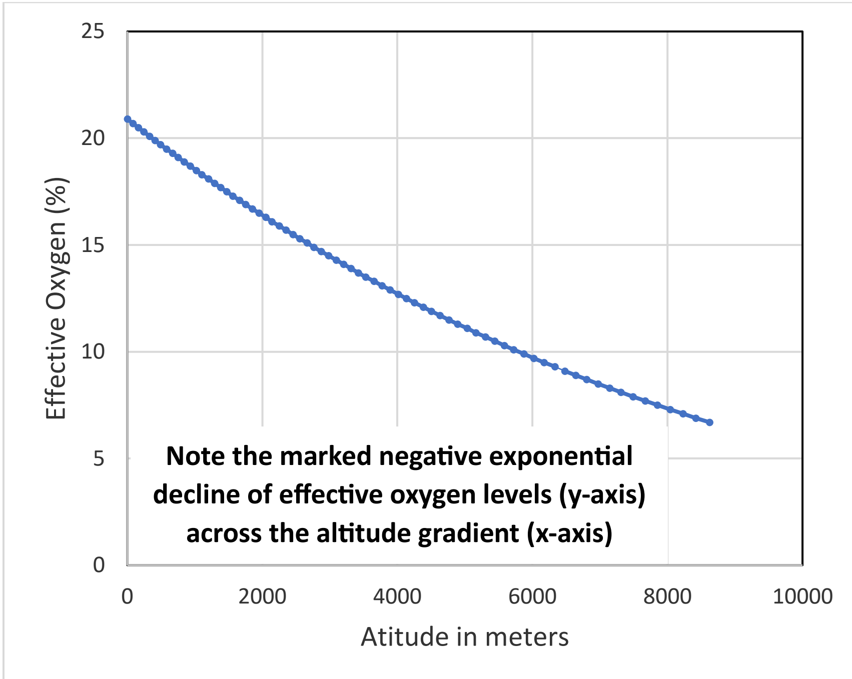
In this case, the urbanization process in the Peruvian Andes, related to developing new cities adjacent to mining areas, allowed clinicians from the early 20th century to conduct medical studies in high-altitude populations (23). Over the past century, much research has been undertaken regarding high-altitude medicine, particularly concerning the physiology of adaptation and the health problems that arise when this adaptation is lost. However, very little has been studied regarding the effects of high altitude on emotional and mental well-being.

To delve into current knowledge regarding the potential effects of high altitude on emotional health, first, I will elaborate on theoretical aspects of hypoxia at high altitudes (i.e., hypobaric hypoxia).

Altitude and hypobaric hypoxia

The oxygen levels in the breathing air are related to the atmospheric pressure. At sea level, the atmospheric pressure is known as one atmospheric pressure or 760 mmHg. At this level, the corresponding oxygen pressure is around 149 mmHg, about 21% of the total atmospheric composition. When the altitude level goes up, the corresponding value of the atmospheric pressure declines in an exponential function (i.e., hypobaric conditions). Accordingly, the partial oxygen pressure decreases exponentially due to the decrease in atmospheric pressure (see Figure 2.1) when altitude levels increase.

Figure 2.1. Effective oxygen level (expressed as a percentage) plotted against altitude (in meters)[1].



The levels of environmentally effective oxygen pressure are directly related to arterial oxygen saturation (SaO2), the percentage of oxygenated hemoglobin usually measured noninvasively by finger pulse oximetry. The values of SaO2 also have an inverse relation with the altitude level (24,25).

Hypobaric hypoxia is related to several health adaptative processes and health problems. Sometimes, the adaptative mechanisms do not appear adequately in people who ascend to high altitudes, and sometimes, the person who lives in the highlands loses their physiologic adaptative mechanisms. Both ways generate some health problems and diseases.

[1] Footnote to figure 2.1: this figure was made using raw data found in https://hypoxico.com/pages/altitude-to-oxygen-chart

Acute altitude sickness

For more than 100 years, an acute sickness related to ascending to high altitudes has been recognized by medical authorities. In 1927, Harold Crane described cases of patients with cough, blood in the sputum, and lung congestion in the Peruvian mining city of Cerro de Pasco. Interestingly, he described a quick recovery after descending to sea level (23). Some years later, Lizarraga described a series of cases with the term “acute soroche” and described these cases with the current medical condition known as pulmonary edema (26). Nowadays, this medical condition is called High-Altitude Pulmonary Edema (HAPE) and is one of the three more important acute diseases related to high-altitude exposure (27).

The other two acute illnesses related to climbing at high altitudes are acute mountain sickness (AMS) and high-altitude cerebral edema (HACE). AMS should be suspected when a recently ascended person has a headache and one or more of the following symptoms: nausea, vomiting, anorexia, insomnia, or dizziness. HACE is diagnosed when some neurologic signs appear in a person with AMS or HAPE, such as altered consciousness, ataxia, or hallucinations (28).

In general, these acute altitude sicknesses appear at elevations above 2,500 meters. However, cases have also been found at lower altitudes, but all three increase with higher altitudes (27). Cases are expected to occur from some hours to five days after the person arrives in high-altitude places.

A study in the Alps found 9% AMS incidence at 2850 m. At 3050 and 3650 m, AMS incidence increased to 13% and 34-57%, respectively. Around 12% of cases at 3600m were hospitalized for treatment (29). HAPE and HACE occur less frequently than AMS. In unacclimatized hikers at 4,243 meters, HAPE and HACE occurred in 2.5% and 1.8% of cases (29).

Chronic Mountain Sickness (CMS)

For adaptative purposes, chronic hypoxia causes the pulmonary arterial vessels to become more pressurized, counteracting the lower partial pressure of oxygen. This condition is called Pulmonary Hypertension (PH) and causes high lung blood pressure. These findings are correlated with the thickening of the pulmonary arterial muscular layers. Shortly after birth, pulmonary arterial musculature thickens differently in children born at sea level versus high altitudes (30,25).

Several other adaptative mechanisms are described among healthy highlanders (i.e., long-term residents of high-altitude dwellings). For example, more ventilation in the Highlands and higher hemoglobin concentrations are well-defined and recognized. Erythropoietin (i.e., the hormone that induces red blood cell production) levels also increase in native highlanders. Some evidence indicates a genetic variation due to evolutionary processes in different native highland populations (31).

Chronic mountain sickness (CMS) was described early in the 20th century by Carlos Monge Sr., and since then, it has been attributed to the loss of altitude adaptation capability (32). Hypoxia and polycythemia are increased in these cases, and pulmonary hypertension is more severe. It is a public health issue in mountainous regions around the world, including the Andes (30).

As adaptability declines, alveolar ventilation decreases, particularly at night. As a result, residents suffer from greater levels of hypoxia than usual. As a result of this lower oxygenation, erythropoietin increases, and polycythemia is exaggerated. Additionally, pulmonary hypertension increases, and in some cases, cardiac morphology (right ventricular hypertrophy) is altered. The most common symptoms include fatigue, sleep problems, headaches, dizziness, and mental fatigue. The treatment usually involves descending to lower altitudes or bleeding (30). According to Carlos Monge's studies, CMS disease increases with aging due to the progressive loss of the native's greater ventilatory capacity (33).

Studies that measure the prevalence of CMS in large populations are rare. I have found reports on a CMS prevalence of around 5% for the Andes, observed at altitudes between 3,600 and 3,800 meters (34,35). In Tibet, lower prevalence values have been found for poorly understood reasons (36).

Extensive research is being conducted on altitude's acute and chronic effects on the cardiovascular, respiratory, and renal systems. Neurological aspects, such as headache, sleep quality, and neurocognitive effects, have been the subject of increased research in recent decades. Also, genetic studies have shown differences between native highlanders and other populations regarding their adaptation to hypoxia. Explanations for the Tibetan and Andean population contrasts have included speculations about variations in evolutionary processes (31,37). Finally, as mentioned earlier in this chapter, some epidemiological evidence has emerged during the 21st century, suggesting that the altitude at which populations live may affect mood and suicidal behavior as a consequence of hypoxia, as described in later sections of this chapter.

2.2.2 Introductory Psychopathology of Affect (concepts of mood, depressed mood, and depressive disorder)

The Bible contains some of the earliest descriptions of depressed mood. In the Old Testament, Saul is despondent after God's rejection and losing battles against enemy armies. He eventually requests to be killed and ends up committing suicide (38).

In ancient Greece, the previously mentioned Hippocrates was the first to provide a clinical description of depression. In the Corpus Hippocraticum, the melancholic temperament is described as particularly prone to depressive episodes, especially during the autumn. This condition was attributed to an excess of black bile, one of the four fundamental elements of the human body. Hippocrates is credited with the following description: "Fear or sadness that lasts a long time means melancholia" (39).

Areteus of Cappadocia (1st century AD) defined melancholia in two dimensions: (a) as an emotional state characterized by anguish and (b) as an intellectual state characterized by a delusional conception. It was centuries later, in Bright's treatise on melancholy (1586), that he described melancholia as being "for the most part sad and fearful accompanied by distrust, doubt, diffidence, and despair"(40). Consistent with these ideas, throughout history, from the earliest medical texts to the present day, deep sadness and its variants, such as hopelessness, sorrow, and emptiness, have been mentioned as the central features of depression (39).

At present, we can understand “affectivity” as an integration of a set of states and tendencies that the individual experiences in a personal and immediate way with influences observed in behavioral manifestations, usually distributed in dual terms (joy-sadness, pleasure-pain). For psychopathologists, affectivity covers a large set of experiences that define people's emotional lives (41).

The American Psychological Association (APA) describes affectivity in these terms (42):

> *n.* the degree of a person's response or susceptibility to pleasure, pain, and other emotional stimuli. Evaluation of affectivity is an important component of a psychological examination; the therapist or clinician may look for evidence of such reactions as blunted affect, inappropriate affect, loss of affect, ambivalence, depersonalization, elation, depression, or anxiety. (Quotation from page 28, APA Dictionary of Psychology, 2015).

There are many ways in which affectivity manifests, but the most important ones are (41):

- Emotions: sudden, intense, and acute reactions related to the psychophysiological concept of reaction. There is an abundant somatic correlation with symptoms or signs that might last for a short time. Fear, sadness, anxiety, and anger are examples of emotions.
- Mood: a disposition or affective state **more stable and persistent than emotions**. Usually, it oscillates between happiness and sadness. It is also described as the sustained and continuous emotion that is subjectively experienced and can be observed by others. The most common mood states are those located on the joy-sadness axis, but mood can also be experienced as irritability, anger, or anxiety. In euthymia, the mood is considered to be in a normal state.

Depressed mood is one of the fundamental criteria for diagnosing depressive episodes (43,44). It is worthwhile to highlight the conceptual difference between mood and emotional states, which are more transitory. The mood is conceptualized as the subject's baseline affective state, established more slowly and progressively than emotions, and is more enduring and stable over time (41,45).

In this line, Bleuler described that emotional states tend to prolong into persistent moods, influencing the person's entire experience. However, the mood is not as dependent on experiences as on the disposition it generates (46).

Affect as a construct is broad and includes both emotions and moods. Within the Affect domain, emotions are defined as biobehavioral systems that present four components: 1) a subjective experience. 2) a physiological reaction. 3) an expressive component (e.g., facial expression), and 4) a behavioral response. These components occur as part of an intense and coordinated response that lasts for brief periods, usually seconds or minutes (47).

Mood also represents a subjective experience of oneself and has an evaluative quality of feeling either positively or negatively. However, mood does not necessarily generate emotional responses since mood does not exhibit the four emotional components mentioned. In emotions, for example, anger involves dramatic manifestations of the four components. In contrast, the experience of an irritable mood does not necessarily involve the other three components (e.g., the face does not necessarily express anger). While emotions are brief and intense, moods can be less dramatic and last longer (41).

Another distinction between emotions and moods is related to activations or triggers. Emotions can have identifiable triggers or events that activate a coordinated response. On the other hand, moods are generally present continuously and without a clear trigger or reference event. They can dissipate without clear intervention or environmental change. That's why a person can experience a depressed or dysphoric mood without knowing why. One reason for this is that moods are strongly influenced by various endogenous processes, such as circadian rhythms (47).

For affectivity research, evaluating mood states rather than emotions is advisable. However, emotions and moods are not mutually exclusive. Similar processes and components can affect both. The emotions we feel can influence our mood, and moods can alter our likelihood of experiencing specific emotions (47).

Depressed mood and depressive episode

A Depressed Mood (DM) and a Major Depressive Episode (MDE) are related. In short, a depressed mood is a core symptom or sign commonly experienced during a Major Depressive Episode. The mood state might not be conveyed by a person's own subjective description of psychological well-being. In some instances, particularly noteworthy in younger children before the Piagetian stages of abstract thinking about one's self, and in later life, there can be 'depression equivalents' more readily seen as signs of disturbed behavior and maladaptation. In children, the equivalents might include acting out, striking others, or striking oneself. In older adults, the equivalents might manifest in irritability or visible shifts in behavioral patterns away from activities that usually have functioned as reinforcers for the individual.

A depressed mood refers to a sustained sadness or hopelessness (44). In general, the subjective feeling of sadness is present most of the time. It is a symptom of MDE but can also be a symptom of other mental health disorders, such as adaptative disorders or dysthymia.

For most of the past 40-50 years, the concept of a depressive episode has referred to a period of two or more weeks where a person experiences a combination of symptoms or signs of depression (or depression equivalents), such as a depressed mood (DM), feelings of worthlessness or guilt, fatigue, changes in appetite and sleep patterns, difficulty concentrating, and in severe cases, thoughts of self-harm or suicide (43,44). Since 1980, the American Psychiatric Association has defined a depressive episode as a necessary requirement to diagnose Major Depressive Disorder (MDD), a type of depression. Table 2.1 shows the full criteria for depressive episodes in DSM and ICD; note that depressed mood is the most important of the core symptoms in both diagnostic systems.

Table 2.1. A Diagnosable Depression as Defined in the Diagnostic and Statistical Manual (5th Edition) of the American Psychiatric Association and the International Classification of Diseases of the World Health Organization Glossary of Mental Disorders (10th edition)[2].

DSM-5 At least five symptoms in total for diagnosis	**ICD-10** At least four symptoms in total for diagnosis
• Depressed mood† • Markedly diminished interest or pleasure† • Significant weight loss or weight gain • Insomnia or hypersomnia • Psychomotor agitation or retardation • Fatigue or loss of energy • Feelings of worthlessness or excessive or inappropriate guilt • Diminished ability to think or concentrate, or indecisiveness. • Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt	• Depressed mood‡ • Loss of interest and enjoyment‡ • Reduced energy and diminished activity‡ • Reduced concentration and attention • Reduced self-esteem and self-confidence • Ideas of guilt and unworthiness • Bleak and pessimistic views of the future • Ideas or acts of self-harm or suicide. • Disturbed sleep • Diminished appetite
† Core symptoms of the DSM-5 criteria: at least one of these two must be present for diagnosis. ‡ Core symptoms of the ICD-10 criteria: at least two of these three must be present for diagnosis.	

2.3 Background

2.3.1 The Hypoxia Theory of mood changes

Multiple pathways might link hypoxia to mood disturbances. First, reduced serotonin function in neurotransmission pathways has been described. Also, inflammatory changes and reduced brain bioenergetics have been found. Finally, several sleep changes have been detected with hypobaric hypoxia and could have a role in the emergence of mood disturbances.

[2] Footnote to Table 2.1: the original of this table was found in Park et. al., 2020 (48), which I then adapted by myself for this doctoral dissertation.

Studies with animal models exposed to chronic hypoxic environments found a significant decrease in serotonin synthesis due to reduced tryptophan hydroxylase activity (49). Also, it has been reported that the effects on mood secondary to exposure to high altitude may be more significant in women due to differences in tryptophan and serotonin metabolism (50).

On the other hand, it has been postulated that hypobaric hypoxia causes inflammatory changes in cells related to depressive symptoms. Specifically, using animal models, it has been found that after exposure to moderate altitudes (i.e., 1,600 m), biological signs of cellular inflammation appear, such as 1) an increased granulocyte/lymphocyte ratio; 2) an increased number of circulating monocytes; and 3) an increased monocyte/lymphocyte ratio. The animal model found that this cellular inflammation was correlated with signs of depression (51).

These animal models have also shown that chronic exposure to hypoxia generates inflammatory changes that could cause structural damage at the cellular level in the hippocampus (52). It has also been reported that these harmful effects are more intense in males and suggest that sex hormones are involved in the susceptibility to present brain damage due to chronic exposure to hypoxia (52).

It was proposed that brain bioenergetics is also involved in the emergence of mood disturbances among people exposed to hypobaric hypoxia (8). The production of adenosine triphosphate (ATP) in hypoxic environments is diminished due to changes in the creatine kinase reaction (53). Deficiencies in ATP production and creatine kinase function are involved in neuronal dysfunction, which can correlate with mood disturbances (54).

Sleep experimental studies with voluntary participants have investigated the effects of acute, subacute, and chronic hypoxia. For example, it has been clearly described that changes in sleep quality and mood state appear very soon under artificial hypoxic conditions. Total sleep time, sleep quality, slow-wave sleep, and REM sleep are reduced (55). Considering that sleep quality and quantity are associated with the development of anxious and depressive symptoms, it would be expected that changes in mood state could also be observed rapidly from the early years of residency in the highlands. It has also been found that these sleep disturbances increase at higher altitudes (56).

A longitudinal study of one year on a group of volunteers found that ascending to high altitudes caused mood changes even within the first year. These changes were related to the magnitude of altitude. It was also found that these changes were mediated by decreased sleep quality (57).

Scientific literature finds a significant association between sleep problems induced by altitude and the emergence of cognitive and anxiety problems, which may later be associated with an increased occurrence of mood symptoms such as anxiety and depression. It has been identified that further research is needed on altitude-associated mood changes (58).

Studies on the negative cognitive effects at high altitudes in lowlanders who ascend to greater heights have found a variation over residency time. An oscillating evolution has been described; in the beginning, there is a marked deterioration of some neuropsychological functions, then a period of acclimatization follows, and finally, in some cases, a deterioration can be seen again (59).

However, there are doubts about whether the findings obtained in individuals who ascend in altitude can be applied to long-term residents who have lived in highlands for several generations (59).

2.3.2 Recent Research Pertinent to the Hypoxia Theory and mood disturbances

The most relevant literature studying the relationship between altitude and mood disturbances started in this century. First, several studies using aggregated data in the United States found more significant suicide proportions among populations at higher altitudes (60,61,6,62). Then, this association was also found in other countries (63,64).

After the reported suicide-altitude relationship, Delmastro 2011 found a positive correlation between depression prevalence proportion in the last year and the altitude of residence at the U.S.A. substate level (5). Then, some studies focusing on the individual level of analysis found the same positive association between depression and hypobaric hypoxia. Kious, in a cohort study and using the Patient Health Questionnaire-9 (PHQ-9), found that changing the altitude of residence to a higher altitude was associated with increased scores of depression, anxiety, and suicidality (4).

Outside of the United States, three large epidemiological studies examined the relationship between altitude and depression with the inclusion of especially high-altitude communities. Most of these prior studies were conducted and then published during the years after I originally proposed the focus of my dissertation research project. These three studies were conducted, one in Nepal (65) and two in Peru, both published in 2022 (66,67). The case definitions for these prior studies are different, but all found an association between altitude and depressive symptoms.

The study in Nepal was nationwide and tried to estimate anxiety and depression prevalence across the country. The Hospital Anxiety and Depression Scale (HADS) included seven questions about depressive symptoms during the last week before the survey. After using score thresholds for defining cases, the multiple logistic regression modeling found that people living above 2,000 meters have a higher risk for depression (65).

The two studies in Peru used data from the Demographic and Family Health Survey (ENDES in Spanish), which included PHQ-9 to evaluate depressive symptoms during the last two weeks before the assessment. These two studies defined different outcome variables. One considered the score of depressive symptoms, as elicited in a multi-item scale, and implemented Gamma and Quantile regression models because of scores overdispersion (66), and the other study imposed a threshold cut point on that summary score and analyzed using Poisson regressions (67). Both studies found that depressive symptoms are associated with altitude, the first using altitude as a continuous variable and the second using three categories of altitude levels.

CHAPTER 3: ESTIMATING THE ALTITUDE-DEPRESSED MOOD ASSOCIATION AT THE DISTRICT LEVEL

3.1 Introduction

This study examines whether estimated prevalence proportions of depressed mood (DM) at the community district level might be greater in communities at higher altitudes across 223 districts from 33 provinces in Peru. For this purpose, nine epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health - "Noguchi Surveys" have been consolidated.

According to the World Health Organization (WHO), depression is the primary cause of the burden of disease globally in terms of nonfatal health outcomes. Also, it is the primary cause of suicide (68). Around 500 million people live in the highlands (69), and millions travel to the highland regions yearly. Confirming the Altitude-Depression relationship is crucial for public health reasons and raising awareness of the need for further research into the underlying mechanisms.

The most prominent prior contributions to the study of the relationship between altitude and depression or suicide have been published during the last 20 years. During the early 2000s, reports were published regarding the correlation between suicide rates and high altitude (6,9,60,70). The study of DelMastro in 2011 was the first large epidemiological study on altitude and depression. It found a positive correlation between depression prevalence proportion in the previous year of the interview and the altitude of residence at the substate level in the US (5). Later, some studies focused on the individual level of analysis and found similar associations between altitude and depressive symptoms (4,65,66,71,72).

The Small Area Estimation (SAE) approach has been described since 1979 (73). It is used to obtain more precise population estimates for small-scale areas than those initially projected in the original studies (74). SAE methods achieve this by combining original data analysis with auxiliary data from other sources (e.g., government data). This auxiliary data addresses related variables but with more precise estimates. In this study, I will use the SAE Fay-Herriot model to calculate more accurate estimates of DM prevalence at the district level.

For estimating DM prevalence proportions at the community district level variations across communities at higher and lower altitudes, I used the direct weighted estimates of survey data analysis, and the standardized estimates (i.e., with direct adjustment for age and sex). Finally, the estimators from the SAE methodology (i.e., Fay-Herriot model) are presented.

3.2 Materials and Methods

This research includes cross-sectional analyses of nine yearly epidemiological studies in Peru. These surveys were completed sequentially between 2003 and 2013 by the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health of Peru. They included 15 regions of Peru, covering a broad range of altitudes above sea level. Each year, the surveys were implemented with almost similar research approaches and questionnaires, addressing sociodemographic variables, mental health problems, alcohol and other drug use (including coca leaf consumption), and other covariates.

Population and Districts Under Study in Peru, 2003-2013

These household surveys are designed to represent four target groups of non-institutionalized community residents of Peru: adolescents, adults (i.e.,18 years or older, including elders), elderly individuals, and married or cohabitant women. (75). In this research, I tapped data only from the adult population modules. Only household residents were included. The Peruvian National Institute of Statistics and Informatics provided the census clusters for the sampling procedures based on the most recent census survey of the Peruvian population available. It is important to note that the population under study was based on the residence of the Peruvian community members (i.e., where they resided).

Each yearly survey examined one or more cities or rural areas. In total, 22 rural or urban areas (i.e., 22 strata) and 223 districts were surveyed (see Tables 1 and 2). The total aggregated target population of adults considered for the survey sampling procedures along these surveys was more than 9.8 million people.

Description of the Sampling Approach and Aggregate Sample Size, Before Analysis Weights

The sample size calculation for each yearly survey was made using the equation recommended by Lohr (76). It was considered a 95% confidence interval for the estimations and different expected prevalence percentages of mental disorders for each survey. For example, for the 2008 survey, it was considered 30%, and for 2012, it was set at 15% based on previous studies (77,78).

Researchers from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health used the same sample selection process for each surveyed area (i.e., urban or rural). It implemented a multistage random sampling process, carried out in three stages. Firstly, a group of census clusters was randomly selected (i.e., primary sampling units) within each stratum (i.e., the city or rural surveyed area). Usually, each census cluster includes around 80 dwelling units. Secondly, dwelling units within each census cluster were randomly selected. Finally, individuals from each target population within each dwelling unit were randomly chosen using the Kish table approach. To accomplish this, the field staff member gathered a roster of dwelling unit residents (75,77). Usually, there is more than one census cluster in each district, but the district level was not necessarily considered for the staging of the sampling.

Multiple institute reports have provided further details about the survey methods and research approaches employed by the “Noguchi” project. One convenient and easily accessible source of information is Dr. Victor Cruz's Master of Science thesis, which is available as an online document from Michigan State University (MSU) (77).

Table 3.1. "Noguchi Surveys"[1] and regions across years. Population characteristics. Peru, 2003-2013.

Region	Year									Total
	2003	2004	2006	2007	2008	2009	2010	2012	2013	
Ancash	Urban Highland		Urban Coast		Rural Highland					3626
Apurimac							Urban Highland			1746
Arequipa			Urban Highland							1332
Ayacucho	Urban Highland				Rural Highland					2324
Cajamarca	Urban Highland				Rural Highland					2310
Huancavelica							Urban Highland			1716
Huanuco									Urban Highland	1496
Ica			Urban Coast							1355
La Libertad			Urban Coast							1222
Lima				Rural Highland				Metropolitan Coast		6981
Loreto		Urban Rain Forest				Rural Rain Forest				2486
Pasco									Urban Highland	1469
Piura			Urban Coast							1312
San Martin		Urban Rain Forest								1340
Ucayali		Urban Rain Forest				Rural Rain Forest				2415
Total	3895	3910	6555	2536	3031	2331	3462	4445	2965	33130

1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado-Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 3.2. Survey areas, population, and samples.

Survey Areas (Strata)	Year	Number of PSUs[1]	Total population considered	Sample
Ancash Urban Highland	2003	117	53080	1319
Ayacucho Urban Highland	2003	117	76556	1301
Cajamarca Urban Highland	2003	117	101277	1275
Loreto Urban Rain Forest	2004	117	241022	1306
San Martin Urban Rain Forest	2004	117	67381	1340
Ucayali Urban Rain Forest	2004	117	129419	1264
Ancash Urban Coast (Chimbote)	2006	117	401417	1334
Arequipa Urban Highland	2006	117	802309	1332
Ica Urban Coast	2006	117	223302	1355
La Libertad Urban Coast (Trujillo)	2006	117	916716	1222
Piura Urban Coast	2006	117	409824	1312
Lima Rural Highland	2007	131	50708	2536
Ancash Rural Highland	2008	70	49696	973
Ayacucho Rural Highland	2008	70	54971	1023
Cajamarca Rural Highland	2008	70	137479	1035
Loreto Rural Rain Forest	2009	40	12648	1180
Ucayali Rural Rain Forest	2009	40	13884	1151
Apurimac Urban Highland	2010	99	33442	1746
Huancavelica Urban Highland	2010	75	25851	1716
Metrop. Lima Coast	2012	700	5899105	4445
Huanuco Urban Highland	2013	172	104166	1496
Pasco Urban Highland	2013	125	39615	1469
Total	9	2879	9843866	33130

1 PSU: primary sampling units

The participation levels for the Peruvian National Institute of Mental Health "Honorio Delgado - Hideyo Noguchi" surveys are described for each of the yearly surveys in Table 3.3. These values varied from 81.7% to 98.4%, most larger than 90%. The number of participants in each yearly survey ranged from 2,331 to 6,555. The total resulting sample consists of 33,130 participants.

Table 3.3. Surveys' response rates.

	Planned households	Rejection	Absence	Response rate (%)	Final sample	Percent
2003 Ancash Ayacucho Cajamarca	4212	74	69	96.3	3895	11.76
2004 Loreto, San Martin Ucayali	5616	42	80	97.8	3910	11.80
2006 Ancash Arequipa Ica La Libertad Piura	9360	108	39	98.4	6555	19.79
	Planned adults	Rejection	Absence /other	Response rate (%)	Final sample	Percent
2007 (Lima Rural)	2628	0.5%	3%	96.5	2536	7.65
2008 (Rural) Ancash Ayacucho Cajamarca	3196	1.4%	3.7%	94.8	3031	9.15
2009 (Rural) Loreto Ucayali	2400	-	-	97.1	2331	7.04
2010					3462	10.45
Apurimac	1824	2.6%	1.6%	95.7	1746	
Huancavelica	1807	3.0%	2.0%	95.0	1716	
2012 (Lima Callao)	5332	10.4%	6.2%	83.4	4445	13.42
2013					2965	8.95
Huánuco	1786	8.9%	7.3%	83.8	1496	
Pasco	1797	13.2%	5.1%	81.7	1469	
Total sample					33130	100.00

Some districts were selected for sampling in two different years; in these cases, a decision was made considering the sample size (i.e., participants from the year with the smallest number were excluded) and the year of sampling (i.e., if equal sample sizes, participants from the last year were excluded). In addition, 49 participants had missing responses to key study variables and were excluded from the estimations. For these reasons, the effective sample size for this research is 31729 (95.8% of the total initial sample). The unweighted numbers of survey participants, district by district, are reported in the first Table of this paper's Results section.

IRB Considerations

The Peruvian National Institute of Mental Health Institutional Review Board for Protection of Human Subjects in Research reviewed and approved all the protocols utilized for the "Noguchi Surveys." Before beginning the interviews, every participant in the study provided their signature on an informed consent form. Participation in the study was entirely voluntary, and participants had the right to decline to answer any questions they found uncomfortable or terminate the interview at any point.

In addition, the protocol for this research was reviewed by the Michigan State University Institutional Review Board for the Protection of Human Subjects in Research (IRB). As this research study was carried out with de-identified data, the IRB considered that this research does not involve human subjects as defined by the US National Institutes of Health.

Instruments and measurement

The survey questionnaire for adults has five sections (i.e., sociodemographic, general adult health, clinical syndromes part A, clinical syndromes part B, and access to health services) and contains 233 questions. Appendix A of this dissertation includes an English translation of the standardized survey items used in this study to assess each participant's mood state during the last four weeks. Questions were applied to participants in their native “mother tongue.” The altitude of households was identified at the district level and retrieved from the Peruvian National Center for Strategic Planning (CEPLAN) (79).

Actively depressed mood (i.e., depressed mood during the last four weeks at the moment of the survey interview) was assessed in two different parts of the questionnaires. The first included a Likert question directly asking about the mood of the participant: “How often do you feel Sad?” (i.e., Question 6, from the “prevalent mood states” part of the questionnaire). This question was applied to all participants.

The second question about depressed mood was included as one of the items for the screening tool SRQ-17 (80). This abbreviated version of the SRQ-20 has 17 questions compared to the original version. These questions were applied to all participants inquiring about depressive and anxiety symptoms in the last four weeks. One of these questions about the previous four weeks was: “Have you felt sad frequently?” (i.e., Question 26). In addition to frequent sadness during the last four weeks, the SRQ screening tool asks about physical symptoms, appetite, anxiety, and other than depressed mood questions.

Actively depressed mood was finally identified in persons who recognized feeling sadness “always” or “almost always” in question #6 and also answered “Yes” to the question “Have you felt sad frequently in the last four weeks?”. The concept of mood in the psychopathology of affect is conceptualized as the subject’s baseline affective state and is more enduring and stable over time (41,45). For DSM 5, a depressed mood refers to a “sustained feeling of sadness or hopelessness” (44). Thus, the subjective feeling of sadness is present most of the time. It is a symptom of Major Depressive Disorder (MDD) but can also be a symptom of other mental health disorders.

The Mini-International Neuropsychiatric Interview - MINI (81), which includes questions that match the criteria of ICD-10 for MDD, was also included in the surveys. However, in MINI, the question about depressed mood was applied over the participant's lifetime.

Prevalence proportions of Depressed Mood (DM) at the district level

Prevalence proportions of DM at the district level (i.e., 223 districts) with the aggregated data were estimated in three different ways. First, I obtained survey proportions estimates using Stata © commands, considering the respective strata, clusters, and weights. These are called the "direct estimates". Then, I calculated the standardized prevalence proportions using the direct standardization method, which was adjusted for sex and age categories. Three age categories were considered: 18-44, 45-64, and >=65 years. These categories are meaningful regarding depression because of the possible relationship between depressive symptoms and postmenopausal ages in women. The reference population for the standardization was the Peruvian census from 2005 (accessible from: censos.inei.gob.pe/Censos2005/redatam/) and their openly available numbers. Finally, I utilized the Small Area Estimation framework to compute the Empirical Best Linear Unbiased Prediction (EBLUP) estimators based on the Fay-Herriot (FH) model (73,82).

The Fay-Herriot (FH) model

The FH model was introduced in 1979 (73) and opened the development of the Small Area Estimation (SAE) methodologies. The general objective of these models is to obtain better estimates from survey data, which was not initially designed for having reliable estimates for more small areas or "domains." Nowadays, the United Nations stimulates the development of SAE models in the Sustainable Development Goal (SDG) agenda (83).

The FH is a two-part model and uses auxiliary data of the small areas or domains. These auxiliary data come from a different data source. The Fay-Herriot model is designed to increase accuracy by using direct estimates from the survey data and the auxiliary data obtained from any official registers or administrative sources at the domain level. This auxiliary data should be measured with greater accuracy and is associated with the outcome of interest, so it contains additional information that is utilized to correct the direct estimates. The FH model uses this additional information to forecast the outcome of interest with a linear regression model.

The FH model is described for "m" small areas (84):

The Sampling Model:

$\hat{Y}_i = \theta_i + e_i \qquad i = 1, 2, \ldots, m$

The Linking Model:

$\theta_i = x'_i\beta + u_i$

Where : θ_i is the population characteristic of interest for the area *i.*
$\hat{Y}_i$ is the direct survey estimate of θ_i.
e_i is the sampling error in $\hat{Y}_i$, generally assumed to be $N(0, v_i)$ with v_i known.
u_i is the area *i* random effect, usually assumed to be *i.i.d* $N(0, \sigma_u^2)$ and independent of the e_i.
"Synthetic estimator" $x'_i\beta$.

The best linear predictor is a linear combination of the "direct estimator" and the "synthetic estimator":

The best linear predictor of θ_i (β and σ_u^2 known):

$$\hat{\theta}_i = (1 - \gamma_i)\hat{Y}_i + \gamma_i x'_i\beta$$

Where:

$$\gamma_i = \frac{v_i}{v_i + \sigma_u^2}$$

The FH models for obtaining EBLUPs estimates were executed in Stata© with the fayherriot command (85). As described by the Stata command authors, the "arcsine of the estimate square root" transformation is a good option when using a proportion variable (i.e., in our case, prevalence proportion) direct estimates. Then, the estimates were back-transformed using the arcsine square root transformation to ensure that EBLUPs are restricted to the interval zero to one (see footnote)[3]. When standard errors of the direct estimates were invalid (i.e., 40 districts, 13 without cases, and 27 with infinitesimal values), they were inputted with the minimum value obtained in the other domains. On the other hand, the FH model without including these 40 districts was also computed for comparison reasons.

The auxiliary data used three domain-level variables with a more reliable estimation provided by the Peruvian National Institute of Statistics and Informatics (INEI) and Peruvian National Center for Strategic Planning (CEPLAN). The other variables for calculating the synthetic estimator were population density, poverty rates, and human development index (HDI). HDI is built based on three indicators: life expectancy at birth, the proportion of the population over 18 with secondary education, and per capita family income. Values of the HDI close to 1 will indicate a better position of human development in the territory.

After obtaining the three estimators for the prevalence proportion of depressed mood in the districts (i.e., direct weighted estimates, standardized estimates adjusting for age and sex, and EBLUPs), I used linear regressions models to examine the relationship between altitude and depressed mood after transforming the estimates with the "arcsine of the estimate square root" function. Then, models were compared using these three different estimates. The relationship between altitude and DM prevalence proportions was tested using altitude as a

[3] asin(x)= the radian value of the arcsine of x. arcsine of x is the angle which their sine is x.

continuous variable and then as categorical with terciles and deciles of altitude. Finally, the prediction command was used to evaluate how the predicted values of the prevalence proportion of DM go along altitude levels.

3.3 Results

Table 3.4 shows the names of all 223 sampled districts sorted by altitude (in meters, m) above sea level. Column four shows the year of the survey. The fifth column shows the unweighted size of the "Noguchi Survey" sample in that district that year, and the last column indicates the number of people with depressed mood (DM).

The methods section described that if a district was selected for sampling in two different years, a decision was made considering the sample size and the year of the study. The estimates in this project, based on samples, are either for the initial year the district was sampled or for the most significant sample size obtained for that district, without considering the weights of the samples.

The analysis-weighted district population sizes are reported in Table 3.10 (Appendix B). Also, the weighted proportions for depressed mood (DM) and the results from direct standardization methods for adjusting for sex and age categories (i.e., 18-44, 45-64, >=65 years). Finally, in Table 3.10, we can also see the results from the Fay Herriot approach for calculating the called empirical best linear unbiased prediction (EBLUP), which incorporates information from the survey and auxiliary data (i.e., population density, poverty rates, and human development index for each district).

Table 3.4. Districts, samples, and cases.

N°	District	Altitude (m)	Year	Total sample	Depressed mood
1	Lurin	12	2012	33	6
2	Bellavista	13	2012	34	1
3	Ancon	14	2012	21	3
4	Victor Larco Herrera	24	2006	93	9
5	Callao	27	2012	225	12
6	La Punta	29	2012	5	0
7	Coishco	31	2006	56	4
8	Castilla	35	2006	457	55
9	La Perla	37	2012	46	1
10	Nuevo Chimbote	40	2006	477	73
11	Ventanilla	43	2012	201	10
12	Chimbote	52	2006	801	97
13	Piura	57	2006	854	109
14	Los Olivos	67	2012	112	5
15	Chorrillos	68	2012	185	11
16	Pachacamac	68	2012	45	4
17	Santa Rosa	72	2012	5	1
18	Trujillo	74	2006	508	54
19	Carmen de la Legua Re	82	2012	25	2
20	San Miguel	84	2012	49	1
21	Magdalena del Mar	90	2012	33	2
22	Magdalena Vieja	90	2012	26	1
23	El Porvenir	92	2006	255	28
24	Florencia de Mora	92	2006	60	5
25	Barranco	97	2012	28	1
26	Mazan	106	2009	146	13
27	Comas	107	2012	160	5
28	Santiago de Surco	107	2012	156	3
29	Iquitos	107	2004	668	73
30	Independencia Lima	111	2012	60	8
31	Belen	116	2004	178	21
32	San Juan Bautista Maynas	120	2009	413	43
33	Punchana	124	2004	220	19
34	Miraflores Lima	125	2012	55	6
35	Surquillo	125	2012	33	1
36	Nauta	127	2009	234	21
37	Yarinacocha	131	2004	233	29
38	San Juan de Miraflore	133	2012	197	9
39	La Esperanza	137	2006	306	44

Table 3.4 (cont'd)

40	San Martin de Porres	138	2012	198	12
41	Jesus Maria	142	2012	20	0
42	La Victoria	142	2012	85	4
43	Lince	150	2012	32	1
44	Masisea	150	2009	107	9
45	Breña	153	2012	44	0
46	Rimac	153	2012	75	4
47	Lima	162	2012	124	8
48	Calleria	162	2004	1028	110
49	San Borja	170	2012	21	1
50	Curimana	181	2009	86	6
51	Nueva Requena	183	2009	29	2
52	Puente Piedra	187	2012	97	12
53	San Isidro	195	2012	37	1
54	El Agustino	200	2012	86	7
55	Campoverde	203	2009	204	24
56	Villa El Salvador	204	2012	235	25
57	Villa Maria del Triun	210	2012	196	26
58	San Luis	214	2012	21	0
59	San Juan de Luriganch	222	2012	596	48
60	Irazola	228	2009	235	24
61	Carabayllo	238	2012	77	11
62	La Molina	262	2012	61	4
63	Padre Abad	275	2009	203	8
64	Santa Anita	285	2012	131	15
65	Coayllo	285	2007	41	2
66	Cieneguilla	287	2012	9	0
67	Morales	290	2004	249	29
68	Tarapoto	342	2004	877	83
69	Ate	378	2012	386	20
70	La Banda de Shilcayo	418	2004	212	14
71	Ica	432	2006	849	96
72	La Tinguina	463	2006	189	30
73	Parcona	472	2006	317	46
74	Llochegua	540	2008	62	11
75	Sivia	561	2008	46	7
76	Chaclacayo	685	2012	26	3
77	Zuniga	827	2007	40	3
78	Lurigancho	879	2012	142	14
79	Santa Rosa de Quives	936	2007	51	6

Table 3.4 (cont’d)

80	Huanchay	1067	2008	30	5
81	Catahuasi	1203	2007	64	8
82	Pariacoto	1264	2008	29	3
83	Magdalena	1298	2008	16	1
84	Antioquia	1573	2007	39	4
85	San Bartolome	1644	2007	63	8
86	Huanuco	1921	2013	729	38
87	Amarilis	1950	2013	529	39
88	Putinza	1985	2007	25	2
89	Pillco Marca	1996	2013	235	16
90	Surco	2049	2007	54	11
91	San Mateo de Otao	2084	2007	37	3
92	Ambar	2084	2007	55	7
93	Cochabamba	2135	2008	16	1
94	Chumuch	2202	2008	15	2
95	Tiabaya	2218	2006	23	5
96	Asuncion	2254	2008	30	5
97	Sachaca	2300	2006	35	7
98	Jacobo Hunter	2309	2006	69	13
99	San Juan	2336	2008	15	2
100	Socabaya	2352	2006	119	14
101	Cortegana	2352	2008	14	2
102	Jose Luis Bustamante	2389	2006	138	11
103	Yanahuara	2402	2006	34	2
104	Arequipa	2429	2006	124	6
105	Cerro Colorado	2441	2006	145	27
106	Miraflores Arequipa	2450	2006	78	17
107	Paucarpata	2453	2006	206	40
108	Manas	2457	2007	73	7
109	Mariano Melgar	2459	2006	90	15
110	Lampian	2467	2007	45	13
111	Cospan	2471	2008	14	0
112	Abancay	2500	2010	1565	183
113	Alto Selva Alegre	2510	2006	128	17
114	Cayma	2531	2006	143	25
115	Arahuay	2533	2007	39	4
116	Huasmin	2543	2008	61	6
117	Bambamarca	2556	2008	221	25
118	Jesus	2568	2008	45	7
119	Pacaycasa	2571	2008	12	1
120	Luricocha	2598	2008	36	7

Table 3.4 (cont'd)

121	Tinco	2606	2008	40	4
122	Marca	2615	2008	15	3
123	Jose Galvez	2618	2008	16	0
124	Tamburco	2620	2010	181	11
125	Llacanora	2621	2008	15	0
126	Celendin	2629	2008	31	2
127	Sucre	2632	2008	28	4
128	Carhuaz	2663	2008	64	15
129	Sorochuco	2663	2008	41	4
130	San Pedro de Pilas	2678	2007	41	5
131	San Lorenzo de Quinti	2682	2007	62	10
132	Huanta	2685	2008	78	18
133	Los Baños del Inca	2685	2008	74	5
134	Acopampa	2692	2008	28	5
135	Cajamarca	2731	2003	1197	123
136	Namora	2765	2008	44	1
137	Chugur	2765	2008	13	0
138	Marcara	2767	2008	65	17
139	Sangallaya	2779	2007	39	5
140	Sanjuan Bautista Huamanga	2786	2003	255	46
141	Ayacucho	2797	2003	792	162
142	Anta	2800	2008	30	4
143	Miguel Iglesias	2813	2008	15	2
144	Jesus Nazareno	2817	2003	127	18
145	Jangas	2824	2008	59	9
146	Pariahuanca	2830	2008	15	5
147	Tarica	2832	2008	42	6
148	Matara	2834	2008	16	4
149	Yungar	2836	2008	26	4
150	Oxamarca	2836	2008	14	1
151	Ihuari	2850	2007	100	19
152	Santo Domingo de Los	2861	2007	43	7
153	Acos Vinchos	2874	2008	47	4
154	Langa	2889	2007	53	6
155	Yauyos	2895	2007	84	19
156	Amashca	2905	2008	14	1
157	Huayllapampa	2908	2008	12	2
158	Carmen Alto	2921	2003	125	28
159	Huachupampa	2938	2007	21	2
160	La Libertad de Pallan	2952	2008	27	5
161	San Miguel de Aco	2956	2008	32	5

Table 3.4 (cont'd)

162	Carhuanca	2980	2008	16	3
163	Llacllin	3020	2008	10	0
164	Shilla	3036	2008	42	10
165	Independencia Huaraz	3047	2003	673	101
166	Gorgor	3049	2007	117	24
167	Concepcion	3061	2008	16	2
168	Iguain	3063	2008	26	5
169	Huaraz	3073	2003	640	85
170	Encañada	3087	2008	91	7
171	Tambillo	3111	2008	29	10
172	Vischongo	3150	2008	45	8
173	Ayauca	3151	2007	76	22
174	Ocros	3153	2008	44	5
175	Vinchos	3155	2008	87	19
176	Huarochiri	3170	2007	38	4
177	Caujul	3185	2007	40	9
178	Huancapon	3187	2007	74	9
179	Santiago de Pischa	3210	2008	16	1
180	Acocro	3251	2008	61	8
181	San Damian	3252	2007	79	9
182	Santillana	3265	2008	45	5
183	Paccho	3275	2007	126	19
184	San Jose de Ticllas	3282	2008	30	5
185	Madean	3292	2007	65	18
186	Huambalpa	3294	2008	31	5
187	Leoncio Prado	3299	2007	60	8
188	Huamanguilla	3300	2008	39	6
189	Quinua	3301	2008	27	3
190	Huantan	3315	2007	46	12
191	Viðac	3315	2007	111	17
192	San Andres de Tupicoc	3321	2007	38	3
193	Socos	3368	2008	45	5
194	Accomarca	3387	2008	15	0
195	Colonia	3399	2007	101	22
196	Pararin	3402	2008	13	1
197	Recuay	3428	2008	15	2
198	Azangaro	3435	2007	68	16
199	Olleros	3443	2008	31	2
200	Carampoma	3459	2007	25	4
201	Ticapampa	3485	2008	32	3
202	Vilcas Huaman	3494	2008	60	16

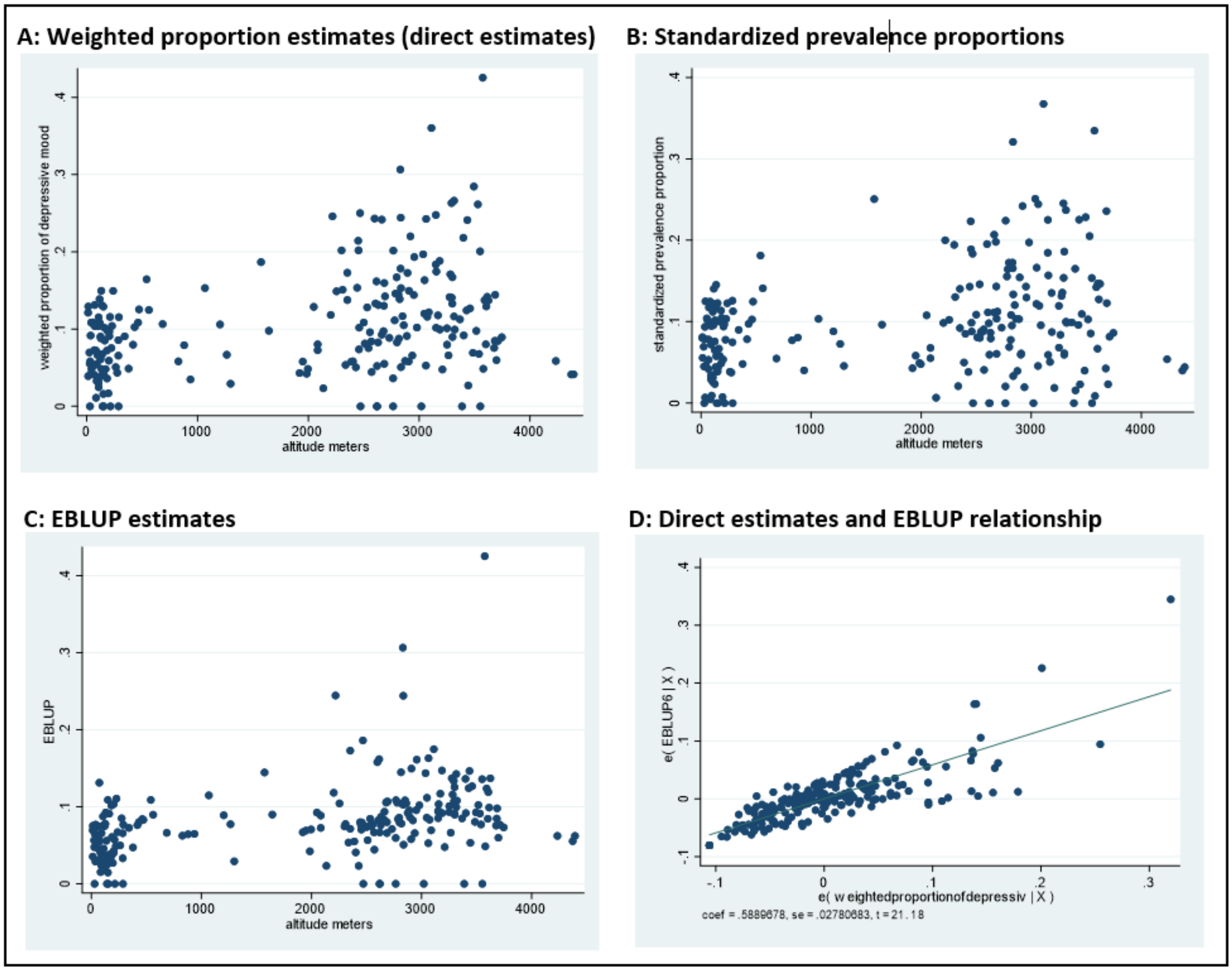
Table 3.4 (cont'd)

203	Lincha	3516	2007	36	6
204	Hualgayoc	3530	2008	46	10
205	Chiara	3540	2008	45	5
206	Santa Cruz de Andamar	3550	2007	109	24
207	Pampas Chico	3552	2008	14	0
208	Saurama	3574	2008	16	8
209	Catac	3579	2008	14	1
210	Huancaya	3591	2007	40	6
211	Pira	3602	2008	45	5
212	Independencia Vilcas H.	3606	2008	31	5
213	Huaros	3614	2007	88	15
214	Vitis	3625	2007	23	4
215	Miraflores Yauyos	3677	2007	37	4
216	Laraos	3683	2007	22	2
217	Lachaqui	3686	2007	43	9
218	Pampas	3698	2008	16	1
219	Ascension	3711	2010	366	40
220	Huancavelica	3746	2010	1350	132
221	Simon Bolivar	4234	2013	257	18
222	Chaupimarca	4373	2013	611	32
223	Yanacancha	4394	2013	601	32
	Total			31729	3588

Different models were tested with the auxiliary data, including another two variables (i.e., alimentary insecurity vulnerability and extreme poverty). Finally, the model with better adjusted R^2 and Fay Herriot R^2 (i.e., 0.83) was selected for using their estimates. Although the SAE framework is used for having more reliable estimates in small areas for governmental public reasons, I am here using it as a novel previous step to have better estimates that will allow us to study the relationship with altitude. The screenshot of the final proposed FH model for the EBLUPs estimates for the prevalence proportion of DM is shown in Figure 3.7 (Appendix B). Although the assumptions of normality for residuals and random effects were not found, I think it is valuable to use the FH estimates to have another way to compare the relationship between altitude and depressed mood. Notably, among all the FH models evaluated with these different auxiliary variables, population density had consistently more significant coefficients (see also Figure 3.8 in Appendix B).

The comparisons of the DM estimate's distribution across the altitude in meters are shown in Figure 3.1. We can see a slight tendency for increasing estimates of DM across the altitude for the three estimates. The direct estimates (i.e., weighted prevalence proportions) and standardized estimates (i.e., using the direct standardized adjustment for sex and age) have very similar patterns (plots A and B). With EBLUPs, the pattern is less dispersed (plot C in Figure 3.1). The association between EBLUPs and the direct estimates is also shown in Figure 3.1 (plot D); after regressing these two estimates, I plotted their relationship.

Figure 3.1. Depressed Mood (DM) Estimates distribution across Altitude. Data from the "Noguchi Surveys,"[1] Peru, 2003-2013.



1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

I used the "arcsine of the estimate square root" transformation for the three different estimates to test linear regressions between the estimates of DM and altitude as a continuous variable. We can see in Table 3.5. a summary of results from the three models. The model with EBLUPs estimates (Model C) performs better. The coefficient for altitude in Model C has a value in the middle of the two other models, but the confidence interval is smaller. All three regressions show a significant association between altitude and DM prevalence proportions in

223 districts of Peru. I include more details on the results of these three models in Table 3.11 (Appendix B).

Table 3.5. Comparing linear regressions between altitude and depressed mood estimates: Direct, Standardized, and EBLUP estimates.

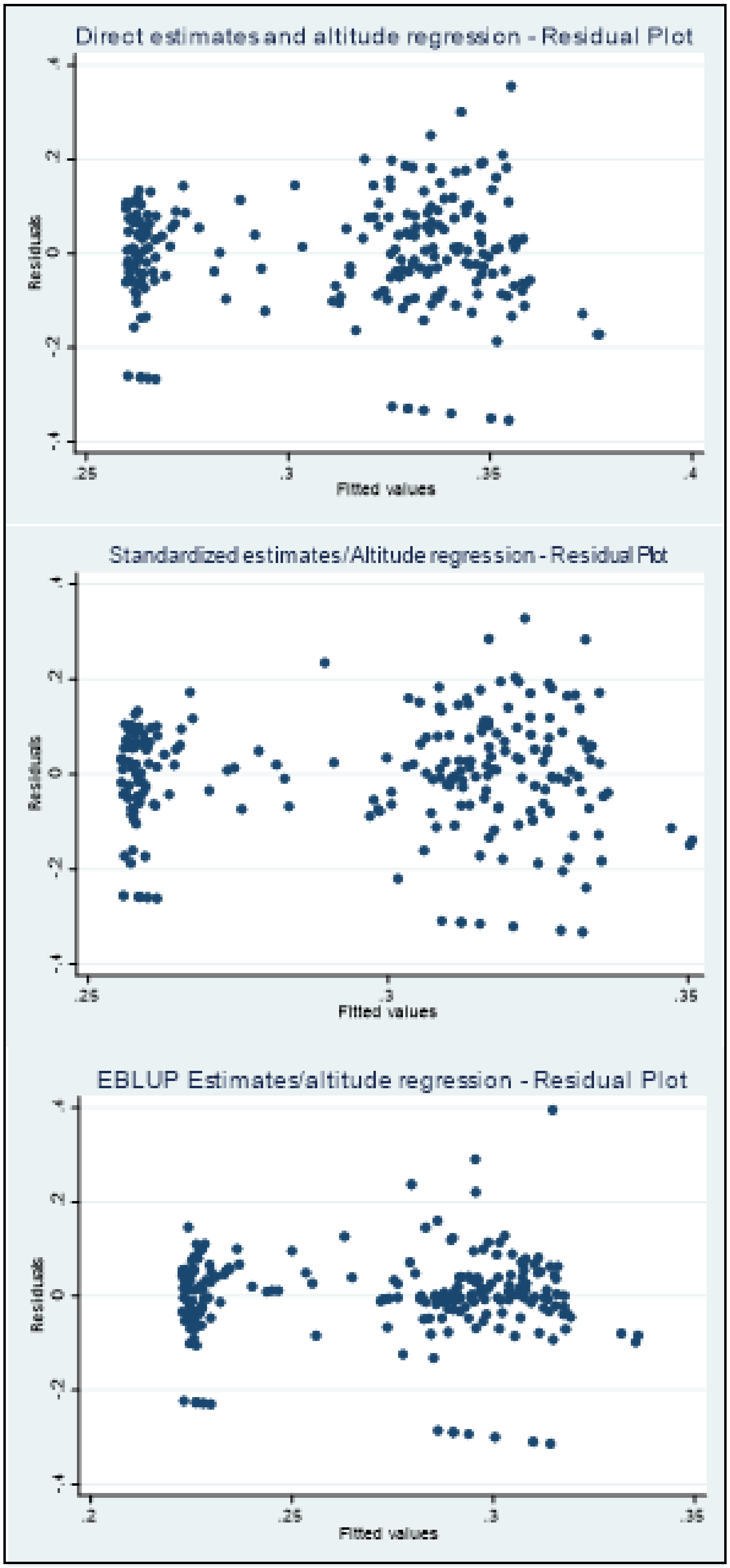
Model	β Altitude(m)	p-value	R^2	Adj.R2	RMSE	Log-likelihood
Model A	0.00002676	<0.00001	0.090496	0.086381	0.116845	1.63e+02
Model B	0.00002172	<0.001	0.058556	0.054296	0.119972	1.57e+02
Model C	0.00002583	<0.0000001	0.130615	0.126682	0.091790	2.17e+02

Model A: with weighted proportion estimates (direct estimates); Model B: with standardized prevalence proportions (direct standardization by sex and age); Model C: with EBLUP estimates. All models use the "arcsine of the estimate square root" transformation.

In addition, the FH model without the forty districts with null standard errors was also computed, and the regression between altitude and DM with this exclusion also showed a significant coefficient (see Figure 3.8 and Table 3.12 in Appendix B).

The residual plots of these three models across the fitted values show less dispersion in Model C. But, in all three models, the range increases at higher values in relationship with higher values of altitude (Figure 3.2).

Figure 3.2. Residual Plots of linear regressions models A, B, and C.



When weighted mean age and the proportion of women in the districts are included as covariates in Models A and C, the parameter for altitude did not change appreciably, and model fit increased modestly. Only the weighted mean age for districts was associated with DM prevalence (Tables 3.6 and 3.7).

Table 3.6. Adjusted Model A, age and sex covariates in the regression with weighted proportion estimates (direct estimates).

	Model A	Model A2	Model A3
Altitude (m)	0.00002676 (<0.01)	0.00002853 (<0.01)	0.00002803 (<0.01)
Age (mean)		-0.00354297 (<0.01)	-0.00341295 (<0.05)
Women (%)			0.09542722 (<0.1)
Intercept	0.25952414 (<0.01)	0.40854368 (<0.01)	0.35551325 (<0.01)
Observations	223	223	223
R-squared	0.09049599	0.11890332	0.12654629

P-values are in parentheses.

Table 3.7. Adjusted Model C, age and sex covariates in the regression with EBLUP[1] estimates.

	Model C	Model C2	Model C3
Altitude (m)	0.00002583 (<0.01)	0.00002708 (<0.01)	0.00002683 (<0.01)
Age (mean)		-0.00248675 (<0.05)	-0.00242422 (<0.05)
Women (%)			0.04589315 (≥0.01)
Intercept	0.22240446 (<0.01)	0.32699872 (<0.01)	0.30149517 (<0.01)
Observations	223	223	223
R-squared	0.13061499	0.15229181	0.15502991

P-values are in parentheses.

1 EBLUP – Empirical best linear unbiased predictor.

Depressed Mood across Altitude Quantiles

Figure 3.3 and Figure 3.4 show density distributions of the prevalence proportions of DM in the total population and across quantiles (i.e., terciles and deciles) using the direct and EBLUP estimates. The exact altitude values that divide the respective tertiles were 204 and 2682 meters. The altitude values for quintiles were 120, 342, 2500, and 3047 meters. Finally, the altitude values that divide the deciles are 67, 120,162, 342, 1921, 2500, 2731, 3047, and 3625 meters.

Figure 3.3. Estimated kernel density distributions of DM prevalence across quantiles. Direct estimates (weighted proportions of DM).

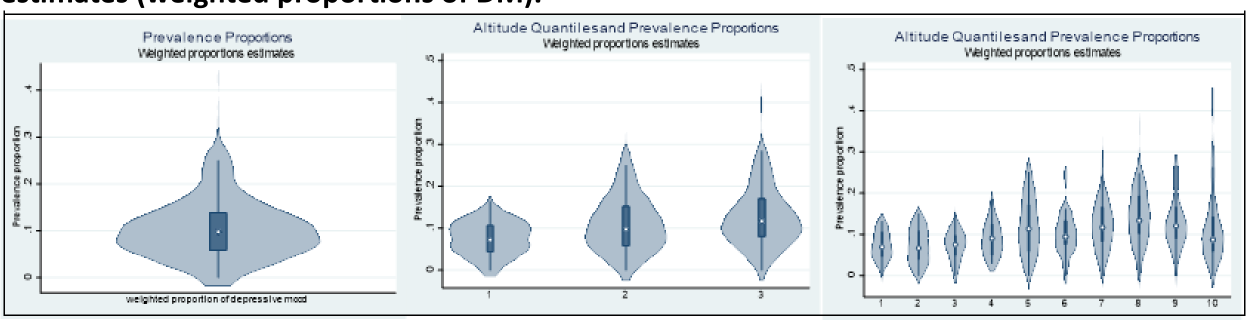
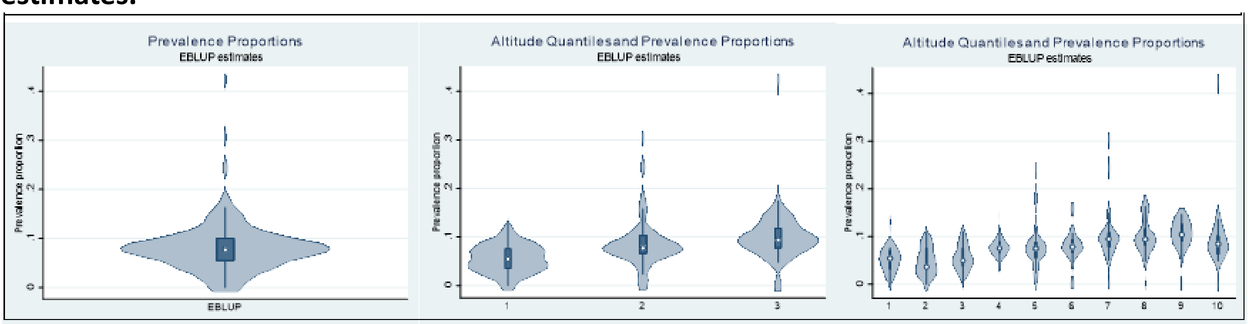


Figure 3.4. Estimated kernel density distributions of DM prevalence across quantiles. EBLUP estimates.



Finally, the regression estimates across altitude quantile levels were estimated using the direct and EBLUP estimates without transformations. It was found consistently that estimates of depressed mood (DM) are increasingly higher when participants are living at higher altitude levels. Tables 3.8 and Table 3.9. show linear regressions using the direct estimates (i.e., weighted proportions) and EBLUPs for three and ten quantiles, respectively. The 'age mean' and the proportion of women in the districts were not associated with DM at this level of analysis.

Interestingly, the association between altitude and DM switches to a significance level at the fifth quantile when looking across ten quantiles. Similar results are obtained when I compare with the FH model excluding the forty districts with null values, confirming this association. With this last model, the significance level starts at the fourth quantile (see Figure 3.9 in Appendix B).

Table 3.8. Altitude terciles as predictors of Depressed Mood estimates. Logistic models with direct[1] and EBLUP[2] estimates.

	Models with direct estimates[1]			Models with EBLUP estimates[2]		
	(1)	(2)	(3)	(4)	(5)	(6)
Tercile range	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)
2nd	0.0358 (<0.01)	0.0355 (<0.01)	0.0356 (<0.01)	0.0312 (<0.01)	0.0311 (<0.01)	0.0311 (<0.01)
3rd	0.0551 (<0.01)	0.0579 (<0.01)	0.0568 (<0.01)	0.0447 (<0.01)	0.0459 (<0.01)	0.0455 (<0.01)
Mean age		-0.0012 (ns)	-0.0011 (ns)		-0.0005 (ns)	-0.0005 (ns)
Female %			.0491 (ns)			0.0181 (ns)
Intercept	0.0757 (<0.01)	0.1256 (<0.01)	0.0976 (<0.05)	0.0553 (<0.01)	0.0757 (<0.01)	0.0654 (<0.05)
Observations	223	223	223	223	223	223
R-squared	0.1123	0.1221	0.1286	0.1460	0.1492	0.1509
Adj R^2	0.1042	0.1101	0.1126	0.1383	0.1375	0.1353
RMSE	0.0646	0.0644	0.0643	0.0456	0.0456	0.0457
Log-likelihood	296.0253	297.2637	298.0860	373.7384	374.1503	374.3720

1: weighted proportion estimates (direct estimates); 2: EBLUP – Empirical Best Linear Unbiased Prediction estimator
p-values are in parentheses. ns: not significant.

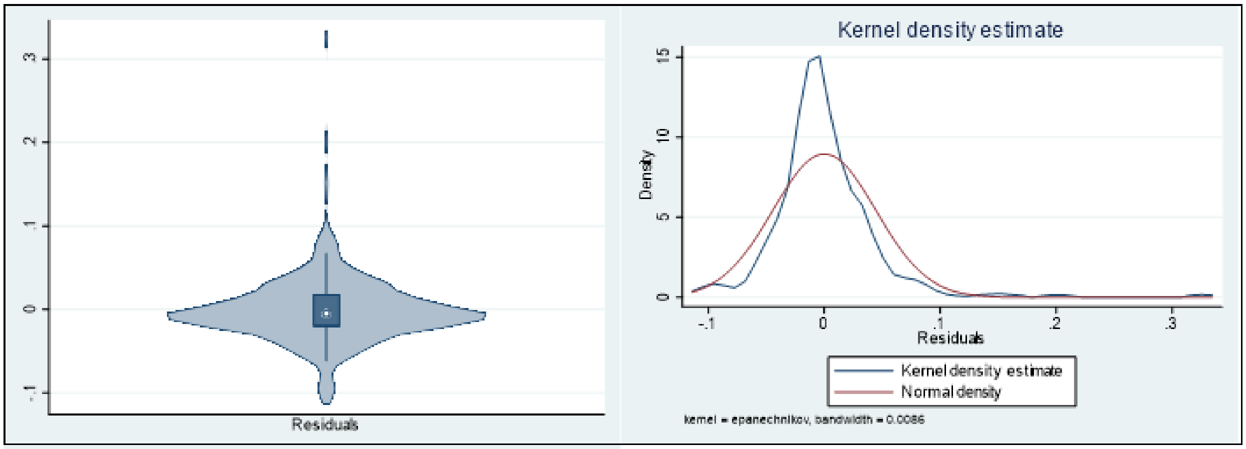
Table 3.9. Altitude deciles as predictors of Depressed Mood estimates. Logistic models with direct[1] and EBLUP[2] estimates.

	Models with direct estimates[1]			Models with EBLUP estimates[2]		
	(1)	(2)	(3)	(4)	(5)	(6)
Decile range	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)	β coef. (p-value)
2nd	0.0006 (ns)	-0.0003 (ns)	-0.0004 (ns)	-0.0037 (ns)	-0.0040 (ns)	-0.0040 (ns)
3rd	-0.0000 (ns)	-0.0026 (ns)	-0.0018 (ns)	0.0033 (ns)	0.0025 (ns)	0.0028 (ns)
4th	0.0187 (ns)	0.0154 (ns)	0.0153 (ns)	0.0251 (ns)	0.0241 (ns)	0.0241 (ns)
5th	0.0498 (<0.01)	0.0473 (<0.05)	0.0487 (<0.05)	0.0322 (<0.05)	0.0315 (<0.05)	0.0320 (<0.05)
6th	0.0332 (ns)	0.0329 (ns)	0.0329 (ns)	0.0271 (<0.05)	0.0270 (<0.05)	0.0270 (<0.05)
7th	0.0537 (<0.01)	0.0519 (<0.01)	0.0519 (<0.01)	0.0528 (<0.01)	0.0523 (<0.01)	0.0523 (<0.01)
8th	0.0762 (<0.01)	0.0771 (<0.01)	0.0759 (<0.01)	0.0462 (<0.01)	0.0465 (<0.01)	0.0460 (<0.01)
9th	0.0574 (<0.01)	0.0589 (<0.01)	0.0579 (<0.01)	0.0499 (<0.01)	0.0503 (<0.01)	0.0500 (<0.01)
10th	0.0504 (<0.01)	0.0513 (<0.01)	0.0505 (<0.01)	0.0467 (<0.01)	0.0470 (<0.01)	0.0467 (<0.01)
Mean age		-0.0011 (ns)	-0.0010 (ns)		-0.0003 (ns)	-0.0002 (ns)
Female %			0.0503 (ns)			0.0189 (ns)
Intercept	0.0719 (<0.01)	0.1199 (<0.01)	0.0909 (<0.05)	0.0526 (<0.01)	0.0668 (<0.01)	0.0559 (<0.1)
Observations	223	223	223	223	223	223
R-squared	0.1486	0.1569	0.1637	0.1757	0.1772	0.1770
Adj R^2	0.1126	0.1172	0.1201	0.1409	0.1383	0.1362
RMSE	0.0643	0.0641	0.0640	0.0455	0.0456	0.0456
Log-likelihood	300.6823	301.7787	302.6720	377.6870	377.8789	378.1269

1: weighted proportion estimates (direct estimates); 2: EBLUP – Empirical Best Linear Unbiased Prediction estimator
p-values are in parentheses. ns: not significant.

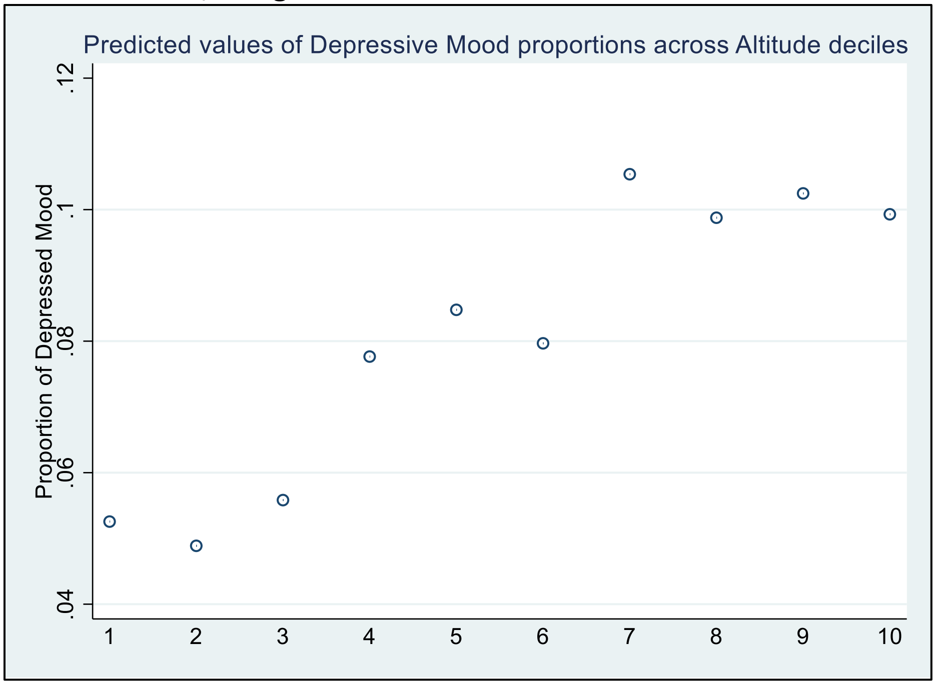
Model Four from Table 3.9 examines the regression of altitude deciles on the EBLUP estimates without covariates, and the residual distribution from this model is shown in Figure 3.5.

Figure 3.5. Residual distribution from Model 4 in Table 3.9.



In a post-estimation procedure, Figure 3.6 shows the predicted values for DM prevalence across deciles of altitude using model four in Table 3.9. The predicted prevalence proportion of DM increases with altitude levels above the sea.

Figure 3.6. Predicted prevalence proportion of Depressed Mood across altitude deciles, using Model 4 in Table 3.9.



3.4. Discussion

The main finding of this study is that districts located at higher altitude levels tend to have larger estimated Depressed Mood (DM) prevalence proportions, based upon three different inter-related estimators. Whereas accurate estimation of DM prevalence at the district level might be the case for government agencies, for this project I used the Fay Herriot model to improve the precision of slope estimates linking altitude-DM and to improve the fit of the subsequent regression models.

Before discussing the results in detail, it is important to acknowledge several study limitations. The surveys were conducted over ten years, but in this study, I did not thoroughly evaluate whether there is a significant variation in the likelihood of living at higher or lower altitudes over the years. Nor did I assess whether there is substantial variability in depression over time. There could be a variation in the incidence or in the duration of depressive symptoms over the years, and if there are differences in residential altitude levels over time, it could affect the study's conclusions. However, as can be seen in Figure 3.10. (see Appendix B), there is no verification of a trend or variation in altitude levels over the years.

Another relevant limitation of this study is that the analyzed surveys were not designed to enable statistical inference at the district level. Although a Small Area Estimation (SAE) methodology was used to improve estimates with the Fay-Herriot model, this does not guarantee that estimates are as precise as if we were to survey at the district level to determine prevalence more accurately. There are currently new SAE methodologies to ensure better precision of BLUPs. Still, these new methodologies require more resources and are usually reserved for situations where the primary goal is to determine precise estimators that guide government agencies' decision-making (e.g., determining extreme poverty rates to allocate government funds). Regarding the Fay-Herriot model used in this study, one limitation was that 40 districts were found to have no usable standard error values for variance calculation. One possible option was to combine districts with very little sample or no cases of depression with neighboring communities with similar altitudes. This approach could allow the use of this data without imputing values in standard errors. This possibility could have the disadvantage of artificially combining populations and introducing noise into the analyses. It would also require greater depth in the geographical recognition of the districts.

It is also important to highlight a limitation in this study related to assessing depressed mood. Although there are validated 2-item questionnaires for depression screening and mood state evaluation (86,87), I combined two questions that do not yet have psychometric validations for depressed mood evaluation. Also, the “prevalent mood states” part of the questionnaire is not validated in other languages than Spanish. However, I believe that when a person says that they experience sadness "always or almost always" and that sadness is experienced "frequently during the last four weeks," it captures the essential concept of “depressed mood,” according to the European psychopathological tradition (41,45,46) and the definition of the American classification for depressed mood (44).

On the other hand, this study did not evaluate other variables that may be relevant to the altitude-depression relationship. In this sense, it is interesting to note that populations living at higher altitudes tend to be made up of predominantly native people. The implications of this relationship are intriguing. Other variables such as poverty or educational level, among others, are also relevant to study, but considering that they could be rather mediators between the altitude-depression relationship. This type of analysis goes beyond the objective of this specific dissertation research project aim.

In addition to the mentioned limitations, a novel idea was unveiled during the dissertation committee presentation that would enable me to assess the relationship between altitude and depressed mood in a dose-response manner using other models with inverse variance weighting estimation. I want to acknowledge this limitation in my dissertation, and I hope to complete the analyses before publication of articles based on my dissertation findings.

Despite the mentioned limitations, the study findings are of interest. To my knowledge, this is the second published ecologic study addressing the relationship between altitude and depression, and it qualifies as one of a few such studies completed outside of the United States. Studies at the community level of analysis are developed less frequently and usually require useful information from a broader range of populations. Compared to the DelMastro study (5), altitude levels are higher in this research, and the relationship appears to increase correspondently. As such the results might have implications for public policies concerning the mental health care of high-altitude populations. Regardless of other potential causal factors associated with the higher likelihood of depressive symptoms at altitude, healthcare services need to consider these findings. Many high-altitude populations may also have limited access to health services, especially in Peru and other Andean countries. Much of this population may require mental health care that is underdiagnosed and undertreated.

Although it is still very preliminary, the relationship between altitude and DM prevalence found in this study could lead us to consider the possibility of an asymptotic relationship between both. The regression coefficient values and the curve of predicted values across altitude deciles show a steeper increase in intermediate deciles and a less pronounced increase after that. While this could have many other explanations (e.g., cultural aspects related to the highest altitudes, or genetic differences of native populations, etc.) that I currently do not expect to discuss deeper, it is also possible that it follows the curve of "effective oxygen pressure" across altitude levels, which is related to the atmospheric pressure and is asymptotically described.

Furthermore, this study is relevant because, in an exploratory manner, it introduces the SAE methodology in evaluating factors associated with depression. To our knowledge, there are very few studies that use SAE methodology to estimate mental health prevalence (88–92). Still, none of them conducted a more analytical approach to factors associated with depression.

The findings of this study raise relevant topics that need further investigation. Native populations can develop changes in their physiology and build adaptation processes to high altitudes, which may, in turn, influence the likelihood of experiencing depressive symptoms. In this first study for my dissertation project, variations across 'diversity' subgroups could not be addressed. As mentioned earlier, in Peru, there is a relationship between belonging to native ethnic groups such as Quechuas or Aymaras and a greater likelihood of living at high altitudes. Although reports have found higher levels of depressive symptoms at higher altitudes within the same native group (93), there is also evidence that native populations have developed adaptive mechanisms over thousands of years (37) that could somehow mitigate the negative effect of hypoxia on mood. Peru is a good scenario to study this aspect since, in addition to the native population at high altitudes, there is also a varied diversity of migrants to the high Andean regions with different types of ancestry.

Related to the above is the topic of migration and the length of time spent or residing in a high-altitude area. Although some reports have followed migrants for up to a year (57) and found increases in depressive levels, further studies are needed that evaluate more extended periods of residency or staying at high altitudes. It is critical to elucidate whether depressive symptoms increase over time as with Chronic Mountain Sickness or whether they remain stable or decrease as the years pass. No studies have evaluated this variation.

Individual-level studies are also necessary to estimate the role of other potentially intervening variables such as poverty, education, religiosity, social support, etc. However, these assessments must be cautious, as some of these variables could mediate the effect of altitude on depression. Some studies demonstrate neurocognitive effects due to exposure to hypoxia (52,55,58,59,94).

Another relevant topic to study is the effect of traditional coca leaf consumption on the mood of people living at high altitudes. In Peru, coca leaf consumption is related to cultural factors of the native population and living in the high Andean regions. The energizing effect of the coca leaf is well recognized because it contains up to 14 different alkaloids, including cocaine.

Finally, it is essential to mention the need to explore the possible association between altitude and other mental disorders, such as anxiety disorders or post-traumatic stress disorder. Living at high altitudes is already a stressor and may confer vulnerability to these problems.

CHAPTER 4: ESTIMATING THE ALTITUDE-DEPRESSED MOOD ASSOCIATION AT THE INDIVIDUAL LEVEL

4.1. Introduction

In the previous report from this series, I discussed the hypoxia theory and its potential connection to depression in higher altitudes. Under Study 1, I estimated the degree to which the odds of active depressed mood (persistent sadness) might vary across altitude levels in Peru, including the Peruvian Andes highlands, with the community district as the unit of analysis. I estimated prevalence proportions for each community district and studied the relationship in what might be described as an "ecological" analysis. As explained below, this investigation extends the evidence base beyond what can be learned in the multiple prior United States studies (4–6,8,9). It differs from studies in Nepal (65), Tibet (72), and recently published Peru studies (66,67) because the case definition for this study is focused more tightly on persistent sadness or depressed mood (DM) during the four-week period before the survey assessment.

In this new report, with the individual as the unit of analysis (in contrast with the Aim1 focus on estimates with the district as the unit of analysis), I present estimates of the association between altitude and DM at the individual level. To be clear, my first paper in this series focused on community-level prevalence proportions with the district as the unit of analysis. Instead, in this paper, I estimate the relative odds of DM being present always or almost always within that four-week interval before assessment, as the odds might vary across altitude levels of the community district in which the participants reside, across the wide range of altitude levels in Peru.

Apart from the estimates for the United States, which are limited regarding altitude levels, as explained in my previous report, only three large epidemiological studies found in the published literature examine the relationship between altitude and depression with the inclusion of especially high-altitude communities. These prior studies were conducted in Nepal (65) and Peru (66,67). The Peruvian studies were published in 2022. However, the case definitions for all these prior studies differ from the one I specified in my dissertation research. The study in Nepal investigated a score based on a multi-item assessment of depressive symptoms in the week interval before assessment. The studies in Peru used the Demographic and Family Health Survey (ENDES in Spanish) data, with a focus on (a) the score of depressive symptoms during the two-week interval before assessment, as elicited in a multi-item scale and (b) the imposition of a threshold cut point on that summary score.

In the present study, the outcome variable is depressed mood, as sadness persists "always" or "almost always" during the four-week interval before the assessment. This case definition of depressed mood (DM) considers a longer and more relevant period. This dissertation research project's approach is more in line with the concept of "depressed mood" in terms of affective psychopathology (41,45). DM is one of the core criteria in current psychiatric diagnostic classifications (43,44).

As such, the estimates based on individual unit-of-analysis estimates for altitude-DM association presented in this study represent a step forward beyond previous research. As noted in the final sections of this paper, as the field continues to gain insight into the relationship between altitude and depression, it should become possible to derive more definitive evidence from longitudinal studies as well as randomized experimental trials that can be devised to eliminate some of the constraints described in the Discussion section.

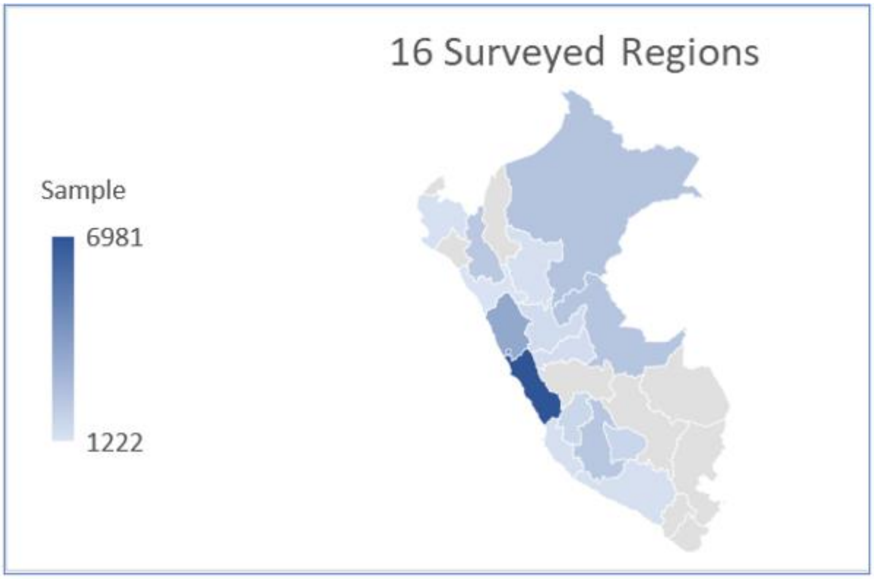
4.2. Materials and Methods

Nine consecutive annual epidemiological surveys on mental health conducted in Peru between 2003 and 2013 by the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health were included in this study. The surveys (i.e., "Noguchi Surveys") employed nearly identical methodology and questionnaires, covering various factors such as sociodemographic variables, mental health problems, substance use, and protective factors for mental health, among others (95,75,78). The surveys were conducted across 33 provinces within 15 regions of Peru, spanning a diverse range of altitudes above sea level.

These household surveys aimed to assess four distinctive groups of non-institutionalized community residents: adolescents, adults (aged 18 years or older, including elders), elderly individuals, and married or cohabitant women. Only household residents were considered for this series of surveys. For this research, I analyzed data only from the adult population modules. The Peruvian National Institute of Statistics and Informatics (i.e., INEI) provided the census clusters for each surveyed city or rural area. INEI used the latest available census survey data of the Peruvian residents to make the census clusters. It is important to note that this study focused on the population residing in Peru, precisely their place of residence.

In the "Noguchi Surveys," the survey sampling procedures were carried out in a total of 22 urban (i.e., cities) or rural areas (usually located near previously surveyed cities) across 15 regions of the country. The total number of people considered for the sampling procedures in all these areas was over 9.8 million.

Figure 4.1. Regions Surveyed (n=15). From the "Noguchi Surveys,"[1] Peru, 2003-2013.



1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

The "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health researchers employed a homogeneous sample selection process for each surveyed area, whether urban or rural. They used a multistage random sampling process consisting of three stages. In the first stage, a group of census clusters was randomly selected as the primary sampling units within each stratum, which referred to the surveyed city or rural area. Each census cluster comprised approximately 80 dwelling units. Then, field workers elaborated a sample frame from the entire cluster. The dwelling units within each census cluster were randomly chosen in the second stage. In the final stage, the Kish table approach randomly selected individuals from the target population within each dwelling unit. For this, the field staff collected a list of residents in each dwelling unit (77).

Participation levels (‘response rates’) for each of the surveys were reported by the "Honorio Delgado – Hideyo Noguchi" National Institute of Mental Health of Peru." Values varied from 81.7% to 98.4%, most above 90%. The number of participants included in each yearly survey ranged from 2331 to 6555. In some years, more than one region was surveyed. The total resulting sample consists of 33130 participants. However, 50 participants had missing responses to crucial study variables and were excluded from this report. The total sample included in this study was 33,080 participants.

IRB Considerations

The "Noguchi Surveys" underwent review and approval by the Peruvian National Institute of Mental Health Institutional Review Board to ensure the protection of human subjects in research. Before conducting the interviews, all participants provided informed consent by signing a form. Participation in the study was voluntary, and participants could decline to answer questions or end the interview at any time if they felt uncomfortable.

Furthermore, the Michigan State University Institutional Review Board for Protection of Human Subjects in Research also reviewed the research protocol. Given no human subjects contact and de-identified data in this project, the IRB determined that my dissertation project did not involve human subjects according to the US National Institutes of Health definition.

Instruments and measurement

The survey administered to adult participants consisted of 233 questions divided into five sections: sociodemographic, general adult health, clinical syndromes part A, clinical syndromes part B, and access to health services. Appendix A of this dissertation provides an English translation of the standardized survey questions used to evaluate the mood state of each participant during the previous four weeks. The questions were posed to participants in their native language. The altitude of households was determined at the district level using data from the Peruvian National Center for Strategic Planning (CEPLAN) (79).

The survey used two questions to assess actively depressed mood within the last four weeks. The first question involved a Likert question that asked participants directly about their mood: "How often do you feel Sad?" This question was included in the "prevalent mood states" section of the questionnaire as Question #6.

The second question involved a screening tool called SRQ-17, a shorter version of the SRQ-20 (80). This tool was used to inquire about depressive and anxiety symptoms experienced by participants in the past four weeks. One of the questions in the SRQ-17 asked if the participant had frequently felt sad during the past four weeks (Question 26). In addition to questions about sadness, the SRQ-17 also asked about physical symptoms, appetite, anxiety, and other non-depressed mood-related issues.

In terms of affective psychopathology, the concept of "mood" refers to an individual's baseline affective state, which tends to be enduring and stable over time(41,45). DSM-5 states a depressed mood is "a sustained feeling of sadness or hopelessness" (44). This definition implies that the subjective feeling of sadness is present most of the time rather than just for a few days or a week. In this study, the actively depressed mood was identified in individuals who reported feeling sadness "always" or "almost always" in response to Question #6 and also answered "Yes" to the question "Have you felt sad frequently in the last four weeks?" (Appendix A). Depressed mood is the most essential symptom of Major Depressive Disorder (MDD) but can also be a symptom of other mental health disorders like dysthymia.

There was another set of depression questions. The Mini-International Neuropsychiatric Interview - MINI (81), which includes questions that match the criteria of ICD-10 for MDD, was also applied in the surveys. However, these questions about MDD were asked over the participant's lifetime and not directly about the last weeks before the interview assessment.

Data analysis

I used Stata 17© software (96) for the analyses. The models were managed to have individual-level estimates, considering the complex survey data characteristics described in Paper 1 (i.e., strata, census clusters, and analysis weights). Stata© survey commands were used to conduct bivariate and covariate-adjusted analyses based on the generalized linear model with a logit link function ('logistic regression') for complex survey data. Taylor series linearization (TSL) methods have been used to yield approximations of variances, from which standard errors, 95% Fisherian confidence intervals, and p-values have been derived. I relied on a two-tailed alpha equal to 0.05, with $p<0.05$, when I drew attention to contrasts between subgroup estimates in the Results section.

To be clear, when I estimated the relationship between the outcome variable (i.e., DM as manifest in persistent sadness) and the covariates, I used logistic regression models with 95% confidence intervals for crude and adjusted models. Collinearity diagnostics on the covariates were performed using the "Collin" command in Stata ©.

My initial plan for hypothesis testing for nested models employed the "Nestreg" command that reports comparative goodness of fit (GoF) statistics. These GoF statistics provide evidence in favor of the null hypothesis of no improvement of fit when new terms are added, or against that null hypothesis. During my dissertation work, I learned that the 'nestreg' approach is no longer deemed appropriate when the context is complex survey samples and the response variable is binary as is the case for studying the odds of being in a state of active depressed mood. For this reason, I am providing the 'nestreg' output for this chapter of my dissertation, but for inference I rely more heavily upon the ratio of the estimated slopes and their respective standard errors derived from Taylor series linearization. In this way, the ratios provide a way of learning whether the residual variation in the response variable depends upon the model's newly added terms.

The altitude variable was categorized in terms of tertiles for the primary analysis, in conformity with the approved specific aims for the dissertation research protocol. However, I show estimates in Appendix C based on other pertinent altitude quantiles (e.g., quintiles and deciles). Appendix C also shows estimates using different altitude categories defined by other conventions.

In the covariate-adjustment process, other predefined demographic covariates were introduced in the models. These covariates were age, sex, mother tongue (an indicator of ethnicity), and civil status. Finally, the time of residence was introduced in the models (i.e., more than two years). Then, a stratified analysis was performed to estimate the degree to which odds of depressed mood (DM) might vary across subgroups defined by duration of residence in the community district. This exploratory analysis addresses an issue not previously covered – namely, whether the period of residence in a high-altitude community district might have something to do with the experience of depressive symptoms. For this analysis, I pre-specified the cutout point based on whether the community participant had lived in the community district for at least two years before the assessment date.

While it might seem that the estimates presented in the previous study and those in this second study are duplicative because they are conducted in the same populations, I believe they are actually complementary studies and not necessarily repetitive. This second study intends to obtain adjusted models while assessing the effects of other individual variables that could not be incorporated into a community-level approach. In other words, in this second study, we can delve deeper into individual-level variables that are not adequately addressed with aggregated data. For example, in this second study and in the upcoming one in this series, which is also designed for individual-level analysis, we can evaluate the relationship between marital status, ancestry, or coca leaf consumption and the presence of depressed mood. This could not have been optimally assessed with aggregated data. In this final version of the dissertation, I present these two approaches (i.e., aggregated or community vs. individual level of analysis) so that readers can evaluate and compare both and decide which one might be preferable under what circumstances.

4.3. Results

Based on unweighted sample data, 3729 participants had experienced persistent sadness (DM) during the four-week interval before assessment. The analysis-weighted prevalence proportion indicates that roughly 8% of the population met the DM case definition.

Table 4.1 shows how the analysis-weighted prevalence proportions vary across relevant subgroups defined by the measured characteristics under study. We can see that weighted DM prevalence proportions increase from seven to 11.5% across the three altitude levels. The lowest altitude level has a significantly lower prevalence of DM compared to the other two higher levels. The age mean is higher in the group of people who experienced DM. The female population has much higher prevalence proportions of DM than males (i.e., around 12% vs. 4%). About ancestry, Quechua/Aymara participants have much higher levels of depressed mood DM. Regarding civil status, divorced and widowed participants also have a much higher proportion of DM.

Table 4.1. Depressed Mood (DM) relative to specified population subgroup membership of individual participants in the study sample. Data from the "Noguchi Surveys,"[1] Peru, 2013-2023.

	Depressed Mood (DM)						
	NO			YES			
	n	Weighted Proportion (%)	CI	n	Weighted Proportion (%)	CI	
Total	29351	91.9	[91.2,92.4]	3729	8.1	[7.5,8.8]	
Altitude Tertile							*p<0.0001*
1st	10001	92.8	[91.9,93.5]	1111	7.2	[6.5,8.0]	
2nd	9821	90.6	[89.4,91.6]	1167	9.5	[8.4,10.7]	
3rd	9529	88.5	[87.6,89.3]	1451	11.5	[10.6,12.4]	
Age (mean)		40.8	[40.3, 41.3]		45.5	[44.0,46.9]	*p<0.0001*
Sex							
Male	13585	96.0	[95.3,96.6]	739	3.9	[3.4,4.7]	
Female	15766	87.9	[86.9,88.9]	2990	12.1	[11.1,13.1]	
Mother tongue							*p<0.0001*
Spanish	24308	92.4	[91.7,92.9]	2765	7.6	[7.0,8.3]	
Quechua /Aymara	4702	86.3	[83.9,88.4]	930	13.7	[11.6,16.1]	
Other	292	95.2	[81.1,98.9]	29	4.8	[1.1,18.9]	
Civil							*p<0.0001*
Married	17938	91.8	[90.9,92.6]	2103	8.1	[7.4,9.1]	
Divorced/ Widowed	4567	86.0	[84.1,87.6]	1139	14.0	[12.3,15.1]	
Single	6835	95.1	[94.1,95.8]	486	4.9	[4.1,5.9]	
Living more >2 years[2]							*p= 0.056*
No	1083	87.5	[80.9,92.0]	122	12.5	[7.9,19.1]	
Yes	28268	91.9	[91.3,92.5]	3607	8.0	[7.4,8.7]	

1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

2: Two or more years of residence here

Table 4.2. Estimated associations from bivariate analyses with depressed mood (DM) expressed as a function of each covariate, one by one. Data from the "Noguchi Surveys,"[1] Peru, 2013-2023.

Variable	Coef.	St.Err.	t-value	p-value	[95% Conf. Interval]	
Altitude Tertiles						
2nd	0.294	0.0898	3.27	0.001	0.118	0.467
3rd	0.509	0.0734	6.94	<0.001	0.365	0.653
Intercept	-2.553	0.0584	-43.70	<0.001	-2.668	-2.439
Age						
Age	.0145	0.0023	6.25	<0.001	0.010	0.019
Intercept	-3.049	0.1081	-28.21	<0.001	-3.261	-2.837
Sex						
Female	1.201	0.0973	12.35	<0.001	1.010	1.391
Intercept	-3.187	0.0853	-37.39	<0.001	-3.35	-3.020
Mother Tongue (Ref. Spanish)						
Quechua/Aymara	0.652	0.1072	6.08	<0.001	0.442	0.862
Other (Amazonia)	-0.484	0.7781	-0.62	.53401	-2.009	1.042
Intercept	-2.495	0.0457	-54.59	<0.001	-2.585	-2.406
Civil status (Ref. Married/Cohab)						
divorce/widow	0.607	0.0932	6.52	<0.001	0.424	0.789
single	-0.536	0.1152	-4.65	<0.001	-0.762	-0.31
Intercept	-2.420	0.0576	-42.06	<0.001	-2.533	-2.308
Two or more years living in the area						
Yes	-0.491	0.2599	-1.89	.05871	-1.001	0.018
Intercept	-1.947	0.2561	-7.60	<0.001	-2.449	-1.445

1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 4.2 estimates are for bivariate associations estimated with the GLM and the logit link function using Stata© "Svy" commands that yield Taylor series linearization (TSL) approximations of variances. With no covariate adjustments, they are presented to provide the reader with information about these associations before any additional covariate adjustments.

In these bivariate analyses, the association between all the previously described demographic variables and DM was confirmed in the logistic regression framework for survey data.

Table 4.3 shows estimates from covariate-adjusted models. The key finding, relative to the study aim, is that in this analysis with individuals as the unit of analysis, there is a statistically robust association that links the altitude of an individual resident of a community district in Peru with the odds of experiencing a recent depressed mood (DM), even with covariate adjustments as shown in Table 4.3. In this depiction of the results, different columns show the estimates for other models, adjusting consecutively the covariates. Estimated odds ratios and estimated p-values based on the TSL approximation for the variances and standard errors are shown. The strength of this association tends to be modest but is consistently confirmed across all the covariate adjustment models.

Table 4.3. Estimated associations from covariate-adjusted analyses with depressed mood (DM) expressed as a function of each covariate. Data from the "Noguchi Surveys,"[1] Peru, 2003-2013.

	Model 1 Un-adjusted		Model 2		Model 3		Model 4		Model 5		Model 6	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value	OR	p-value
Altitude Tertiles												
2nd altitude tertile	1.34	0.001	1.39	<0.001	1.41	<0.001	1.36	0.001	1.36	0.001	1.36	0.001
3rd altitude tertile	1.66	<0.001	1.76	<0.001	1.78	<0.001	1.60	<0.001	1.61	<0.001	1.61	<0.001
Age			1.02	<0.001	1.02	<0.001	1.01	<0.001	1.01	0.001	1.01	0.001
Female					3.37	<0.001	3.36	<0.001	3.14	<0.001	3.15	<0.001
Mother tongue (reference: Spanish)												
Quechua/Aymara							1.47	0.001	1.44	0.002	1.44	0.002
Other (Amazonia)							0.71	0.633	0.70	0.626	0.67	0.59
Civil status (reference: married)												
divorce/widow									1.38	0.001	1.37	0.002
single									0.76	0.026	0.75	0.024
Two or more years living here												
Long residence											0.54	0.011
Observations		33080		33078		33078		33024		33013		33013

1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

As promised in my dissertation proposal, I completed goodness of fit (GoF) comparisons. However, as described in the Methods section, these results are presented here but cannot be regarded as definitive evidence due to uncertainty about GoF evaluations when the context is that of a complex sample survey. Results are shown in Figure 4.2 (i.e., in Appendix C).

Questions about multicollinearity might be of interest to some readers. My evaluation of multicollinearity suggested that my estimates were not distorted due to violations of assumptions about multicollinearity. Figure 4.3 in Appendix C shows the Stata© output of Model 6 from Table 4.3.

Finally, when the relationship between altitude and depressed mood (DM) was estimated using stratification for the elapsed residence time in the community district, the association between altitude and DM was found only for those living there for two or more years.

Table 4.4. Stratified analyses of beta estimates of altitude's effect on depressed mood by length of residence in the district. Data from the "Noguchi Surveys,"[1] Peru, 2003-2013.

Length of residence	Altitude						
	Tertile 1	Tertile 2			Tertile 3		
		β Coef.	95% CI	p-value	β Coef.	95% CI	p-value
People living two years or more (n=31,875)	Ref.	0.32	0.14; 0.50	0.001	0.53	0.38; 0.67	<0.001
People living less than 2 years (n=1,205)	Ref.	-0.57	-1.53; 0.39	0.246	-0.13	-1.28;1.03	0.828

1: Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

4.4. Discussion

As for the main finding of this study, with the individual as the unit of analysis, I postulated a tangible association between altitude and the prevalence of active and persistent depressed mood (DM). My resulting estimates show this association when altitude is sorted by tertiles and other quantiles, as shown in Table 4.5. (see Appendix C).

Before discussing the results in detail, it is important to acknowledge some of the most relevant limitations of the study. Concerning the assessment of depressed mood, the recently active experience of persistent sadness (DM) was measured via two combined questions that have not yet been validated with psychometric studies. However, it is entirely plausible that when a person says that they experience sadness "always or almost always" and that sadness is experienced "frequently during the last four weeks," it captures the essential concept of the "persistent sadness" facet of a "depressive mood," according to the European psychopathological tradition (41,45,46) and the definitions used in the American classification for depressed mood (44).

Other key limitations involve the cross-sectional character of the data with no specification of the age of onset of DM relative to the time of residence at the current altitude. In addition, this study did not evaluate other community characteristics that might be covarying with the altitude-depression relationship (e.g., exposure to trauma). However, careful consideration is required to sort these potential influences about a Directed Acyclic Graphing logic so that "ancestor" variables are included as covariates, but "mediators" and "descendants" are not included in the analyses (97).

The association between altitude and depression I found in this study goes in line with the previous paper in this series with the district as the unit of analysis and with the other epidemiological studies that have evaluated shorter periods of depressive symptoms (i.e., one or two weeks). In this case, I examined a more extended period of persistent sadness or depressed mood (DM) that has been regarded as a crucial criterion on the path to a Major Depressive Disorder (MDD) (44).

As for prior studies, it might be of interest that the estimated prevalence of depression in the Tibetian Plateau was considerably higher (72) (i.e., 28% versus 8% in this study). However, this variation might be traced to different case definitions and time intervals. Please note that in the Tibetan research, the time interval evaluated was one week, and for this dissertation, the time interval was four weeks. In Nepal, another nationwide study found around 10% prevalence of depression. They also found that living at high altitudes (i.e., 2000 m) was associated with depression (65).

As for the other two studies in Peru from the ENDES surveys (66,67), these studies also showed an altitude-depression association. However, the ENDES studies did not disclose any association with the mother tongue (Quechua or Aymara), and the result is that the mother tongue association deserves greater scrutiny, as described in a later section on future directions for research.

To the best of my knowledge, this work represents the first study evaluating the time of residence concerning the association between altitude and depressive symptoms (DM). Estimates from the duration-of-residence stratified analyses prompt a speculative hypothesis that the effect of altitude on people's mood might be more salient when at least two years of exposure have passed. It has been reported that adverse cognitive effects at high altitude levels fluctuate over time. Initially marked deterioration, a period of acclimatization follows, and finally, in some cases, worsening can be seen again (59). This pattern of deterioration-acclimatization-deterioration was described previously and played a central role in Chronic

Mountain Sickness (30). Maybe something similar might happen with persistent sadness, with initial acute sadness forming and then fluctuating but persisting as residence in higher altitudes increases in duration.

Potential implications for public health deserve mention. With over 11% of the population, particularly those in higher altitudes, potentially experiencing a persistent state of depressed mood, this could have repercussions on both physical and mental health (98). Furthermore, it could lead to adverse economic and social consequences in highland populations (99,100). Health policymakers should remain vigilant in developing more preventive, early diagnostic, and intervention measures related to depression, especially for high-altitude residents.

These findings are also interesting because recent data from a new Peruvian National Institute of Mental Health survey will soon be available to evaluate and replicate what was presented here. The relationship between altitude and depression should be studied more in-depth with more and larger data.

Studies on migration, their different patterns, and their relationship with mood changes are also needed. Furthermore, if these findings are confirmed, we must develop and design future preventive interventions and incorporate the altitude variable in managing patients with depression in the highlands. If feasible, developing these epidemiological, preventive, and treatment-related studies should enhance the public health significance of this dissertation research project.

In the final chapter of my dissertation research report, I will provide some additional ideas about future directions for research, with coverage of both treatment intervention studies and preventive trials. Suppose hypoxia is one of the determining influences in this relationship. In that case, there are some motivating opportunities for randomized controlled trials to evaluate how oxygen supplementation might help alleviate depression once it starts. In some instances, the relationship might guide preventive interventions. This topic will be covered in the final chapter of my dissertation research report.

CHAPTER 5: THE ESTIMATED EFFECT OF COCA-LEAF USE IN THE ASSOCIATION BETWEEN ALTITUDE AND DEPRESSED MOOD

5.1. Introduction

I evaluated the relationship between altitude and mood in the previous two studies of this series. In the first study, with ecological units of analysis, districts located at higher altitudes had more residents with depressed mood (i.e., larger prevalence proportions). The second study found this association at the individual level while controlling for relevant covariates. This third investigation will focus on the possible role of coca leaf consumption in the relationship between residence altitude and mood state. As we will see, in the Peruvian Andes, not only is the issue of environmental stress caused by hypobaric hypoxia relevant (25,31,32,37,101), but traditional coca leaf consumption is also a prevalent ancestral practice (10,11,102,103) that must be considered and studied.

In the South American Andes, coca leaf has been consumed for millennia. Traces of evidence dating back 3000 years have been found to support this assertion (104). There is also evidence that coca has been cultivated in the central region of Peru for almost 2000 years (105). Its use seems quite widespread in the Andean South American region from that time. Even before the Inca era, its use was ceremonial and religious. During the Inca period, the coca leaf was used in special ceremonies, was associated with the highest royalty (105), and was considered the "most sacred plant of all" (106).

With the arrival of the Spanish (i.e., in the 16th century) and after their unsuccessful attempts to eradicate its use, coca leaf chewing apparently became more widespread. A custom of providing daily coca leaves to workers in the fields and mines emerged (102). Since then, the use of coca leaves has been sustained (107), and the practice of taking coca leaf rations during work tasks remains in the high Andean areas.

Since colonial times, it was recognized that coca leaves could better withstand mining and farming tasks. Due to this, coca leaves were highly valued, and even taxes and payments to farmers were made using them (105).

Elsewhere in the world, interest in the coca leaf surfaced in the 19^{th} century. In 1863, in Paris, Angelo Mariani developed the "coca wine tonic" based on coca leaf, which became very popular in Europe. Mariani even received recognition from the Pope, and Thomas Edison was an enthusiastic consumer of this tonic (108). Research interest in coca leaves surfaced at about the same time (109). In 1859, it was already described in Europe that coca leaf had properties such as "reducing fatigue and improving mood" (102).

Currently, the consumption of coca leaves is still quite widespread in the Andean region (10,11). Consumption mainly involves coca leaf chewing or coca tea preparations. Typically, using coca leaves involves more of a sucking action than actual chewing. Initially, a bundle of dried coca leaves is placed inside the mouth, between the gums and cheek, then slowly soaked with saliva. Then, to assist in separating the alkaloids of the leaf, including cocaine, a small amount of lime or a similar substance is inserted into the center of the coca bundle. Additionally, there can be a ceremonial aspect to this process (110). In some Andean communities, the consumption of coca leaves is seen as part of the cultural identity of Quechua and Aymara native populations (110).

Advances in medicinal chemistry and pharmacognosy since the mid-19th century have disclosed at least 18 alkaloids in coca leaves (102). The 'cocaine' extraction has received most attention. However, it is believed that these alkaloids can work synergistically and that their effects should not be solely attributed to the effect of cocaine. More studies are needed in this regard (111).

Even though chewing coca leaves cannot be equated to consuming purified and crystallized cocaine (111,112), research has demonstrated that consuming coca leaves via chewing or as tea (111) can result in the rapid detection of cocaine in the body. For example, a study comparing traditional coca leaf users to non-users found that after one hour, levels of 70 ng/ml of cocaine were detected in the blood (113).

Because coca-leaf consumption is more frequent in the Andean highlands, several decades ago, it was hypothesized that the consumption of coca leaves may play a role in adapting to high altitudes (114). For example, it has been suggested that coca products might better regulate the increase in red blood cell production (i.e., erythropoiesis) (112). A mild beneficial effect on body temperature management has also been described, which could be helpful in the adaptive process to high altitudes (115). Additionally, it has been proposed that coca leaf consumption could help maintain stable blood glucose levels and improve nutrient availability in the body in environments with scarce food (116). However, studies have not provided conclusive evidence in these areas. Some even argue that the association between altitude and coca leaf consumption is due to cultural factors rather than high altitude adaptation (117).

In a study conducted with a limited number of participants, it was observed that regular consumers of coca leaves had comparable levels of adrenergic activity (i.e., epinephrine and norepinephrine in the bloodstream) relative to non-consumers. However, coca users exhibited higher levels of fatty acids in their blood. Furthermore, during strenuous physical activity, coca users could tolerate lower oxygen saturation levels while maintaining similar ventilatory capacities (113). Another experiment involving non-regular coca users demonstrated that consuming coca leaves did not elicit significant changes at rest but did enhance oxygenation, cardiac function, and other related factors during exercise compared to those who did not consume coca leaves (118).

I have not found any reports of controlled studies assessing the potential mood-altering effects of coca leaf consumption. Nevertheless, given that cocaine does have mood-altering effects (13–15,119), the consumption of coca leaves may have some potential impact on how consumers experience their moods.

These background details help motivate the present study and its investigation of the possibility that coca product consumption, especially coca leaf chewing, might modulate the altitude-affectivity association described in earlier chapters of this dissertation. That is, the primary objective of this study is to evaluate whether coca leaf consumption has a modifying effect and might modulate the altitude-affectivity association described in this dissertation research project's initial inquiries. A starting expectation might be that the recent use of coca leaf might attenuate an observed greater likelihood of an active depressed mood at the higher altitudes of residences in the Andean communities of Peru. Studied across tertiles (or other quantiles) of altitude, the recent users of coca products might experience a mood-elevating effect of the alkaloids in the coca leaf such that these coca product users would have lower prevalence of active depressed mood as compared with non-users of these products who are residing at the same altitude levels.

5.2. Materials and Methods

For this study, as described in prior chapters of this dissertation report, I turned to data from the nine consecutive annual epidemiological surveys on mental health conducted in Peru between 2003 and 2013 by the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health. The surveys (i.e., "Noguchi Surveys") were implemented across 15 regions and 33 provinces of Peru, utilizing almost identical methodology and questionnaires for each year. Several mental health-related factors were assessed, such as sociodemographic variables, mental health problems, substance use, etc.

These household surveys were conducted to evaluate four distinct groups of non-institutionalized individuals within the community: adolescents, adults (18 years of age or older, including seniors), elderly individuals, and women who were married or cohabitating (75). Only household residents were included. Only data from the adult population modules were analyzed for this study series. The Peruvian National Institute of Statistics and Informatics provided the census clusters for the surveys using the latest available survey data. The surveys were focused on the population residing in Peru. Field workers from "Noguchi Institute" created sampling frames within each census cluster, from which sampled dwelling units were derived.

In the "Noguchi Surveys," the survey sampling procedures were carried out in 22 urban or rural areas across the country. The total number of people in the populations considered for the sampling procedures in all these areas was over 9.8 million.

The "Noguchi Institute" researchers employed a multistage random sampling method that consisted of three stages. In the first stage, a set of census clusters was randomly chosen as the primary sampling units within each stratum, which referred to either the surveyed city or rural area. Each census cluster was comprised of approximately 80 dwelling units. Next, field workers created a sample frame from the entire cluster. In the second stage, dwelling units were randomly selected from each census cluster. In the final stage, individuals from the target population were randomly chosen within each dwelling unit using the Kish table approach. For this, the field staff obtained a list of residents in each dwelling unit (75,77,78).

The "Noguchi Institute" survey participation levels ('response rates') varied from 81.7% to 98.4% across the surveys. Most values exceeded 90%. The number of participants in each annual survey ranged from 2,331 to 6,555. In some years, more than one region was surveyed. The resulting overall sample comprised 33,130 participants. However, due to missing responses on crucial study variables, 101 participants were excluded from this report. Thus, the total sample included in this study was 33,029 participants.

IRB Considerations

The "Noguchi Surveys" were subjected to review and approval by the Peruvian National Institute of Mental Health Institutional Review Board to safeguard the rights and welfare of research participants. Before conducting interviews, all participants were required to provide informed consent by signing a form. Participation in the study was voluntary, and participants could decline to answer questions or terminate the interview at any point. In addition, the research protocol for dissertation research project with de-identified datasets was reviewed by the Michigan State University Institutional Review Board for the Protection of Human Subjects in Research. Because no human contact was required for this de-identified data analysis project, the Institutional Review Board (IRB) determined that the study did not fall under the category of human subjects research as outlined by the US National Institutes of Health.

Instruments and measurement

The survey questionnaires given to adult participants comprised 233 questions, organized into five sections. The five sections included items on sociodemographic characteristics, general adult health, clinical syndromes part A, clinical syndromes part B, and access to health services.

The dissertation's Appendix A contains an English translation of the standardized survey questions utilized to assess the mood of each participant over the previous four weeks. In this study, the actively depressed mood was identified in individuals who reported feeling sadness "always" or "almost always" in response to Question 6 and also answered "Yes" to the question "Have you felt sad frequently in the last four weeks?". A depressed mood (DM) is a manifestation of the 'affectivity' facet of the mental life of individuals as described in earlier chapters of this dissertation. Depressed mood qualifies as the essential symptom of Major Depressive Disorder (MDD) but can also be a symptom of other mental health disorders.

Appendix A also contains an English translation of questions about alcohol and other drug use, including coca-leaf consumption. Whereas these questions assessed presence of abuse or dependence on each substance, for this study, the covariate was specified as any coca leaf use during the month prior to the survey assessment. The questions were posed to participants in their native language. Both groups of questions about mood and coca-leaf use were asked to all participants without gated or branching questions as might be embedded within questionnaire skip patterns.

The altitude of households was determined at the district level using data from the Peruvian National Center for Strategic Planning (CEPLAN) (79). The specific details have been described in prior chapters of this dissertation.

Data analysis

I used two complementary approaches to evaluate the effect of coca leaf use on the previously found altitude-mood relationship. As in prior chapters, the altitude variable was categorized in terms of tertiles for the primary analysis, in conformity with the approved specific aims for the dissertation research protocol.

First, I conducted a stratified analysis, grouping individuals based on their coca leaf consumption. Then, after stratified analyses, I studied coca leaf users and non-users as separate subpopulations, searching for evidence of non-overlapping 95% confidence intervals for the estimated slopes that convey the altitude→depressed mood association. I then evaluated the possibility of subgroup variation or an interaction between altitude and coca leaf consumption using product terms. In this dissertation, subgroup variation in slope estimates does not count as an example of 'interaction' because the underlying mechanisms remain hidden from view. To be confident about any 'interaction,' the researcher must be able to specify the nature of the variation as can be true when studying a neurotransmitter agonist with effects blocked by an antagonist, or when a partial agonist's effects are boosted by co-administration of some other drug or alteration of an extraneous variable under the control of the researcher (e.g., ambient temperature). For this reason, the term 'interaction' is used sparingly, and the pattern of evidence generally is described as one of 'subgroup variation' in the slope estimates.

For the just-described stratified analysis and assessment of the product terms, I used the final model from the second study in this series of papers (i.e., Chapter four of this dissertation), which includes altitude divided into tertiles. I then considered covariates mentioned previously: age, sex, marital status, mother tongue, and length of residence in the current location (i.e., whether they have lived in the place for two or more years) as covariates.

The project's estimation models were fit using Stata 17© software to account for the complex survey data characteristics described previously (i.e., strata, census clusters, and analysis weights). The initial analyses were from stratifications with estimation of point prevalence proportions and their standard errors via fairly simple cross-tabulations of altitude, coca consumption, and depressed mood for coca users versus non-users. Corresponding estimates from a general linear model for complex survey data were derived using an 'identity' link function and the standard regression model. Then, covariates were accommodated via my use of the generalized linear model with a logit link function. In this work, I utilized Stata survey commands to carry out bivariate and covariate-adjusted analyses on complex survey data. To obtain approximations of variances, I utilized the Taylor series linearization method and derived standard errors, 95% Fisherian confidence intervals, and p-values. My statistical analysis used a two-tailed alpha level of 0.05. When comparing subgroup variations, I specified alpha and p-values less than 0.05 as indicative of what traditionally has been termed "statistical significance." For hypothesis testing on nested models, I used the "Nestreg" command, which provides F statistics for the comparison tests between the nested models. Collinearity between coca-leaf use, altitude, mother tongue, and other variables was evaluated using the "Collin" command. For example, the collinearity analysis produced variance inflation factor coefficients below 1.1 and tolerance coefficients all were above 0.9, indicating that no further investigation was required.

5.3. Results

Table 5.1 presents each covariate under study and its association with coca leaf consumption in Peru. Approximately two percent of the population consumed coca leaves the month before the surveys. However, this percentage increases from 0.5% in the lowest level to almost 12% in the group living at higher altitudes above the sea. Table 5.2 shows the estimates from stratified analyses with three tertiles of altitude crossed with the prevalence of active depressed mood for users of coca versus non-users.

Table 5.2 shows clearly an unexpected finding about coca leaf consumption and being a case of actively depressed mood. Contrary to expectations, altitude level by level and gauged by the point prevalence estimates, it is the coca leaf users who are more likely to experience active depressed mood. The 95% confidence intervals (CI) overlap considerably and suggest that we should not make too much of this subgroup variation. Nevertheless, these simple stratified analyses provide an initial challenge to the idea that coca leaf use might be protecting the users from otherwise mood-affecting circumstances involved with living at the highest altitudes in Peruvian communities.

Table 5.1. Unweighted sample counts and weighted estimates that contrast coca leaf users versus non-users. Data from the "Noguchi surveys,"[1] Peru, 2003-2013.

	Coca-leaf use during the last month						
	No			Yes			
	n	Weighted Proportion %	CI	n	Weighted Proportion %	CI	
Total	30683	97.9	[97.6,98.2]	2367	2.1	[1.8, 2.4]	
Altitude Tertile							P<0.0001
1	11032	99.5	[99.2,99.7]	59	0.5	[0.3,0.8]	
2	10342	96.1	[95.3,96.8]	641	3.9	[3.2,4.7]	
3	9309	88.1	[87.0,89.1]	1667	11.9	[10.7,13.0]	
Age (mean)		41.1	[40.6, 41.6]		44.9	[42.8, 47.0]	-
Sex							P<0.0015
Male	13111	97.5	[97.0,97.9]	1190	2.5	[2.1,3.0]	
Female	17572	98.3	[97.9,98.6]	1177	1.7	[1.5,2.1]	
Mother Tongue							P<0.0001
Spanish	25855	98.6	[98.3,98.8]	1190	1.4	[1.2,1.8]	
Quechua/ Aymara	4461	90.8	[89.2,92.2]	1168	9.2	[7.8,10.8]	
Other (Amazonia)	313	99.7	[99.1,99.9]	9	0.3	[0.1,0.9]	
Civil status							P<0.0001
Married/	18409	97.4	[97.0,97.8]	1603	2.6	[2.2,3.0]	
Divorced/	5223	98.1	[97.5,98.6]	484	1.9	[1.5,2.5]	
single	7038	98.8	[98.1,99.2]	280	1.2	[0.8,1.9]	
More than 2 years							P<0.0183
No	1138	95.6	[91.8,97.7]	67	4.4	[2.3,8.2]	
Yes	29545	97.9	[97.7,98.2]	2300	2.1	[1.8,2.3]	
Depressed mood							P<0.0001
No	27344	98.2	[97.9,98.4]	1957	1.9	[1.6,2.1]	
Yes	3319	95.2	[93.7,96.3]	409	4.8	[3.70,6.3]	

p-values from Pearson Design-based F statistics for weighted data, bivariate analysis between each variable and coca use. 1: "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 5.2. Estimated prevalence proportions for active depressed mood, stratified by coca leaf use and by altitude. Data from the "Noguchi surveys,"[1] Peru, 2003-2013.

		Tertiles of Altitude in Peru		
		Lowest	**Middle**	**Highest**
Recent Use of Coca Leaf	**YES**	9.4%	22.0%	17.1%
	95% CI	3.4%, 23.5%	16.0%, 29.5%	14.5%, 20.1%
Recent Use of Coca Leaf	**NO**	7.2%	8.9%	10.7%
	95% CI	6.5%, 8.0%	7.9%, 10.1%	9.8%, 11.7%

1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

With 'svy' commands, and before covariates are introduced, it is possible to quantify the prevalence differences illustrated in these tables via a general linear model and 'identity' link function, and after converting the tertiles to the median elevation above sea level in kilometers. Based on this analysis with median km altitude as the covariate of interest, the occurrence of actively depressed mood among non-users of the coca leaf shows an increase in estimated DM prevalence of one percentage points for each km increase in altitude, with p-value less than 0.001. The corresponding slope estimate for coca users is not appreciably different from the null slope (p = 0.637). Evaluated via a product term for the total population (coca=yes * tertile as product term), the Wald statistic has a p-value of 0.133, well above the conventional alpha specifications for product-terms in epidemiological analyses. That is, the evidence does not suggest the anticipated modulation of the altitude-DM association as evaluated across the subgroups of recent coca users versus non-users.

The results of the stratified analysis with covariate adjustment, in relation to coca leaf consumption, are presented in Tables 5.3 and 5.4. The first row of Table 5.3 illustrates the altitude-depressed mood association irrespective of coca leaf use, and the next two rows show corresponding estimates of the association for the subgroups of coca leaf users at each level of attitude. If we were to study only non-users, the altitude-DM association would qualify as not appreciably distant from what is seen for all residents of these Peruvian communities. If we were to study coca leaf users only, there is an association with altitude (tertile levels) but there is no clear or robust association of altitude and depressed mood in the third row of estimates in Table 5.3.

In Table 5.4, the stratified analysis shows the ORs using the group at the lowest altitude level who do not consume coca leaf as the reference group, following a format recommended by some authors (120). Please note that there are only 59 participants who consumed coca leaves in the last month and live in the lowest altitude level.

Table 5.3. Stratified analyses of the estimated association between altitude (by tertiles) and mood, by coca-leaf use in the last month. Data from the "Noguchi Surveys"[1], Peru, 2003-2013.

	Tertile 1	Tertile 2			Tertile 3		
	OR (Ref.)	OR	95% CI	p-value	OR	95% CI	p-value
Total sample (n=33,013)	1	1.36	1.13, 1.64	0.001	1.61	1.36, 1.89	<0.001
Coca-leaf nonusers (n=30,596)	1	1.29	1.07, 1.56	0.007	1.50	1.27, 1.78	<0.001
Coca-leaf users (n=2,366)	1	1.79	0.54, 5.94	0.342	1.48	0.47, 4.68	0.505

Survey data analysis using generalized linear model with a logit link function, with covariate adjustment for: age, sex, maternal tongue, civil status, and time of residence (>2 years). OR: odds ratio, persistent sadness or depressed mood (DM) is the outcome. 1: "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 5.4. Stratified analysis of the estimated association between altitude (by tertiles) and mood, by coca-leaf use in the last month, with one group as reference (lower altitude and coca nonusers). Data from the "Noguchi Surveys,"[1] Peru 2003-2013.

	Altitude Tercile 1			Altitude Tercile 2			Altitude Tercile 3		
	DM Cases/ No cases	OR *(p-value)*	95% CI	DM Cases/ No cases	OR *(p-value)*	95% CI	DM Cases/ No cases	OR *(p-value)*	95% CI
Coca-leaf Nonusers	1,100/ 9,927	1		1,061/ 9,275	1.29 *(p=0.006)*	[1.08, 1.56]	1,158/ 8,142	1.52 *(p<0.001)*	[1.29, 1.80]
Coca-leaf Users	11/48	2.10 *(p=0.182)*	[0.71,6.27]	105/536	3.31 *(p<0.001)*	[2.14, 5.13]	293/ 1373	2.43 *(p<0.001)*	[1.83, 3.23]

Survey data analysis using generalized linear model with a logit link function, with covariate adjustment for: age, sex, maternal tongue, civil status, and time of residence (>2 years). DM: depressed mood. OR: odds ratio. 1 "Noguchi Surveys": epidemiological surveys from "Honorio Delgado – Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 5.5 displays the stratified analysis using only two altitude levels divided by the median (i.e., 1921 meters). In this case, the sample size in the group of coca users at the lowest altitude level has increased by over 200 individuals (n=277). However, the stratified analysis still shows that the increase in depressed mood as altitude increases is tangible for the population that does not consume coca leaves (p-value<0.001). As in the prior analysis, among coca leaf consumers, the altitude-DM association is not robust.

Table 5.5. Stratified analysis of the estimated association between altitude (two groups) and mood, by coca-leaf use in the last month, with one group as reference (lower altitude and coca nonusers). Data from the "Noguchi Surveys,"[1] Peru 2003-2013.

	Low Altitude (under median)			High Altitude (above median)			ORs (95% CI) for the effect of Altitude on mood within strata of coca leaf use	
	DM Cases/ No cases	OR *(p-value)*	95% CI	DM Cases/ No cases	OR *(p-value)*	95% CI		
Coca-leaf Nonusers	1,630/15,128	1		1,689/12,216	1.54 *(p<0.001)*	[1.28, 1.84]	1.52 *(p<0.001*	[1.27, 1.83]
Coca-leaf Users	42/235	1.57 *(p=0.19)*	[0.79, 3.10]	367/1,722	3.24 *(p<0.001)*	[2.26, 4.63]	2.00 *0.077)*	[0.93, 4.31]

Survey data analysis using generalized linear model with a logit link function, with covariate adjustment for: age, sex, maternal tongue, civil status, and time of residence (>2 years). DM: persistent sadness or depressed mood. OR: odds ratio. 1: "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 5.5 adds covariate-adjusted evidence about coca users and depressed mood. If we specify the low altitude non-users as a reference group, the odds of active DM among high altitude non-users is 1.54 times greater. Note, however, that the corresponding odds of active DM among coca users at the high altitude is 3.24 times greater than the odds in that reference group (p = 0.001). Here again, the idea of a protective effect of coca use at higher altitudes is not supported by the evidence from this analysis.

5.4. Discussion

The main finding of this part of my dissertation research project on the occurrence of active depressed mood (DM) in Peru is the absence of evidence that consumption of coca leaf actually modifies the altitude-DM association. If anything, the coca users are more likely than non-users to experience active depressed mood, even at the higher altitudes.

This discovery was an unexpected finding in this study but is in line with similar associations found with alcohol and other drugs as well (14,121–125). However, due to the study's cross-sectional nature, it is impossible to evaluate this association's temporality. To my knowledge, this association between coca leaf use and depressive symptoms was not previously reported. It is plausible that people, when experiencing depressive symptoms, may seek to consume coca leaf more frequently to alleviate symptoms such as fatigue or lethargy. This behavior could be due to the coca leaf's energizing effects. However, a psychostimulant like coca leaf would only have a temporary impact and would not reduce the duration of depressive symptoms or affect the prevalence of depression. (Appendix D provides some additional results from post-estimation exploratory data analyses that help to confirm the results presented in this chapter.)

The initial stratified analysis disclosed that in the subgroup of coca leaf consumers, the estimated effect of altitude on people's mood is not very substantial (Table 5.3), although a relationship was seen for non-coca-users. Regrettably, the few people who consume coca leaves and live in low-altitude areas limit the certainty of these results.

As I consider limitations in my work, I must mention a measurement issue. It is possible that the measurement of depressed mood is not entirely equivalent across subgroups in Peruvian communities, possibly traced to genetic traits or to cultural variations. Measurement equivalence (126,127) studies are needed in this regard with the instruments used in this study but also with other questionnaires.

Notwithstanding my evidence, I wonder whether the potential role of the coca leaf as a mitigator of altitude effects (e.g., loss of energy or depressive symptoms) might remain worthy of consideration. This would align with ideas proposed for decades that suggest that the coca leaf is not only related to cultural factors but also could play a role in counteracting the effects of high altitudes (112,114,116). Let's imagine that the prevalence of active depressed mood would be even higher among coca users in the higher altitudes than it now is found to be, and that the coca use dampens the DM prevalence from what otherwise would be a remarkably high prevalence proportion.

This idea prompts consideration of a randomized trial to encourage highlanders to stop using coca and to see whether those who stop their use have lower levels of depression after a suitable washout interval. This is the kind of evidence that might be needed in order to clarify the altitude-DM association that might be modified by coca use.

Some other study limitations deserve mention. Several have already been mentioned in this series's discussion sections of previous studies. For example, there is a possible measurement error of depressed mood with the questions used, whether this can vary among the population according to their ethnic origin or the chance that other relevant confounding variables were not included in the models. However, this time, I want to emphasize the cross-sectional nature of the present research, which does not allow for a more detailed evaluation of the temporality of the variables studied, which is of great importance in this case.

Lastly, the findings of this study suggest lines of research that need to be developed to elucidate the role of coca leaf in depressive symptoms in the Andean population. Particular attention should be paid to evaluating these conditions in residents not belonging to the

Quechua and Aymara ethnic groups. They may more frequently show coca leaf consumption unrelated to cultural factors but rather to physical or mental symptoms.

From a public health perspective, the management of patients in high-altitude areas may be influenced by the findings of this study. It will be necessary to evaluate whether it is required to implement preventive, diagnostic, and treatment measures for cases of depression at high altitudes in a different way than at sea level. For example, developing criteria to determine in which cases it is convenient to indicate a change of residence to lower places. Assessing whether the currently universally used criteria for depression need to be refined for the people living at high altitudes, etc. These are just a few examples of what could be proposed as a research agenda for the coming years.

CHAPTER 6: CONCLUSIONS AND FUTURE DIRECTIONS FOR RESEARCH

Based on the results obtained in this dissertation, it can be stated that evidence has been found to support the association between altitude and depressed mood (DM). In this chapter, I will first summarize the main conclusions from the first two studies, which address this relationship. Then, I will discuss the findings related to the estimated effect of coca leaf use on the association between altitude and DM. Finally, I will propose suggestions for relevant lines of research based on these findings.

6.1. At the community level

The first article of this series of studies showed that at the community level (i.e., district level), those localities located at higher altitudes also had higher prevalence proportions of depressed mood. It was found by evaluating the direct estimates of survey data analysis, using standardized estimates (i.e., with direct adjustment for age and sex), and finally using estimators corresponding to the Small Area Estimation methodology (i.e., Fay-Herriot model).

These findings could have implications for public policies regarding the mental health care of highlanders. Given that many high-altitude populations, especially in Peru and other Andean countries, have limited access to health services, there may be a significant need for mental health care that is currently being underdiagnosed and undertreated.

To my knowledge, the study presented in the chapter three of this dissertation is one of the very few epidemiological surveys conducted outside the United States to investigate the relationship between altitude and depression. Compared to the DelMastro study, this research examines higher altitude levels and finds that the relationship between altitude and depression also increases at higher altitudes. It also is the first to consider coca leaf chewing as a potential modifier of the altitude-DM relationship.

The broader range of exposure to hypobaric hypoxia suggests that the relationship between altitude and the prevalence of DM may follow an asymptotic pattern. The regression coefficient values and the predicted value curve across altitude deciles indicate a steeper increase in middle deciles, followed by a less pronounced increase. While this pattern might be attributed to various factors, it is also possible that it mirrors the curve of "effective oxygen pressure" across altitude levels, which is related to atmospheric pressure and can be asymptotically described.

6.2. At the individual level

Upon analyzing the relationship between altitude and DM at the individual level, I added new evidence about the previously described association at the district level. That is, for individuals residing in higher altitude tertiles there is an association with a higher probability of experiencing DM. The prevalence proportion using weighted analysis indicates that approximately 8% of the population met the DM case definition. However, this proportion ranges from 7% to 11%, depending on the altitude tertile. The association between altitude and DM remains after covariate adjustment (i.e., age, sex, mother tongue, marital status, and length of residence). It also remains stable using different altitude categories, such as other quantiles (i.e., quintiles, deciles) or other altitude divisions.

Another novelty in this study is examining the association between altitude and mood (DM) regarding the duration of residence. By stratifying the analysis according to the length of stay, the findings indicate a tentative hypothesis that the estimated effect of high altitude on a person's mood may be more pronounced after a minimum of two years of residing at such heights.

6.3. Coca leaf and the Altitude-mood Association

The third study investigated the consumption of coca leaf products. The results showed, for the first time, that active users of coca leaf are more likely to be experiencing active depressed mood (DM) states, even after adjusting for relevant covariates. However, the study's cross-sectional design makes it impossible to establish the direction of causal sequences in this relationship. That is, a prior mood state might have prompted the use of coca leaf products rather than vice versa.

The role of coca-leaf use in the association between altitude and DM was evaluated via stratification and interaction terms (i.e., product terms). The stratified analysis suggests that among the coca leaf users, the estimated effect of altitude on DM is not as relevant compared to the non-users of coca. However, this preliminary evidence is not conclusive because the sample size is much smaller in the coca users' group. This finding could suggest a possible effect modifier role of coca use in the estimated effect of altitude on mood. The product terms analysis between altitude and coca leaf does not show evidence of subgroup variation between people who use coca and live at higher altitudes and the basal non-users of coca leaf.

6.4. Future directions for research

Further investigation is necessary to explore the relationship between altitude and mood thoroughly. This research could have significant implications for the well-being of roughly 500 million people living in high-altitude areas(69). It may also shed light on the mechanisms that underlie depression and related disorders. If some are viable, these ideas for future research should enhance the public health significance of this dissertation research project.

I will categorize the research proposals outlined here into two main groups of studies. First, I will review the intervention and longitudinal studies necessary to complement the existing evidence on the possible causal effect of altitude on depressive symptoms. Second, I will address the research that can be done with available data from cross-sectional surveys carried out in Peru and other countries while longitudinal studies are being implemented. By combining these approaches, we can obtain a complete picture of the impact of altitude on mental health and develop effective strategies to address these problems.

In the history of epidemiology, as with other suspected causes, cessation-of-effect studies could be seen as the first option concerning intervention studies. It is highly plausible to conduct randomized studies where a group of participants living at high altitudes is assigned to receive supplemental oxygen at different levels and modalities. Alternately, coca users might be randomly encouraged to stop such use, for an estimate of the effects on current depressed mood.

Some studies suggest poor sleep quality is associated with hypobaric hypoxia and could trigger altitude-related cognitive and mood problems (55–58). I can envision the following groups in a randomized clinical study conducted in a high-altitude city, ideally with volunteers experiencing depressive symptoms and working sedentary jobs for most of the day:

Group A: No supplemental oxygen; they continue their daily routine.

Group B: Supplemental oxygen only during sleeping hours at night.

Group C: Supplemental oxygen during sleeping hours at night and intermittently during the day.

Group D: Continuous supplemental oxygen during both daytime and nighttime.

Longitudinal follow-up studies could also be performed on people who migrate from high-altitude areas to lower-altitude locations. These studies could also be done through randomized controlled trials (RCTs). For example, to facilitate their relocation to lower-altitude cities, economic or other incentives could be provided to participants. Cohort studies without intervention by the researchers could also be achieved. These longitudinal studies on migrants would ideally involve participants with depressive symptoms and close monitoring by healthcare personnel so that the possibility of medical treatment can be evaluated closely if necessary. Clinical treatment guidelines for Major Depressive Disorder (MDD) allow for delaying the initiation of medication when a patient has mild depression and is closely monitored by the therapeutic team (128).

Cohort studies evaluating migration in the opposite direction are also necessary. These studies would follow individuals who migrate from lower-altitude cities to higher-altitude locations, usually for work-related reasons. Many questions surround this topic, and only small and short-term studies have been conducted so far(57). The finding reported in the second study of this series shows that the estimated effect of altitude on mood would be significant after at least two years. This suggests that follow-up studies of more than two years in migrants going to higher altitudes are necessary to measure a more substantial effect on mood.

Overall, these new longitudinal studies will help to resolve uncertainties related to the association between altitude and depression, as well as their temporality, whether with participants migrating from high to low altitude or vice versa. These studies will also be crucial because they will contribute to understanding the possible mechanisms involved in the association found in this series of studies.

The association between coca leaf consumption and depressive symptoms is particularly intriguing. It is plausible that people with depressive symptoms such as fatigue or low mood seek the energizing effect of coca leaf to alleviate those symptoms. Cohort studies can adequately evaluate the temporal relationship by examining these variables' onset.

The combined use of alcohol and coca leaf in the Andean population has been reported for decades (129,130). This combination leads to the appearance of Cocaethylene in the body (131,132). Cocaethylene is described as a substance that generates higher levels of dependency than alcohol or cocaine alone. Therefore, evaluating the interaction of these substances and whether it causes greater cognitive impairment or more significant mood disturbances is essential.

To prevent depression, it is worth assessing the potential advantages of including the hypobaric hypoxia variable in preventive interventions. For example, research should evaluate the impact of moving individuals with genetic predispositions (e.g., those with genetic variants linked to severe depressive episodes or those with a family history of severe or refractory depression) to lower-altitude cities or using supplemental oxygen. Furthermore, these measures could be initiated as soon as mild depressive symptoms appear, such as at the start of a brief depression spell (e.g., 1-3 days of depressive symptoms) (133). The implementation of such measures could have a significant impact on public health.

Regarding depression treatment, research must explore methods to identify more specific criteria for incorporating hypobaric hypoxia in patient management. For example, a particular patient profile may require supplementary oxygen or a recommendation to descend to lower-altitude cities for better depression management, like how Chronic Mountain Sickness is currently managed. Defining a subtype of Altitude-related Depression is relevant.

The specific study of what could be referred to as Altitude-related Depression could lead to the determination of the biochemical mechanisms that are specifically involved in this association. One published paper suggests that changes in tryptophan metabolism may be related to changes in mood at high altitudes (50). This highlights the need for studies that evaluate the effects of specific interventions with substances linked to these mechanisms, such as tryptophan supplementation in the diet.

On the other hand, before or in parallel with conducting longitudinal or experimental studies, there is also a need for further research using population-based cross-sectional survey data. Numerous databases still require more analysis in this line of research.

The "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health periodically runs its surveys. A recent study has been carried out throughout Peru that will provide more data for replicating and evaluating the results described in this dissertation. Extending the study to other populations will also be possible.

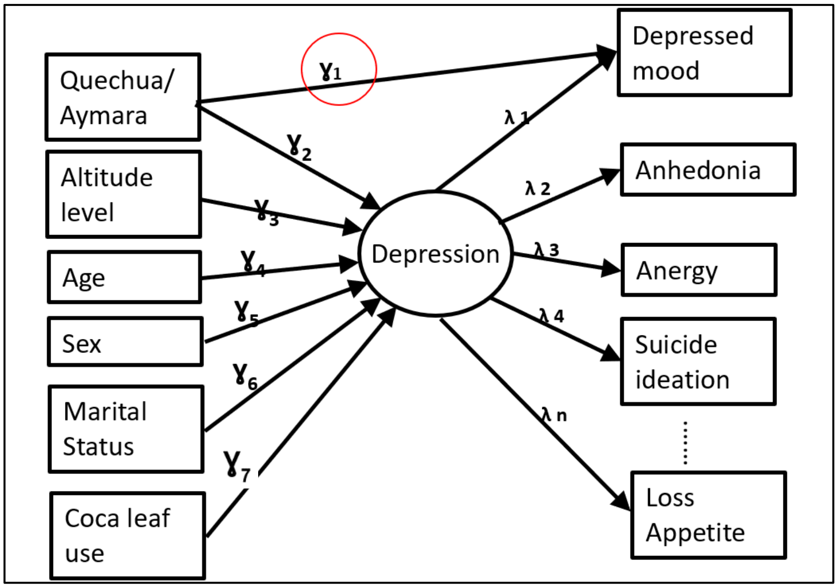
New studies can be achieved using the current and recently collected data, for example, concerning the age of onset of depressive symptoms and the length of residence in high-altitude cities. Further research regarding migration and its effects on depressive symptoms is also needed and plausible with existing data.

There is also a need for a more in-depth study of the various forms of depression manifestations, such as Major Depressive Disorder (MDD) or dysthymia, and intermediate syndromes, such as a sustained depression spell (without MDD). By doing so, it may be possible to determine at what stage in the pathogenesis of MDD living at a higher altitude appears to have the most significant influence.

It is also worth noting other surveys with data still to be analyzed. For example, the Demographic and Health Surveys (DHS) Program has been conducted in up to 90 different countries worldwide, many of which include questions addressing depressive symptoms and are easily accessible. For example, Peru (i.e., ENDES survey), Bolivia, and Colombia have DHS surveys in the Andean region. These and other national surveys from various countries that are currently freely accessible can be integrated to conduct analyses that cover multiple countries simultaneously. As such, the DHS surveys might make it possible to study residents in a range of high-altitude countries around the world.

Another relevant aspect to explore with the available or soon-to-be-accessible data is the evaluation of models with latent variables. For example, models that allow for the assessment of Differential Item Functioning (DIF) between the native population and the rest of the people. Figure 6.1 shows a MIMIC (Multiple Indicators Multiple Causes) model (134–136) that evaluates the possibility that the Quechua or Aymara population may endorse the presence of depressive mood differently from the Major Depressive Episode (MDE) construct or latent variable.

Figure 6.1. Path diagram for MIMIC model. Differential Item Functioning on Depressed Mood.



Note: The right column represents Major Depressive Episode criteria.

Latent variable models can also aid in evaluating whether there is a greater prevalence of suicidal ideation or behavior at high altitudes, above what would be expected based on depressive symptoms alone. This would involve testing the estimated direct effect of altitude level on suicidal ideation and assessing whether this association varies across different altitude subgroups.

Finally, it will be important to explore the potential link between altitude and other mental disorders, such as anxiety disorders or post-traumatic stress disorder. Living at high altitudes is already a stressor, which may increase susceptibility to these conditions. Therefore, further research is necessary not only on depression but also on other mental health problems. Elaborated in this fashion, epidemiological research can help guide public health tactics that ultimately should improve the health of our populations.

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APPENDIX A: DEPRESSED MOOD AND COCA USE QUESTIONS FROM EPIDEMIOLOGICAL SURVEYS OF THE PERUVIAN NATIONAL INSTITUTE OF MENTAL HEALTH “HONORIO DELGADO – HIDEYO NOGUCHI” (“NOGUCHI SURVEYS”)

Epidemiological Surveys of The Peruvian National Institute of Mental Health “Honorio Delgado – Hideyo Noguchi” (“Noguchi Surveys”) employed a survey questionnaire for adults that has five sections (i.e., sociodemographic, general adult health, clinical syndromes part A, clinical syndromes part B, and access to health services).

Here, we include an English language translation of the standardized survey items used in this dissertation to assess the mood state during the last four weeks and to determine participants who were coca-leaf users in the last month before the interview. All questions were applied to participants in their native “mother tongue.”

Depressed mood during the last four weeks before the survey interview was evaluated using two different parts of the questionnaires. The first included a Likert question directly asking about the participant's mood (i.e., Question 6, from the “prevalent mood states” part of the questionnaire). The second question was included as one of the items for the screening tool SRQ-17, which asks about depressive and anxiety symptoms in the last four weeks. One of these questions concerns frequent sadness (i.e., Question 26). Actively depressed mood was finally identified in persons who recognized feeling sadness “always” or “almost always” in question #6 and also answered “Yes” to the question “Have you felt sad frequently in the last four weeks?”.

Coca-leaf use during the last month was assessed in the Clinical Syndromes part A module, which assesses substance use.

ADULT GENERAL HEALTH SECTION

QUESTION 6: Prevalent Mood States ("estados anímicos prevalentes")

6. HOW OFTEN DO YOU FEEL…? CARD 2 Codes 1. Never 4. Almost always 2. Rarely 5. Always 3. Occasionally 6. Doesn't respond						
a. Sad?	1	2	3	4	5	6
b. Tense?	1	2	3	4	5	6
c. anguished?	1	2	3	4	5	6
d. Irritable (or rabid)?	1	2	3	4	5	6
e. Worried?	1	2	3	4	5	6
f. Calm?	1	2	3	4	5	6
g. Happy?	1	2	3	4	5	6
h. Bored?	1	2	3	4	5	6
z. Other?(specify)	1	2	3	4	5	6

ADULT GENERAL HEALTH SECTION

QUESTION 26: SRQ

26. ABOUT YOUR HEALTH IN THE PAST 4 WEEKS: (YES / NO)

a) Have you had headaches, neck, back, or pain in other parts of the body?

b) Has your appetite decreased? or c) Has your appetite increased?

d) Have you had heartburn?

f) Have you slept badly?

g) Are you easily scared?

h) Have you had a hand tremor?

i) Have you felt nervous or tense? or j) Have you felt bored?

k) Have you had poor digestion?

n) Have you been able to think clearly?

o) ***<u>Have you felt sad frequently?</u>***

p) Have you cried frequently?

q) Do you enjoy your daily activities less?

r) Has your ability to make decisions decreased?

u) Have you lost interest in things?

v) Has a person felt useless?

w) Have you often felt tired?

24) Have you ever wanted to die in your life? and 25) In the last month?

CLINICAL SYNDROMES - PART B

QUESTIONS ABOUT SUBSTANCE USE (INCLUDING COCA LEAF)

INTERVIEWER: CIRCLE THE LETTERS CORRESPONDING TO THE POSITIVE RESPONSES	Tabaco (Cigarette)	Tranquilizers	Sleeping Pills	Pills For	Cough Syrup	Stimulants (To Lose Weight)	Ectasis	Marihuana	Cocaine Chlorhyd.	Pasta Basica (PBC)	Heroine	Hallucinogens (LSD) Trip	**Coca Leaf**	Inhalants
51. Which of 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
52. At what age did you consume for the first time?														
53. 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
b. More than one month but less than a year	A	B	C	D	E	F	G	H	I	J	K	L	M	N
c. More than one year	A	B	C	D	E	F	G	H	I	J	K	L	M	N
54. 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
55. Have you ever wanted (or do you want) to stop consuming? *YES = 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

APPENDIX B: CHAPTER 3

Table 3.10.A. Direct estimates for depressed mood prevalence proportions at the district level.

District	altitude (m)	total sample	Weighted population	depressed mood cases	weighted proportion of depressed[1]	Linearized Std Error	Lower Lim 95%	Upper Lim 95%
Lurin	12	33	30968	6	0.1212542	0.045376	0.05649	0.241298
Bellavista	13	34	44671	1	0.0391081	0.035472	0.00635	0.205764
Ancon	14	21	28659	3	0.1292439	0.05119	0.05735	0.265853
Victor Larco Herrera	24	93	68445	9	0.0696910	0.035359	0.02507	0.179158
Callao	27	225	316857	12	0.0553846	0.015956	0.03123	0.09635
La Punta	29	5	5078	0	0.0000000	.	.	.
Coishco	31	56	17515	4	0.0581787	0.019229	0.03011	0.109467
Castilla	35	457	135512	55	0.0916007	0.014472	0.0669	0.124202
La Perla	37	46	47858	1	0.0422082	0.036471	0.00746	0.205374
Nuevo Chimbote	40	477	186049	73	0.1084768	0.016138	0.08065	0.144404
Ventanilla	43	201	186835	10	0.0485669	0.020422	0.02101	0.108279
Chimbote	52	801	197853	97	0.1086564	0.014754	0.08293	0.141143
Piura	57	854	274312	109	0.1066528	0.012012	0.08529	0.132597
Los Olivos	67	112	208440	5	0.0408607	0.017744	0.01723	0.093799
Chorrillos	68	185	227417	11	0.0726931	0.02795	0.0336	0.150202
Pachacama	68	45	45724	4	0.0529263	0.029389	0.01739	0.149972
Santa Rosa	72	5	5472	1	0.1312135	.	.	.
Trujillo	74	508	496572	54	0.1036768	0.017654	0.07381	0.143747
Carmen de la Legua Reynoso	82	25	34045	2	0.0722279	0.032166	0.02948	0.166346
San Miguel	84	49	126159	1	0.0110495	0.010805	0.00161	0.07206
Magdalena Del Mar	90	33	85095	2	0.0547858	0.036757	0.01421	0.189056
Magdalena Vieja	90	26	40621	1	0.0327417	0.031894	0.00468	0.19606

Table 3.10.A. (cont'd)

El Porvenir	92	255	130446	28	0.1051776	0.026135	0.06384	0.168475
Florencia de Mora	92	60	55497	5	0.0697695	0.023813	0.03524	0.133448
Barranco	97	28	21329	1	0.0663885	0.050509	0.01418	0.260062
Mazan	106	146	1577	13	0.1037132	0.024725	0.06427	0.163134
Comas	107	160	361708	5	0.0305209	0.013927	0.01235	0.073413
Santiago de Surco	107	156	185770	3	0.0247187	0.015543	0.00711	0.082339
Iquitos	107	668	127568	73	0.1152850	0.016173	0.08716	0.150981
Independen	111	60	98000	8	0.1089592	0.031586	0.06069	0.187933
Belen	116	178	34678	21	0.1388504	0.041917	0.075	0.242782
San Juan Bautista	120	413	3957	43	0.1071972	0.021865	0.07125	0.158194
Punchana	124	220	47952	19	0.0903451	0.021277	0.05641	0.141634
Miraflores	125	55	78344	6	0.0608853	0.034382	0.01955	0.174094
Surquillo	125	33	52517	1	0.0386351	0.032473	0.00719	0.182443
Nauta	127	234	2658	21	0.0880361	0.016899	0.06005	0.127291
Yarinacocha	131	233	22726	29	0.1495833	0.037689	0.08958	0.239227
San Juan de Miraflores	133	197	241112	9	0.0483178	0.019702	0.02145	0.105243
La Esperanza	137	306	165756	44	0.1308429	0.022492	0.09268	0.181575
San Martin de Porres	138	198	389709	12	0.0673708	0.021385	0.03574	0.123419
Jesus Maria	142	20	42375	0	0.0000000	.		
La Victoria	142	85	139829	4	0.0409254	0.022625	0.01359	0.116713
Lince	150	32	41571	1	0.0160208	0.013716	0.00295	0.08229
Masisea	150	107	1410	9	0.1290780	0.042348	0.06613	0.236766
Breña	153	44	80822	0	0.0000000	.		
Rimac	153	75	159995	4	0.0406763	0.018648	0.01634	0.097659
Lima	162	124	209166	8	0.0851238	0.027095	0.04492	0.155452
Calleria	162	1028	106693	110	0.1014977	0.012324	0.07976	0.128339
San Borja	170	21	43525	1	0.0482022	0.049379	0.0061	0.294725

Table 3.10.A. (cont'd)

Curimana	181	86	1332	6	0.0720721	0.020237	0.04115	0.123257
Nueva Requena	183	29	471	2	0.0360934	4.34E-19	0.03609	0.036093
Puente Piedra	187	97	179820	12	0.0977422	0.023793	0.06	0.155309
San Isidro	195	37	49038	1	0.0168033	0.016745	0.00234	0.110872
El Agustino	200	86	105562	7	0.0590894	0.016058	0.03442	0.099619
Campoverde	203	204	2265	24	0.0966887	0.02323	0.05974	0.152769
Villa El Salvador	204	235	263244	25	0.0908987	0.025181	0.05214	0.153785
Villa Maria Del Triunfo	210	196	206200	26	0.1157565	0.022516	0.07838	0.167713
San Luis	214	21	31229	0	0.0000000	.	.	.
San Juan de Lurigancho	222	596	633358	48	0.0754879	0.012654	0.05412	0.104353
Irazola	228	235	2066	24	0.1040658	0.026096	0.06288	0.167419
Carabayllo	238	77	141874	11	0.1494284	0.05615	0.0688	0.294663
La Molina	262	61	65850	4	0.0507517	0.023404	0.02021	0.12173
Padre Abad	275	203	3040	8	0.0434211	0.016333	0.02056	0.089368
Santa Anita	285	131	124334	15	0.0856941	0.0235	0.04948	0.144394
Coayllo	285	41	693	2	0.0655632	0.00272	0.06043	0.071103
Cieneguilla	287	9	7737	0	0.0000000	.		
Morales	290	249	13378	29	0.1154281	0.029327	0.06916	0.186447
Tarapoto	342	877	43535	83	0.0906306	0.01137	0.07067	0.115531
Ate	378	386	352291	20	0.0487892	0.010876	0.03138	0.075111
La Banda De Shilcayo	418	212	10468	14	0.0797129	0.025437	0.04204	0.145998
Ica	432	849	144321	96	0.1025769	0.015165	0.07643	0.136355
La Tinguina	463	189	27137	30	0.1084866	0.02842	0.06402	0.177976
Parcona	472	317	51844	46	0.1254533	0.02097	0.08976	0.172645
Llochegua	540	62	4958	11	0.1644763	0.023965	0.12269	0.216979
Sivia	561	46	3226	7	0.1247241	0.02892	0.07814	0.193256

Table 3.10.A. (cont'd)

Chaclacayo	685	26	24163	3	0.1064851	0.054012	0.03768	0.266189
Zuðiga	827	40	3649	3	0.0581796	0.027063	0.02292	0.139933
Lurigancho	879	142	134734	14	0.0791263	0.018058	0.0502	0.122568
Santa Rosa De Quives	936	51	3895	6	0.0347893	0.028682	0.00671	0.161356
Huanchay	1067	30	1044	5	0.1531222	0.035502	0.0956	0.236224
Catahuasi	1203	64	1208	8	0.1059964	0.066812	0.02889	0.32086
Pariacoto	1264	29	1208	3	0.0667477	0.018196	0.03877	0.112547
Magdalena	1298	16	1530	1	0.0292257	7.37E-18	0.02923	0.029226
Antioquia	1573	39	1139	4	0.1867312	0.019025	0.15225	0.226928
San Bartolome	1644	63	1080	8	0.0978018	0.03957	0.04306	0.207089
Huanuco	1921	729	45009	38	0.0431107	0.007843	0.0301	0.061391
Amarilis	1950	529	38985	39	0.0579364	0.010826	0.04002	0.083187
Putinza	1985	25	1065	2	0.0421715	1.08E-17	0.04217	0.042172
Pillco Marca	1996	235	20172	16	0.0483964	0.018715	0.02241	0.101388
Surco	2049	54	1194	11	0.1287751	0.033662	0.07585	0.210235
San Mateo De Otao	2084	37	2740	3	0.0726108	0.000728	0.0712	0.074051
Ambar	2084	55	694	7	0.0802309	0.021807	0.04659	0.134729
Cochabamb	2135	16	1018	1	0.0233441	1.30E-18	0.02334	0.023344
Chumuch	2202	15	1930	2	0.1182837	6.07E-18	0.11828	0.118284
Tiabaya	2218	23	15931	5	0.2459984	0.002372	0.24138	0.25068
Asuncion	2254	30	4342	5	0.1489309	0.034771	0.09272	0.230567
Sachaca	2300	35	10700	7	0.2018692	0.090855	0.07725	0.433168
Jacob Hunter	2309	69	41133	13	0.1509007	0.048337	0.07818	0.271341
San Juan	2336	15	1651	2	0.0535630	1.04E-17	0.05356	0.053563
Socabaya	2352	119	55143	14	0.1376603	0.048971	0.06638	0.263866
Cortegana	2352	14	2803	2	0.1729343	1.04E-17	0.17293	0.172934

Table 3.10.A. (cont'd)

Jose Luis Bustamante	2389	138	113604	11	0.0579293	0.014695	0.035	0.094417
Yanahuara	2402	34	24942	2	0.0582552	0.053965	0.00891	0.298564
Arequipa	2429	124	83377	6	0.0505295	0.023117	0.02027	0.120409
Cerro Colorado	2441	145	97706	27	0.1534501	0.032133	0.1004	0.227449
Miraflores	2450	78	48656	17	0.2143826	0.053676	0.12746	0.337648
Paucarpata	2453	206	115064	40	0.2019485	0.048081	0.12356	0.312343
Manas	2457	73	482	7	0.0737177	0.012517	0.05263	0.10234
Mariano Melgar	2459	90	67484	15	0.1018464	0.02285	0.06497	0.156161
Lampian	2467	45	672	13	0.2501439	0.015313	0.22133	0.281352
Cospan	2471	14	1242	0	0.0000000	.		
Abancay	2500	1565	29779	183	0.1084948	0.009653	0.09097	0.128922
Alto Selva Alegre	2510	128	52231	17	0.0812544	0.022479	0.04671	0.137645
Cayma	2531	143	76338	25	0.1280620	0.039376	0.06852	0.226752
Arahuay	2533	39	601	4	0.0796215	0.012494	0.05832	0.10782
Huasmin	2543	61	8365	6	0.0753670	0.016102	0.04926	0.113654
Bambamarca	2556	221	26708	25	0.0959410	0.02618	0.05546	0.160931
Jesus	2568	45	5601	7	0.0840636	0.038452	0.03332	0.19637
Pacaycasa	2571	12	742	1	0.0443948	6.07E-18	0.04439	0.044395
Luricocha	2598	36	2043	7	0.2430948	0.020738	0.20476	0.286022
Tinco	2606	40	3119	4	0.1331871	0.05477	0.05715	0.280327
Marca	2615	15	245	3	0.1617828	1.13E-17	0.16178	0.161783
Jose Galvez	2618	16	1874	0	0.0000000	.		
Tamburco	2620	181	3663	11	0.0522157	0.012926	0.03196	0.084201
Llacanora	2621	15	1809	0	0.0000000	.		
Celendin	2629	31	3063	2	0.0827215	0.066618	0.01587	0.335277
Sucre	2632	28	2907	4	0.1311303	0.041332	0.06899	0.235109
Carhuaz	2663	64	4489	15	0.2417230	0.076981	0.12274	0.420741
Sorochuco	2663	41	4178	4	0.0927269	0.0251	0.05387	0.155019

Table 3.10.A. (cont'd)

San Pedro De Pilas	2678	41	1291	5	0.0973511	0.016383	0.06962	0.134534
San Lorenzo De Quinti	2682	62	657	10	0.1301827	0.040807	0.06876	0.232773
Huanta	2685	78	3812	18	0.1596776	0.0578	0.07549	0.306619
Los Baños Del Inca	2685	74	12008	5	0.0549839	0.02496	0.02218	0.129854
Acopampa	2692	28	1150	5	0.1423890	0.028617	0.09491	0.208156
Cajamarca	2731	1197	97516	123	0.0885711	0.009481	0.07166	0.109008
Namora	2765	44	5943	1	0.0362618	0.030445	0.00677	0.171956
Chugur	2765	13	2390	0	0.0000000	.		
Marcara	2767	65	2857	17	0.2016173	0.036593	0.1392	0.282831
Sangallaya	2779	39	743	5	0.1113378	0.029532	0.06523	0.183639
San Juan Bautista	2786	255	15801	46	0.1459350	0.017593	0.1147	0.18391
Ayacucho	2797	792	46842	162	0.1670890	0.015437	0.13897	0.199584
Anta	2800	30	1513	4	0.0827145	0.02427	0.04595	0.14445
Miguel Iglesias	2813	15	1437	2	0.1448737	6.94E-18	0.14487	0.144874
Jesus Nazareno	2817	127	7652	18	0.0876457	0.019189	0.05661	0.133287
Jangas	2824	59	2097	9	0.1388774	0.028115	0.09232	0.203645
Pariahuanc	2830	15	1532	5	0.3066157	2.26E-17	0.30662	0.306616
Tarica	2832	42	2315	6	0.1783122	0.035404	0.11903	0.258456
Matara	2834	16	2524	4	0.2442460	2.08E-17	0.24425	0.244246
Yungar	2836	26	1233	4	0.1530339	0.0408	0.08881	0.250907
Oxamarca	2836	14	1847	1	0.0507303	9.11E-18	0.05073	0.05073
Ihuari	2850	100	1516	19	0.1167042	0.021176	0.08115	0.165037
Santo Domingo De Los	2861	43	841	7	0.1050430	0.007331	0.09151	0.12031
Acos Vinchos	2874	47	1861	4	0.0587863	0.053492	0.0093	0.293676
Langa	2889	53	572	6	0.0910606	0.010656	0.07221	0.114223

Table 3.10.A. (cont'd)

Yauyos	2895	84	2424	19	0.1727309	0.027885	0.12466	0.234377
Amashca	2905	14	547	1	0.0580088	1.73E-18	0.05801	0.058009
Huayllapamp	2908	12	344	2	0.1496042	5.20E-18	0.1496	0.149604
Carmen Alto	2921	125	6260	28	0.2200759	0.034994	0.15909	0.2962
Huachupamp	2938	21	501	2	0.0657959	1.13E-17	0.0658	0.065796
La Libertad De Pallan	2952	27	2910	5	0.1441236	0.043031	0.07831	0.250223
San Miguel De Aco	2956	32	1217	5	0.1932970	0.013395	0.16838	0.220924
Carhuanca	2980	16	399	3	0.1020116	4.34E-19	0.10201	0.102012
Llacllin	3020	10	537	0	0.0000000	.		
Shilla	3036	42	2212	10	0.1968203	0.028794	0.14636	0.259393
Independenc	3047	673	26550	101	0.1200595	0.012149	0.0982	0.145992
Gorgor	3049	117	195	24	0.1632999	0.026579	0.11761	0.222277
Concepcion	3061	16	1068	2	0.0527453	5.64E-18	0.05275	0.052745
Iguain	3063	26	1322	5	0.2425729	0.021359	0.20317	0.286861
Huaraz	3073	640	26530	85	0.1159611	0.014063	0.0911	0.146508
Encañada	3087	91	14818	7	0.1217696	0.036566	0.06622	0.21327
Tambillo	3111	29	2004	10	0.3604221	0.0349	0.29517	0.43127
Vischongo	3150	45	1825	8	0.1836713	0.072999	0.07971	0.368882
Ayauca	3151	76	552	22	0.2477332	0.049672	0.16337	0.35707
Ocros	3153	44	1809	5	0.1017419	0.035525	0.0502	0.195319
Vinchos	3155	87	3803	19	0.1744624	0.035418	0.11542	0.254999
Huarochiri	3170	38	1364	4	0.1178047	0.003923	0.11033	0.125717
Caujul	3185	40	1040	9	0.1882301	0.017394	0.15647	0.224725
Huancapon	3187	74	834	9	0.0994341	0.046792	0.03812	0.235248
Santiago De Pischa	3210	16	403	1	0.0477326	9.11E-18	0.04773	0.047733
Acocro	3251	61	3842	8	0.1010243	0.028523	0.05723	0.172205
San Damian	3252	79	1061	9	0.0798327	0.035528	0.03252	0.182981

Table 3.10.A. (cont'd)

Santillana	3265	45	3089	5	0.0659849	0.003	0.06034	0.072117
Paccho	3275	126	1236	19	0.1414185	0.048415	0.07008	0.264698
San Jose De Ticllas	3282	30	2244	5	0.1709370	0.027525	0.12349	0.231801
Madean	3292	65	201	18	0.2631673	0.044587	0.18536	0.359231
Huambalpa	3294	31	1286	5	0.1406767	0.08989	0.0367	0.412984
Leoncio Prado	3299	60	3116	8	0.1329162	0.008867	0.11647	0.151286
Huamanguilla	3300	39	2141	6	0.1671351	0.056974	0.08252	0.309272
Quinua	3301	27	1230	3	0.0897240	0.002148	0.0856	0.094026
Huantan	3315	46	784	12	0.2662035	0.022989	0.22361	0.313628
Viðac	3315	111	666	17	0.1163343	0.024159	0.07667	0.172673
San Andres De Tupicoc	3321	38	1161	3	0.0993926	0.023551	0.06181	0.156025
Socos	3368	45	2218	5	0.1126035	0.064175	0.03477	0.308933
Accomarca	3387	15	509	0	0.0000000	.		
Colonia	3399	101	1013	22	0.2182210	0.026285	0.17106	0.274092
Pararin	3402	13	349	1	0.0918476	1.91E-17	0.09185	0.091848
Recuay	3428	15	451	2	0.1242236	4.68E-17	0.12422	0.124224
Azangaro	3435	68	136	16	0.2411326	0.021445	0.20161	0.285633
Olleros	3443	31	997	2	0.0269720	0.019403	0.00646	0.105652
Carampoma	3459	25	278	4	0.1267429	2.08E-17	0.12674	0.126743
Ticapampa	3485	32	1073	3	0.0692478	0.027964	0.0308	0.148355
Vilcas Huaman	3494	60	3066	16	0.2845998	0.065383	0.17488	0.427495
Lincha	3516	36	935	6	0.0977272	0.030025	0.05263	0.174356
Hualgayoc	3530	46	6966	10	0.2614837	0.039487	0.19167	0.34585
Chiara	3540	45	2815	5	0.0678484	0.041691	0.01959	0.20955
Santa Cruz De Andamar	3550	109	3836	24	0.2006279	0.012345	0.17751	0.22593
Pampas Chico	3552	14	417	0	0.0000000	.		

Table 3.10.A. (cont'd)

Saurama	3574	16	876	8	0.4255405	9.02E-17	0.42554	0.425541
Catac	3579	14	657	1	0.0486437	8.67E-18	0.04864	0.048644
Huancaya	3591	40	925	6	0.1374064	0.014493	0.11138	0.168367
Pira	3602	45	1826	5	0.0802828	0.015192	0.0551	0.115568
Independen	3606	31	1463	5	0.1293494	0.017644	0.09851	0.16805
Huaros	3614	88	511	15	0.1417445	0.037946	0.08223	0.233391
Vitis	3625	23	893	4	0.1370189	3.12E-17	0.13702	0.137019
Miraflores	3677	37	1072	4	0.0755937	0.001053	0.07355	0.077684
Laraos	3683	22	578	2	0.0847354	4.34E-18	0.08474	0.084735
Lachaqui	3686	43	664	9	0.1443052	0.066232	0.05563	0.325579
Pampas	3698	16	587	1	0.0597973	1.04E-17	0.0598	0.059797
Ascension	3711	366	6172	40	0.0845755	0.015013	0.05941	0.119044
Huancavelica	3746	1350	19679	132	0.0894354	0.010353	0.07111	0.11192
Simon Bolivar	4234	257	6778	18	0.0586937	0.017445	0.03248	0.103791
Chaupimarca	4373	611	14364	32	0.0412328	0.010706	0.02466	0.068154
Yanacancha	4394	601	18474	32	0.0413926	0.010068	0.02558	0.066308

1 Direct estimate using survey set settings and Taylor Series Linearization.

Table 3.10.B. Standardized, and Fay-Herriot (EBLUP) estimates for depressed mood prevalence proportions at the district level.

District	altitude (m)	total sample	depress mood cases	Standardized prevalence proportion[2]	linzd Std Error Input[3]	variance input	EBLUP6[4]
Lurin	12	33	6	0.079947	0.045376	0.067946	0.0696348
Bellavista	13	34	1	0.080987	0.035472	0.04278	0.0353903
Ancon	14	21	3	0.055609	0.05119	0.055028	0.0753254
Victor Larco Herrera	24	93	9	0.069257	0.035359	0.116274	0.0564733
Callao	27	225	12	0.044958	0.015956	0.057283	0.0475560
La Punta	29	5	0	0.000000	0.000728	2.65E-06	0.0000000
Coishco	31	56	4	0.078877	0.019229	0.020705	0.0647712
Castilla	35	457	55	0.093621	0.014472	0.095707	0.0734788
La Perla	37	46	1	0.006968	0.036471	0.061187	0.0288702
Nuevo Chimbote	40	477	73	0.125021	0.016138	0.124232	0.0768325
Ventanilla	43	201	10	0.046284	0.020422	0.083825	0.0545014
Chimbote	52	801	97	0.104098	0.014754	0.174369	0.0752259
Piura	57	854	109	0.102355	0.012012	0.12322	0.0739734
Los Olivos	67	112	5	0.041981	0.017744	0.035262	0.0308278
Chorrillos	68	185	11	0.078213	0.02795	0.144521	0.0448812
Pachacama	68	45	4	0.053190	0.029389	0.038867	0.0597304
Santa Rosa	72	5	1	0.117366	0.000728	2.65E-06	0.1312001
Trujillo	74	508	54	0.100086	0.017654	0.158331	0.0548859
Carmen de la Legua Reynoso	82	25	2	0.124677	0.032166	0.025866	0.0409197
San Miguel	84	49	1	0.004874	0.010805	0.00572	0.0152636
Magdalena Del Mar	90	33	2	0.033989	0.036757	0.044587	0.0290729
Magdalena Vieja	90	26	1	0.029405	0.031894	0.026448	0.0238478

Table 3.10.B. (cont'd)

El Porvenir	92	255	28	0.094772	0.026135	0.174173	0.0658213
Florencia De Mora	92	60	5	0.071790	0.023813	0.034022	0.0330000
Barranco	97	28	1	0.009280	0.050509	0.071432	0.0366740
Mazan	106	146	13	0.122491	0.024725	0.08925	0.0875277
Comas	107	160	5	0.031699	0.013927	0.031036	0.0352315
Santiago De Surco	107	156	3	0.025930	0.015543	0.037686	0.0354732
Iquitos	107	668	73	0.112090	0.016173	0.174735	0.0754414
Independen	111	60	8	0.095623	0.031586	0.059859	0.0456306
Belen	116	178	21	0.140553	0.041917	0.312748	0.0768533
San Juan Bautista	120	413	43	0.116561	0.021865	0.197446	0.0748603
Punchana	124	220	19	0.075820	0.021277	0.099592	0.0771518
Miraflores	125	55	6	0.065032	0.034382	0.065016	0.0365880
Surquillo	125	33	1	0.023490	0.032473	0.034798	0.0183966
Nauta	127	234	21	0.101794	0.016899	0.066825	0.0777898
Yarinacocha	131	233	29	0.118808	0.037689	0.330974	0.0927122
San Juan de Miraflores	133	197	9	0.044313	0.019702	0.076472	0.0310653
La Esperanza	137	306	44	0.145227	0.022492	0.154808	0.0559470
San Martin de Porres	138	198	12	0.057664	0.021385	0.090546	0.0349525
Jesus Maria	142	20	0	0.000000	0.000728	1.06E-05	0.0000000
La Victoria	142	85	4	0.038740	0.022625	0.043512	0.0246574
Lince	150	32	1	0.038754	0.013716	0.00602	0.0146491
Masisea	150	107	9	0.122819	0.042348	0.191886	0.1088924
Breña	153	44	0	0.000000	0.000728	2.33E-05	0.0000000
Rimac	153	75	4	0.043309	0.018648	0.026082	0.0347675
Lima	162	124	8	0.066914	0.027095	0.091036	0.0378552
Calleria	162	1028	110	0.100221	0.012324	0.156121	0.0909357
San Borja	170	21	1	0.057992	0.049379	0.051203	0.0374694

Table 3.10.B. (cont'd)

Curimana	181	86	6	0.113677	0.020237	0.035222	0.1016307
Nueva Requena	183	29	2	0.048774	0.000728	1.54E-05	0.0361466
Puente Piedra	187	97	12	0.104760	0.023793	0.054911	0.0607501
San Isidro	195	37	1	0.007468	0.016745	0.010374	0.0270461
El Agustino	200	86	7	0.053699	0.016058	0.022176	0.0422409
Campoverde	203	204	24	0.097876	0.02323	0.110085	0.1034860
Villa El Salvador	204	235	25	0.094072	0.025181	0.149005	0.0405010
Villa Maria del Triunfo	210	196	26	0.096697	0.022516	0.099363	0.0572620
San Luis	214	21	0	0.000000	0.000728	1.11E-05	0.0000000
San Juan de Lurigancho	222	596	48	0.077806	0.012654	0.095435	0.0488270
Irazola	228	235	24	0.103495	0.026096	0.160033	0.1106470
Carabayllo	238	77	11	0.122686	0.05615	0.242766	0.0670984
La Molina	262	61	4	0.038612	0.023404	0.033413	0.0498861
Padre Abad	275	203	8	0.037559	0.016333	0.054153	0.0850321
Santa Anita	285	131	15	0.074712	0.0235	0.072345	0.0331790
Coayllo	285	41	2	0.125841	0.00272	0.000303	0.0657050
Cieneguilla	287	9	0	0.000000	0.000728	4.77E-06	0.0000000
Morales	290	249	29	0.112885	0.029327	0.214154	0.0767559
Tarapoto	342	877	83	0.089918	0.01137	0.113372	0.0726437
Ate	378	386	20	0.048069	0.010876	0.045659	0.0472055
La Banda de Shilcayo	418	212	14	0.078471	0.025437	0.137176	0.0761008
Ica	432	849	96	0.097347	0.015165	0.19524	0.0801667
La Tinguina	463	189	30	0.102733	0.02842	0.152651	0.0841299
Parcona	472	317	46	0.124654	0.02097	0.139401	0.0830169
Llochegua	540	62	11	0.181293	0.023965	0.035606	0.1089162
Sivia	561	46	7	0.141068	0.02892	0.038472	0.0896776
Chaclacayo	685	26	3	0.054737	0.054012	0.075851	0.0661602
Zuðiga	827	40	3	0.077173	0.027063	0.029296	0.0624724

Table 3.10.B. (cont'd)

Lurigancho	879	142	14	0.080537	0.018058	0.046304	0.0643181
Santa Rosa de Quives	936	51	6	0.040213	0.028682	0.041956	0.0648836
Huanchay	1067	30	5	0.103450	0.035502	0.037812	0.1148265
Catahuasi	1203	64	8	0.088139	0.066812	0.285684	0.0890247
Pariacoto	1264	29	3	0.072704	0.018196	0.009602	0.0773745
Magdalena	1298	16	1	0.045639	0.000728	8.48E-06	0.0292428
Antioquia	1573	39	4	0.250594	0.019025	0.014117	0.1445636
San Bartolome	1644	63	8	0.096362	0.03957	0.098643	0.0898827
Huanuco	1921	729	38	0.042887	0.007843	0.04484	0.0669651
Amarilis	1950	529	39	0.058293	0.010826	0.061997	0.0692121
Putinza	1985	25	2	0.049331	0.000728	1.32E-05	0.0422053
Pillco Marca	1996	235	16	0.047872	0.018715	0.082311	0.0705608
Surco	2049	54	11	0.107871	0.033662	0.061189	0.0924860
San Mateo de Otao	2084	37	3	0.055145	0.000728	1.96E-05	0.0726392
Ambar	2084	55	7	0.067798	0.021807	0.026154	0.0886489
Cochabamba	2135	16	1	0.006640	0.000728	8.48E-06	0.0233664
Chumuch	2202	15	2	0.098513	0.000728	7.95E-06	0.1182717
Tiabaya	2218	23	5	0.200014	0.002372	0.000129	0.2444341
Asuncion	2254	30	5	0.102316	0.034771	0.03627	0.1043668
Sachaca	2300	35	7	0.194364	0.090855	0.288914	0.0745249
Jacob Hunter	2309	69	13	0.130347	0.048337	0.161217	0.0776495
San Juan	2336	15	2	0.020893	0.000728	7.95E-06	0.0535749
Socabaya	2352	119	14	0.140321	0.048971	0.28538	0.0714195
Cortegana	2352	14	2	0.092203	0.000728	7.42E-06	0.1728861
Jose Luis Bustamante	2389	138	11	0.049894	0.014695	0.029801	0.0550670
Yanahuara	2402	34	2	0.085099	0.053965	0.099014	0.0408212
Arequipa	2429	124	6	0.038322	0.023117	0.066262	0.0232999
Cerro Colorado	2441	145	27	0.143074	0.032133	0.149713	0.0799007
Miraflores	2450	78	17	0.223277	0.053676	0.224729	0.0764839

Table 3.10.B. (cont'd)

Paucarpata	2453	206	40	0.189008	0.048081	0.476219	0.0704244
Manas	2457	73	7	0.098725	0.012517	0.011437	0.0797613
Mariano Melgar	2459	90	15	0.087979	0.02285	0.046989	0.0774522
Lampian	2467	45	13	0.183524	0.015313	0.010552	0.1861476
Cospan	2471	14	0	0.000000	0.000728	7.42E-06	0.0000000
Abancay	2500	1565	183	0.108660	0.009653	0.145824	0.0737195
Alto Selva Alegre	2510	128	17	0.080756	0.022479	0.06468	0.0566242
Cayma	2531	143	25	0.145982	0.039376	0.22172	0.0757226
Arahuay	2533	39	4	0.080101	0.012494	0.006088	0.0845180
Huasmin	2543	61	6	0.087633	0.016102	0.015816	0.0744675
Bambamarca	2556	221	25	0.087440	0.02618	0.151473	0.0770769
Jesus	2568	45	7	0.090665	0.038452	0.066536	0.0668614
Pacaycasa	2571	12	1	0.040790	0.000728	6.36E-06	0.0444103
Luricocha	2598	36	7	0.195352	0.020738	0.015483	0.1580106
Tinco	2606	40	4	0.111455	0.05477	0.119989	0.0823937
Marca	2615	15	3	0.098188	0.000728	7.95E-06	0.1617417
Jose Galvez	2618	16	0	0.000000	0.000728	8.48E-06	0.0000000
Tamburco	2620	181	11	0.059515	0.012926	0.030243	0.0667397
Llacanora	2621	15	0	0.000000	0.000728	7.95E-06	0.0000000
Celendin	2629	31	2	0.086481	0.066618	0.137578	0.0760677
Sucre	2632	28	4	0.079366	0.041332	0.047833	0.0870447
Carhuaz	2663	64	15	0.206867	0.076981	0.379272	0.0936068
Sorochuco	2663	41	4	0.111423	0.0251	0.025831	0.0827519
San Pedro de Pilas	2678	41	5	0.198081	0.016383	0.011004	0.1055394
San Lorenzo De Quinti	2682	62	10	0.143245	0.040807	0.103242	0.1063442
Huanta	2685	78	18	0.103737	0.0578	0.260589	0.0801333
Los Baños del Inca	2685	74	5	0.060533	0.02496	0.046102	0.0658663
Acopampa	2692	28	5	0.112468	0.028617	0.02293	0.1067876
Cajamarca	2731	1197	123	0.092653	0.009481	0.107602	0.0710803

Table 3.10.B. (cont'd)

Namora	2765	44	1	0.020492	0.030445	0.040784	0.0595534
Chugur	2765	13	0	0.000000	0.000728	6.89E-06	0.0000000
Marcara	2767	65	17	0.224114	0.036593	0.087037	0.1085737
Sangallaya	2779	39	5	0.155614	0.029532	0.034013	0.1053622
San Juan Bautista	2786	255	46	0.164363	0.017593	0.078923	0.0840430
Ayacucho	2797	792	162	0.172509	0.015437	0.188742	0.0858912
Anta	2800	30	4	0.068917	0.02427	0.017671	0.0795653
Miguel Iglesias	2813	15	2	0.077686	0.000728	7.95E-06	0.1448389
Jesus Nazareno	2817	127	18	0.108223	0.019189	0.046761	0.0782104
Jangas	2824	59	9	0.095242	0.028115	0.046637	0.1036216
Pariahuanc	2830	15	5	0.172609	0.000728	7.95E-06	0.3064933
Tarica	2832	42	6	0.165560	0.035404	0.052646	0.1048648
Matara	2834	16	4	0.320784	0.000728	8.48E-06	0.2441453
Yungar	2836	26	4	0.133534	0.0408	0.04328	0.1027020
Oxamarca	2836	14	1	0.033264	0.000728	7.42E-06	0.0507383
Ihuari	2850	100	19	0.120405	0.021176	0.044842	0.1084179
Santo Domingo de Los	2861	43	7	0.103388	0.007331	0.002311	0.1045488
Acos Vinchos	2874	47	4	0.039507	0.053492	0.134486	0.0920432
Langa	2889	53	6	0.103196	0.010656	0.006018	0.0952761
Yauyos	2895	84	19	0.154428	0.027885	0.065314	0.0863232
Amashca	2905	14	1	0.059496	0.000728	7.42E-06	0.0580248
Huayllapamp	2908	12	2	0.060904	0.000728	6.36E-06	0.1495862
Carmen Alto	2921	125	28	0.242069	0.034994	0.153072	0.0823295
Huachupamp	2938	21	2	0.019559	0.000728	1.11E-05	0.0658186
La Libertad de Pallan	2952	27	5	0.143127	0.043031	0.049995	0.0956578
San Miguel de Aco	2956	32	5	0.129659	0.013395	0.005741	0.1612086
Carhuanca	2980	16	3	0.197380	0.000728	8.48E-06	0.1020017
Llacllin	3020	10	0	0.000000	0.000728	5.3E-06	0.0000000
Shilla	3036	42	10	0.250955	0.028794	0.034823	0.1436752

Table 3.10.B. (cont'd)

Independenc	3047	673	101	0.121834	0.012149	0.099325	0.0858664
Gorgor	3049	117	24	0.166361	0.026579	0.082651	0.1117200
Concepcion	3061	16	2	0.045639	0.000728	8.48E-06	0.0527629
Iguain	3063	26	5	0.244365	0.021359	0.011861	0.1630653
Huaraz	3073	640	85	0.119571	0.014063	0.126572	0.0832834
Encañada	3087	91	7	0.095605	0.036566	0.121674	0.0694840
Tambillo	3111	29	10	0.367439	0.0349	0.035321	0.1747842
Vischongo	3150	45	8	0.184673	0.072999	0.239796	0.0939462
Ayauca	3151	76	22	0.225058	0.049672	0.187518	0.0852323
Ocros	3153	44	5	0.059239	0.035525	0.05553	0.0948775
Vinchos	3155	87	19	0.156922	0.035418	0.109138	0.1034588
Huarochiri	3170	38	4	0.050611	0.003923	0.000585	0.1170430
Caujul	3185	40	9	0.135313	0.017394	0.012102	0.1471109
Huancapon	3187	74	9	0.087316	0.046792	0.162024	0.0918449
Santiago De Pischa	3210	16	1	0.018726	0.000728	8.48E-06	0.0477489
Acocro	3251	61	8	0.119461	0.028523	0.049626	0.0931438
San Damian	3252	79	9	0.068111	0.035528	0.099719	0.1008816
Santillana	3265	45	5	0.083911	0.003	0.000405	0.0663510
Paccho	3275	126	19	0.131507	0.048415	0.295348	0.1371170
San Jose De Ticllas	3282	30	5	0.135804	0.027525	0.022728	0.1158605
Madean	3292	65	18	0.245299	0.044587	0.129222	0.1336052
Huambalpa	3294	31	5	0.153852	0.08989	0.250485	0.1069616
Leoncio Prado	3299	60	8	0.059456	0.008867	0.004718	0.1255297
Huamanguilla	3300	39	6	0.186132	0.056974	0.126593	0.0908418
Quinua	3301	27	3	0.061112	0.002148	0.000125	0.0897736
Huantan	3315	46	12	0.237040	0.022989	0.02431	0.1425700
Viðac	3315	111	17	0.099947	0.024159	0.064786	0.0995365
San Andres De Tupicoc	3321	38	3	0.098601	0.023551	0.021076	0.1080302
Socos	3368	45	5	0.099122	0.064175	0.185327	0.0849915

Table 3.10.B. (cont'd)

Accomarca	3387	15	0	0.000000	0.000728	7.95E-06	0.0000000
Colonia	3399	101	22	0.165006	0.026285	0.069778	0.1362414
Pararin	3402	13	1	0.015644	0.000728	6.89E-06	0.0918526
Recuay	3428	15	2	0.096058	0.000728	7.95E-06	0.1242041
Azangaro	3435	68	16	0.225303	0.021445	0.031272	0.1464752
Olleros	3443	31	2	0.022988	0.019403	0.011671	0.0531877
Carampoma	3459	25	4	0.109409	0.000728	1.32E-05	0.1267116
Ticapampa	3485	32	3	0.039959	0.027964	0.025024	0.0804289
Vilcas Huaman	3494	60	16	0.228409	0.065383	0.256498	0.0926997
Lincha	3516	36	6	0.102883	0.030025	0.032453	0.1023138
Hualgayoc	3530	46	10	0.205148	0.039487	0.071722	0.0911615
Chiara	3540	45	5	0.085554	0.041691	0.078218	0.0770576
Santa Cruz de Andamar	3550	109	24	0.153664	0.012345	0.016612	0.1358383
Pampas Chico	3552	14	0	0.000000	0.000728	7.42E-06	0.0000000
Saurama	3574	16	8	0.334581	0.000728	8.48E-06	0.4253369
Catac	3579	14	1	0.008768	0.000728	7.42E-06	0.0486578
Huancaya	3591	40	6	0.142419	0.014493	0.008401	0.1237612
Pira	3602	45	5	0.066806	0.015192	0.010385	0.0843879
Independen	3606	31	5	0.146897	0.017644	0.009651	0.1190456
Huaros	3614	88	15	0.127416	0.037946	0.12671	0.0990310
Vitis	3625	23	4	0.146478	0.000728	1.22E-05	0.1369873
Miraflores	3677	37	4	0.042581	0.001053	4.1E-05	0.0756507
Laraos	3683	22	2	0.235806	0.000728	1.17E-05	0.0847409
Lachaqui	3686	43	9	0.122780	0.066232	0.188629	0.0979619
Pampas	3698	16	1	0.023194	0.000728	8.48E-06	0.0598082
Ascension	3711	366	40	0.081539	0.015013	0.082495	0.0768907
Huancavelica	3746	1350	132	0.086282	0.010353	0.144691	0.0732809
Simon Bolivar	4234	257	18	0.053885	0.017445	0.078214	0.0622410
Chaupimarca	4373	611	32	0.039955	0.010706	0.070032	0.0553758

Table 3.10.B. (cont'd)

Yanacancha	4394	601	32	0.044289	0.010068	0.060924	0.0622228

2 Direct standardization methods adjusting for sex and age categories (i.e., 18-44, 45-64, >=65 years).

3 Replacing null values and using the lower plausible value obtained in other districts.

4 Empirical best linear unbiased prediction (EBLUP) with Fay-Herriot model, using auxiliary data: population density, poverty rates, and human development index at district level.

Figure 3.7. The Output of the final Fay-Herriot model[1] for obtaining EBLUP[2] estimates.

```
. fayherriot y idh_2019 pct_pobreza_total pob_densidad_2020 , variance(var)
eblup(EBLUPFinal) mse(MSEFinal) sigmamethod(reml) arcsin reps(999)

Iteration 0:   f(p) = -79563.708
Iteration 1:   f(p) =  28.517064
Iteration 2:   f(p) =  28.693705
Iteration 3:   f(p) =  28.695044
Iteration 4:   f(p) =  28.695044

 Bootstrap
......50.....100.....150.....200.....250.....300.....350.....400.....450.....500.....550...
....650.....700.....750.....800.....850.....900.....950....

Sigma2_u estimation method:     reml             N in sample      =        223
Transformation of depvar:       arcsine          N out of sample  =          0
EBLUP and MSE bias correction:  none             Sigma2_u         =     0.0169
                                                 Adj R-squared    =     0.1397
                                                 FH R-squared     =     0.8277
------------------------------------------------------------------------------
           y | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
 HDI_2019    |  -.2748443   .1563296    -1.76   0.079    -.5812447    .0315561
pct_poverty  |  -.0018669   .0011864    -1.57   0.116    -.0041922    .0004584
pop_density  |  -3.80e-06   2.13e-06    -1.78   0.075    -7.99e-06    3.79e-07
       _cons |   .4709515   .0984947     4.78   0.000     .2779054    .6639975
------------------------------------------------------------------------------
Shapiro-Wilk test for normality:
 Residuals e (standardized)  V =    9.738  p-value = 0.000
 Random effects u            V =   41.711  p-value = 0.000
------------------------------------------------------------------------------
```

1: Model using Fayherriot Stata© command, including human development index, poverty proportions, and population density for each district as auxiliary data.
2: Empirical best linear unbiased prediction (EBLUP).

Table 3.11. Simple linear regressions between altitude and three depressed mood (DM) estimates, using the "arcsine of the estimate square root" transformation[1] for all three estimates. Data from the "Noguchi Surveys,"[2] Peru, 2003-2013.

Model A: with Weighted proportion estimates (direct estimates)							
Variable	**β Coef.**	**St.Err.**	**t-value**	**p-value**	**[95% Conf Interval]**		
Altitude (m)	0.00002676	5.710e-06	4.69	<0.00001	0.00001551	0.00003801	
Intercept	0.25952414	0.01351199	19.21	<0.00001	0.23289531	0.28615298	
Model metrics				**Cameron & Trivedi's decomposition of IM-Test**			
Mean dependent var	0.31118119	SD dependent var	0.12224400	Source	chi2	df	p
R-squared	0.09049599	Number of obs	223	Heteroskedasticity	5.34	2	0.0692
F-test	21.98958416	Prob > F	0.00000480	Skewness	5.93	2	0.0149
Akaike crit. (AIC)	-322.6828677	Bayesian crit. (BIC)	-315.8685242	Kurtosis	11.88	1	0.0006
				Total	23.15	4	0.0001
Model B: with Standardized prevalence proportions (direct standardization by sex and age)							
Variable	**β Coef.**	**St.Err.**	**t-value**	**p-value**	**[95% Conf Interval]**		
Altitude (m)	0.00002	5.860e-06	3.71	<0.001	0.0000102	0.00003327	
Intercept	0.25526	0.01387362	18.40	<0.001	0.2279189	0.28260189	
Model metrics				**Cameron & Trivedi's decomposition of IM-Test**			
Mean dependent var	0.29719	SD dependent var	0.12336821	Source	chi2	df	p
R-squared	0.058556	Number of obs	223	Heteroskedasticity	1.54	2	0.04631
F-test	13.7456794	Prob > F	0.0002647	Skewness	2.14	1	0.01433
Akaike crit. (AIC)	-310.902991	Bayesian crit. (BIC)	-04.0886472	Kurtosis	10.60	1	0.0011
				Total	14.28	4	0.0064

Table 3.11. (cont'd)

Model C: with EBLUP estimates							
Variable	**β Coef.**	**St.Err.**	**t-value**	**p-value**	**[95% Conf Interval]**		
Altitude (m)	0.000026	4.480e-06	5.76	<0.00001	0.000017	<0.000035	
Intercept	0.222405	0.01061463	20.95	<0.00001	0.2014856	0.24332	
Model metrics				**Cameron & Trivedi's decomposition of IM-Test**			
Mean dependent var	0.27226918	SD dependent var	0.09822218	Source	chi2	df	p
R-squared	0.13061499	Number of obs	223	Heteroskedasticity	5.99	2	0.500
F-test	33.20267926	Prob > F	0.00000003	Skewness	9.03	1	0.0027
Akaike crit. (AIC)	-430.32216	Bayesian crit. (BIC)	-423.507815	Kurtosis	6.73	1	0.0095
				Total	14.28	4	0.0002

1 asin(x)= the radian value of the arcsine of x.

2 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Figure 3.8. Output results of Fay-Herriot model, analysis excluding forty districts with missing values and infinitesimal values of the standard errors in the weighted proportion estimation of depressed mood (i.e., 'direct estimator').

```
. *FH model without infinitesimal or missing value
. fayherriot y idh_2019 pct_pobreza_total pob_densidad_2020 if (linzdserroriginal>0.0007270 &
> linzdserroriginal!=.) , variance(var) eblup(EBLUPWoMiss) mse(MSEWomiss) sigmamethod(reml) ar
> csin reps(500)

Iteration 0:   f(p) = -74.514345
Iteration 1:   f(p) =  38.846693
Iteration 2:   f(p) =  39.288431
Iteration 3:   f(p) =  39.289228
Iteration 4:   f(p) =  39.289228

 Bootstrap
......50.....100.....150.....200.....250.....300.....350.....400.....450.....500

Sigma2_u estimation method:     reml             N in sample      =        183
Transformation of depvar:       arcsine          N out of sample  =          0
EBLUP and MSE bias correction:  none             Sigma2_u         =     0.0037
                                                 Adj R-squared    =     0.2458
                                                 FH R-squared     =     0.9989

------------------------------------------------------------------------------
           y | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
    idh_2019 |  -.0776961   .1541651    -0.50   0.614    -.3798542    .2244619
pct_pobrez~l |  -.0003595   .0013051    -0.28   0.783    -.0029174    .0021984
pob_den~2020 |  -5.00e-06   2.21e-06    -2.26   0.024    -9.33e-06   -6.65e-07
       _cons |    .380521   .0975895     3.90   0.000     .1892492    .5717929
------------------------------------------------------------------------------

Shapiro-Wilk test for normality:
 Residuals e (standardized)  V =     7.926  p-value = 0.000
 Random effects u            V =    59.714  p-value = 0.000
------------------------------------------------------------------------------
```

Table 3.12. Simple Linear regression between altitude and Depressed Mood with EBLUP estimates omitting infinitesimal and missing values of standard errors, using the "arcsine of the estimate square root" transformation[1] of the EBLUP. Data from the "Noguchi Surveys,"[2] Peru, 2003-2013.

Variable	**β Coef.**	**St.Err.**	**t-value**	**p-value**	**[95% Conf Interval]**
Altitude (m)	0.00001911	2.340e-06	8.17	<0.01	[0.00001449, 0.00002372]
Intercept	0.27675127	.0053655	51.58	<0.01	[0.2661643, 0.28733823]

Model Metrics

Mean dependent var	0.31159345	SD dependent var	0.05135301
R-squared	0.26928040	Number of obs	183
F-test	66.70103338	Prob > F	<0.00000001
Akaike crit. (AIC)	-621.74862668	Bayesian crit. (BIC)	-615.32965437

Cameron & Trivedi's decomposition of the IM-test

Source	Chi2	df	p-value
Heteroskedasticity	11.13	2	0.0038
Skewness	3.31	1	0.0688
Kurtosis	3.37	1	0.0665
Total	17.81	4	0.0013

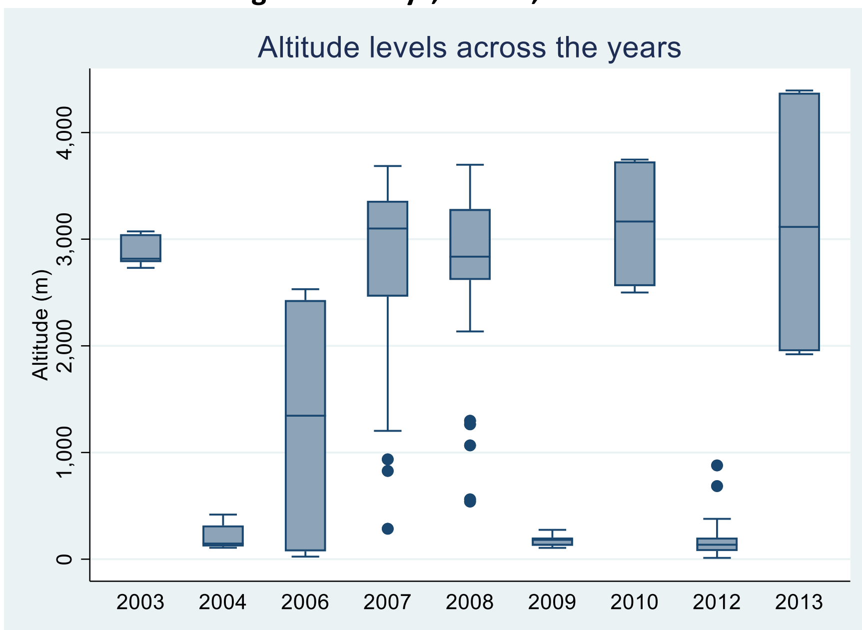
1: asin(x)= the radian value of the arcsine of x.

2: "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Figure 3.9. Output results of regressing altitude deciles as predictors of Depressed Mood EBLUP estimates. Same as Model 4 from Table 3.9 but omitting infinitesimal and missing values of standard errors.

```
. xi: glm EBLUPWoMiss i.alt10, link(identity)
i.alt10           _Ialt10_1-10        (naturally coded; _Ialt10_1 omitted)

Iteration 0:   log likelihood =  435.94743

Generalized linear models                         Number of obs   =        183
Optimization     : ML                             Residual df     =        173
                                                  Scale parameter =   .0005281
Deviance         =  .0913694861                   (1/df) Deviance =   .0005281
Pearson          =  .0913694861                   (1/df) Pearson  =   .0005281

Variance function: V(u) = 1                       [Gaussian]
Link function    : g(u) = u                       [Identity]

                                                  AIC             =  -4.655163
Log likelihood   =  435.9474305                   BIC             =  -901.1497

------------------------------------------------------------------------------
             |                 OIM
 EBLUPWoMiss | Coefficient  std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
   _Ialt10_2 |   .0004275   .0071003     0.06   0.952    -.0134888    .0143438
   _Ialt10_3 |   .0104455    .007304     1.43   0.153      -.00387    .0247611
   _Ialt10_4 |   .0313505   .0070112     4.47   0.000     .0176088    .0450921
   _Ialt10_5 |   .0297004   .0074212     4.00   0.000     .0151551    .0442457
   _Ialt10_6 |   .0343465    .007304     4.70   0.000     .0200309     .048662
   _Ialt10_7 |   .0363326   .0075509     4.81   0.000     .0215332    .0511321
   _Ialt10_8 |   .0461259   .0074212     6.22   0.000     .0315806    .0606712
   _Ialt10_9 |   .0403036    .007304     5.52   0.000      .025988    .0546191
  _Ialt10_10 |   .0348755   .0075509     4.62   0.000      .020076     .049675
       _cons |   .0708802   .0048997    14.47   0.000      .061277    .0804834
------------------------------------------------------------------------------
```

Figure 3.10. Altitude of districts in nine surveys across the years. Data from the "Noguchi Surveys,"[1] Peru, 2003-2013.



1: "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

APPENDIX C: CHAPTER 4

In this Appendix, I will show two Stata© outputs with results mentioned in Chapter 4. First, the output results from the "Nestreg" command fitting nested models by sequentially adding blocks of variables and then reports comparison tests between the nested models included in Table 4.3. Then, in Figure 4.3, I will show the output from the covariate-adjusted logistic regression analysis of model 6 in Table 4.3. Finally, in Table 4.5, several results of survey logistic regressions between different altitude quantiles or categories and depressed mood will be presented.

Figure 4.2. The output of Nested model statistics using the "Nestreg" command for model 6 from Table 4.3.

Block	F	Block df	Design df	Pr > F
1	8.42	1	2855	0.0037
2	48.18	1	2855	0.0000
3	42.09	1	2855	0.0000
4	154.69	1	2855	0.0000
5	10.80	1	2855	0.0010
6	0.23	1	2855	0.6330
7	12.67	1	2855	0.0004
8	4.95	1	2855	0.0262
9	6.40	1	2855	0.0115

Figure 4.3. Estimated associations from covariate-adjusted analysis with depressed mood (DM) expressed as a function of each covariate included in model 6. Data from the "Noguchi Surveys,"[1] Peru, 2003-2013.

```
Survey: Logistic regression

Number of strata =     22                  Number of obs   =     33,013
Number of PSUs   = 2,877                   Population size = 9,816,114
                                           Design df       =      2,855
                                           F(9, 2847)      =      29.53
                                           Prob > F        =     0.0000
```

depress_mood	Coefficient	Linearized std. err.	t	P>|t|	[95% conf.	interval]
_Ialtitude__2	.3095751	.093563	3.31	0.001	.1261173	.493033
_Ialtitude__3	.4736971	.083853	5.65	0.000	.3092786	.6381156
age	.0093971	.0028097	3.34	0.001	.0038878	.0149064
_Ifemale_1	1.146587	.1007094	11.39	0.000	.9491167	1.344058
_Imater_ton_2	.3619393	.1179571	3.07	0.002	.1306496	.5932289
_Imater_ton_3	-.3936253	.7313046	-0.54	0.590	-1.827564	1.040313
_Icivil_sta_2	.3160335	.0997787	3.17	0.002	.1203879	.511679
_Icivil_sta_3	-.2840387	.1256191	-2.26	0.024	-.530352	-.0377253
_Ilong_resi_1	-.6217411	.2457789	-2.53	0.011	-1.103663	-.139819
_cons	-3.116399	.2675886	-11.65	0.000	-3.641085	-2.591713

1 "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

Table 4.5. Survey Logistic Regressions for associations between different altitude categories and depressed mood. Data from the "Noguchi Surveys,"[1] Peru, 2003-2013.

Survey Logistic regression: altitude continuous variable						
	Coef.	St.Err.	t-value	p-value	[95% Conf. Interval]	
Altitude	0.0002	0.00003	6.03	p<0.001	0.00013	0.00025
Constant	-2.53876	0.05201	-48.81		-2.64075	-2.43678
Mean dependent var		0.11273	SD dependent var			0.31626
Number of obs		33080	F-test			36.32610
Survey Logistic regression: altitude tertiles						
3 quantiles of altitude	Coef.	St.Err.	t-value	p-value	[95% Conf. Interval]	
2nd	0.294	0.08979	3.27	0.001	0.118	0.469
3rd	0.509	0.07337	6.94	p<0.001	0.365	0.653
Constant	-2.55323	0.05843	-43.70		-2.6678	-2.43867
Mean dependent var		0.11273	SD dependent var			0.31626
Number of obs		33080	F-test			24.16555
Survey Logistic regression: altitude quintiles						
5 quantiles of altitude	Coef.	St.Err.	t-value	p-value	[95% Conf. Interval]	
2nd	0.018	0.10752	0.17	0.86	-0.192	0.229
3rd	0.299	0.1089	2.75	p<0.01	0.086	0.513
4th	0.445	0.10401	4.28	p<0.001	0.241	0.649
5th	0.476	0.09964	4.78	p<0.001	0.281	0.671
Constant	-2.52199	0.0704	-35.83		-2.660	-2.383
Mean dependent var		0.11273	SD dependent var			0.31626
Number of obs		33080	F-test			9.47256
Survey Logistic regression: altitude deciles						
10 quantiles of altitude	Coef.	St. Err.	t-value	p-value	[95% Conf. Interval]	
2nd	-0.08312	0.13893	-0.60	.54971	-.35553	.1893
3rd	-0.18617	0.14986	-1.24	.21422	-.48001	.10767
4th	0.10567	0.13246	0.80	.42509	-.15406	.3654
5th	-0.05839	0.13072	-0.45	.65512	-.31471	.19792
6th	0.51303	0.14178	3.62	p<0.001	.23502	.79104
7th	0.27388	0.14089	1.94	0.052	-.00237	.55013
8th	0.63507	0.10671	5.95	p<0.001	.42584	.84431
9th	0.70497	0.11625	6.06	p<0.001	.47703	.93291
10th	-0.2247	0.12029	-1.87	0.06186	-.46056	.01116
Constant	-2.47724	0.08093	-30.61		-2.63592	-2.31856
Mean dependent var		0.11273	SD dependent var			0.31626
Number of obs		33080	F-test			14.95134

Table 4.5. (cont'd)

Survey Logistic regression: altitude in four categories from the International Society of Mountain Medicine						
Altitude in 4 categories (m)	Coef.	St.Err.	t-value	p-value	[95% Conf. Interval]	
1500-2499	0.51219	0.12703	4.03	p<0.0001	0.26312	0.76127
2500-3499	0.4737	0.07934	5.97	p<0.0001	0.31813	0.62927
≥3,500	0.21141	0.13832	1.53	0.127	-0.0598	0.48262
Constant	-2.51295	0.04934	-50.93		-2.6097	-2.41619
Mean dependent var		0.11273	SD dependent var			0.31626
Number of obs		33080	F-test			14.23816

Survey Logistic regression: High Altitude definition from International Society of Mountain Medicine						
Altitude in HA categories (m)	Coef.	St.Err.	t-value	p-value	[95% Conf. Interval]	
≥2,500	0.38843	0.07278	5.34	p<0.0001	0.24572	0.53114
Constant	-2.45837	0.04557	-53.95		-2.54773	-2.36902
Mean dependent var		0.11273	SD dependent var			0.31626
Number of obs		33080	F-test			28.48359

1: "Noguchi Surveys": epidemiological surveys from the "Honorio Delgado - Hideyo Noguchi" Peruvian National Institute of Mental Health.

APPENDIX D: CHAPTER 5

Figure 5.1. Stata© output of the model with coca leaf use included. Altitude is in three categories. Beta Coefficients shown.

```
. svy: glm depress_mood  i.altitude_ter c.age i.female i.mater_tong3 i.civil_stat3c i.long_resid
>                                             i.cocause_lastm, family(binomial) link(logit)
(running glm on estimation sample)

Survey: Generalized linear models

Number of strata =    22                         Number of obs   =    32,962
Number of PSUs   = 2,877                         Population size = 9,787,461
                                                 Design df       =     2,855

------------------------------------------------------------------------------
                |             Linearized
   depress_mood | Coefficient  std. err.      t    P>|t|     [95% conf. interval]
----------------+-------------------------------------------------------------
   altitude_ter |
             2  |   .2703481   .0938718     2.88   0.004     .0862847    .4544115
             3  |   .3632523   .0879249     4.13   0.000     .1908495    .5356552
                |
            age |   .0092437   .0028219     3.28   0.001     .0037106    .0147769
       1.female |   1.158246   .1014215    11.42   0.000     .9593789    1.357112
                |
    mater_tong3 |
Quechua/Aymara  |   .3105942   .1231856     2.52   0.012     .0690524     .552136
         other  |  -.3933291   .7346649    -0.54   0.592    -1.833857    1.047198
                |
   civil_stat3c |
  divorc/widow  |    .319238   .1002576     3.18   0.001     .1226535    .5158226
        single  |  -.2788178   .1257789    -2.22   0.027    -.5254445   -.0321911
                |
     long_resid |
           Yes  |  -.5986412   .2493677    -2.40   0.016      -1.0876   -.1096822
                |
  cocause_lastm |
           Yes  |   .8001697   .1650433     4.85   0.000     .4765535    1.123786
          _cons |     -3.138   .2703271   -11.61   0.000    -3.668056   -2.607944
------------------------------------------------------------------------------
```

Figure 5.2. Stata © output of the model with coca-leaf use and product terms included. Altitude is in three categories.

```
. svy: glm depress_mood  i.altitude_ter c.age i.female i.mater_tong3 i.civil_stat3c i.long_resid
>                                            i.cocause_lastm i.altitude_ter#i.cocause_lastm , family(binomial) link(logit)
(running glm on estimation sample)

Survey: Generalized linear models

Number of strata =    22                          Number of obs   =    32,962
Number of PSUs   = 2,877                          Population size = 9,787,461
                                                  Design df       =     2,855

-------------------------------------------------------------------------------------------
                            |             Linearized
               depress_mood | Coefficient  std. err.      t    P>|t|     [95% conf. interval]
----------------------------+--------------------------------------------------------------
               altitude_ter |
                         2  |   .2596872   .0952188     2.73   0.006     .0729826    .4463918
                         3  |   .4208586   .0846753     4.97   0.000     .2548276    .5868895
                            |
                        age |   .0092608   .0028237     3.28   0.001     .0037241    .0147974
                   1.female |   1.156223   .1017639    11.36   0.000      .956685    1.355761
                            |
                mater_tong3 |
             Quechua/Aymara |   .3145321   .1230337     2.56   0.011     .0732882    .5557759
                     other  |  -.3905772   .7352566    -0.53   0.595    -1.832265     1.05111
                            |
               civil_stat3c |
              divorc/widow  |   .3201676   .1002891     3.19   0.001     .1235212    .5168141
                    single  |  -.2782146   .1258165    -2.21   0.027    -.5249151   -.0315142
                            |
                 long_resid |
                       Yes  |  -.5895157   .2505725    -2.35   0.019    -1.080837   -.0981943
                            |
              cocause_lastm |
                       Yes  |   .7435659   .5571587     1.33   0.182    -.3489081     1.83604
                            |
altitude_ter#cocause_lastm  |
                     2#Yes  |   .1944652   .5968856     0.33   0.745    -.9759053    1.364836
                     3#Yes  |  -.2769698   .5688402    -0.49   0.626    -1.392349    .8384093
                            |
                      _cons |  -3.146464   .2715267   -11.59   0.000    -3.678872   -2.614056
-------------------------------------------------------------------------------------------
```

Figure 5.3. Stata © output of the model with coca-leaf use and product terms included. Altitude is in two categories. Coefficients shown.

```
. svy: glm depress_mood  i.altitude_2grp c.age i.female i.mater_tong3 i.civil_stat3c i.long_resid
>                                             i.cocause_lastm i.altitude_2grp#i.cocause_lastm , family(binomial) link(logit)
(running glm on estimation sample)

Survey: Generalized linear models

Number of strata =    22                          Number of obs   =    32,962
Number of PSUs   = 2,877                          Population size = 9,787,461
                                                  Design df       =     2,855

----------------------------------------------------------------------------------------------
                             |             Linearized
                depress_mood | Coefficient  std. err.      t    P>|t|     [95% conf. interval]
-----------------------------+----------------------------------------------------------------
             2.altitude_2grp |    .4288299   .0933748     4.59   0.000     .2457411    .6119188
                         age |    .0090015    .002805     3.21   0.001     .0035015    .0145015
                    1.female |    1.153983   .1016222    11.36   0.000     .9547231    1.353244
                             |
                 mater_tong3 |
              Quechua/Aymara |     .322034    .122373     2.63   0.009     .0820856    .5619823
                       other |   -.4013506   .7520063    -0.53   0.594    -1.875881     1.07318
                             |
                civil_stat3c |
                divorc/widow |    .3190803   .1008701     3.16   0.002     .1212947    .5168658
                      single |   -.2959775   .1260187    -2.35   0.019    -.5430743   -.0488807
                             |
                  long_resid |
                         Yes |   -.6149051   .2473904    -2.49   0.013    -1.099987   -.1298232
                             |
               cocause_lastm |
                         Yes |    .4510093   .3467164     1.30   0.193    -.2288307    1.130849
                             |
altitude_2grp#cocause_lastm  |
                       2#Yes |    .2942971   .3873822     0.76   0.447    -.4652801    1.053874
                             |
                       _cons |   -3.066912   .2650815   -11.57   0.000    -3.586683   -2.547142
----------------------------------------------------------------------------------------------
```