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Leveraging Remote Sensing and Machine Learning to Assess the Impact of Home Proximity to Agriculture on Pesticide Exposure, Depression, and Anxiety in an Ecuadorian Agricultural Community.

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Leveraging Remote Sensing and Machine Learning to Assess the Impact of Home Proximity to Agriculture on Pesticide Exposure, Depression, and Anxiety in an Ecuadorian Agricultural Community.

A Dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Public Health (Global Health)

by

Briana Nadine Cortez Chronister

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2024

The Dissertation of Briana Nadine Cortez Chronister is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

Chair

University of California San Diego

San Diego State University

2024

DEDICATION

To my grandparents, Macario and Oliva Carranza, and Alfonso and Elodia Cortez, whom with only an elementary education migrated their families to the United States, overcoming language, culture, and economic barriers in hopes of giving their families a chance of having a better life. No words are sufficient to thank my parents, Vianey and Alfonso Cortez. You both embraced me and let me discover my true self and aspirations. You always allowed me to spread my wings while providing me with a landing pad whenever I needed support and courage. I know you put your dreams on hold so that I can achieve mine, and for that I will forever be indebted and grateful. To my husband, Will Chronister, I could not have chosen a better partner to have with me on this journey. You always provided me clarity and confidence in moments when I felt so uncertain of my capabilities or future. The sacrifices I made to complete this program were not only my own, but I know also extended to you. Thank you for supporting me throughout this journey despite the challenges. And to my daughter, Clementine. When I entered the program, I aimed to obtain my PhD for my own goals and aspirations. When you arrived, my purpose changed to obtaining this PhD for you, my love. I hope this serves as a testament that you can accomplish all things with hard work, dedication, courage, and faith. I can only dream that this will someday inspire you, in a way that my mother's accomplishments inspired me.

EPIGRAPH

"Nothing great is ever achieved without much enduring" – **St. Catherine of Siena**

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LIST OF ABBREVIATIONS

2,4-D	2,4-Dichlorophenoxyacetic acid
3-PBA	3-phenoxybenzoic acid
4F-3PBA	4-fluoro-3-phenoxybenzoic acid
D	Dark Fraction
EM	Endmember
ESPINA	The Study of Secondary Exposures to Pesticides among Children and Adolescents
EVI	Enhanced Vegetation Index
EVI2	Enhanced Vegetation Index 2
GWR	Geospatially Weighted Regression
home-ag SA	Surface area of agriculture within a buffer around the home. The subscript distance (e.g., 50m) indicates the radii used for that buffer.
home-ag distance	Distance from the home to the boundary of the nearest agricultural field
INEC	National Institute of Statistics and Census
ln	Natural Log
MDA	Malathion dicarboxylic acid
NDVI	Normalized difference vegetation index
NIR	Near Infrared Red
OXY2	2-isopropyl-4-methyl-6-hydroxypyrimidine
PNP	Para-nitrophenol
RMSEs	Root Mean Square Errors
ROI	Region of Interest
SAM	Segment Anything Model
SA	Surface Area

SD	Standard Deviation
S	Substrate Fraction
SMA	Spectral Mixture Analysis
TCC	trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
TCPY	3,5,6-Trichloro-2-pyridinol
TMA	Temporal Mixture Analysis
tEM	Temporal Endmember
UCSD	University of California San Diego
UMAP	Nonlinear dimensionality reduction with Uniform Manifold Approximation and Projection
USGS	United States Geological Survey
V	Vegetation Fraction
VI	Vegetation Indices

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I would like to thank Fundación CIMAS del Ecuador and all ESPINA staff members for their incredible support, and their dedication to helping serve the Pedro Moncayo community. I would like to thank every participant of the ESPINA study, this research would have been impossible without them. I know that behind every data point are individuals with their own aspirations, wants, and needs. It is through their own involvement that we, as public health researchers, are able to better understand their potential health risks to someday improve the health of their community. I hope that my work helps these community members, even in the smallest of ways.

To my cohort, it was incredible to be a part of such a supportive group of students. Everyone always lifted each other up, cheered on each other's successes, and helped each other throughout the program, from pre-, during- and post-pandemic times. I would like to thank my mother and father-in-law for their support throughout the PhD program, and for believing in me. The first time I met you I told you I was going to be a doctor someday. I know it is not that kind of doctor, but I kept to my word! It has been a privilege to be a part of such an amazing family like the Chronisters. Lastly, Thank you to all of my family (there is a lot of them!), whether they are Chronister's, Boyer's, Babb's, Carranza's, Cortez's, Velazquez's, Huezo's, Gonzalez's, New's, Morales's, Mukherjee's, Antaya's and all the others not mentioned. You all have played such a special role throughout my life and have been my greatest cheerleaders. For you all I am forever grateful.

Chapter 1, in part, is currently being prepared for submission for publication of the material. Briana N.C. Chronister; Sarai Reyes; Franklin De La Cruz; Dolores Lopez-Paredes; Jose R. Suarez-Lopez; and Daniel Sousa. *Using manifold learning and segment anything to identify small- and large-scale agriculture in an equatorial agricultural community.* The dissertation author was the primary investigator and author of this paper.

Chapter 2, in part, is currently being prepared for submission for publication of the material. Briana N.C. Chronister; Ariana Huezo; Daniel Sousa; Harvey Checkoway; Jose Suarez-Torres; Franklin de la Cruz; Raeanne C. Moore; Jenny Quintana; Humberto Parada Jr.; Tommi Gaines; Jose R. Suarez-Lopez. *Home distance to agriculture and organophosphate, pyrethroid, and herbicide urinary metabolite concentration in Ecuadorian adolescents and young adults*. The dissertation author was the primary investigator and author of this paper.

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Sousa; Humberto Parada Jr.; Jenny Quintana; Tommi Gaines; Raeanne C. Moore; Jose R. Suarez-Lopez. *Home proximity to agriculture is associated with greater depression and anxiety symptoms in adolescents and young adults living in an Ecuadorian agricultural community.* The dissertation author was the primary investigator and author of this paper.

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PUBLICATIONS

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FIELD OF STUDY

Major Field: Public Health
    Studies in Global Health
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ABSTRACT OF THE DISSERTATION

Leveraging Remote Sensing and Machine Learning to Assess the Impact of Home Proximity to Agriculture on Pesticide Exposure, Depression, and Anxiety in an Ecuadorian Agricultural Community.

by

Briana Nadine Cortez Chronister

Doctor of Philosophy in Public Health (Global Health)

University of California San Diego, 2024
San Diego State University, 2024

Professor Jose Suarez, Chair

Introduction: Living near agriculture increases exposure risks through movement of volatilized pesticides, known as pesticide drift. Evidence from the Study of Secondary Exposures to Pesticides among Children and Adolescents (ESPINA) found suspected floricultural pesticide drift and subsequent worse mood for individuals living in Pedro Moncayo, Ecuador, underscoring the need to assess contributions from broader agriculture. Yet this region lacks contemporary agriculture maps.

Methods: To map agriculture (Aim 1), Uniform Manifold Approximation and Projection for Dimension Reduction (UMAP) and the Segment Anything Model (SAM) helped identify temporal endmembers for time series of Sentinel-2 spectrally unmixed vegetation fractions and PlanetScope enhanced vegetation index 2 imagery. Aim 2 and 3 used the agriculture map from Aim 1 and 2022 ESPINA data. These Aims assessed the relationship between home distance to the nearest agricultural field boundary (home-ag distance) and surface areas of agriculture within buffers around the home (home-ag SA) with urinary organophosphate, pyrethroid, and herbicide metabolite concentrations (Aim 2, n=500), and with anxiety and depression symptoms (Aim 3, n=484). Associations were estimated using generalized estimating equations, logistic regression, Getis-ord Gi* hotspot analysis, and geospatially weighted regression (GWR), adjusting for confounders.

Results: SAM identified more agricultural plots for PlanetScope compared to Sentinel-2 and UMAP pre-processing enhanced performance. Compared to PlanetScope, Sentinel-2 agricultural maps provided greater accuracy and sensitivity. The final agriculture map was 72.6% accurate and 75.3% precise (Aim 1). Greater home-ag distance was negatively associated with 2,4-Dichlorophenoxyacetic acid (2,4-D) and malathion dicarboxylic acid (MDA). GWR found the strongest associations between home-ag distance and 2,4-D near an industrial agriculture plot. Conversely, having a greater agricultural presence was negatively associated with para-nitrophenol and 3-phenoxybenzoic acid (Aim 2). Living farther from agriculture was associated with lower anxiety and depression symptoms. Spatial variations of home-ag distance with anxiety and depression symptoms was observed (Aim 3).

Conclusion: This study demonstrates that integrating manifold learning and SAM for agricultural characterization of high- and low-resolution imagery can achieve moderately accurate agricultural maps. Our results found that pesticide drift of 2,4-D and MDA may be stemming from agricultural production, and pesticide drift may increase risk of worse depression and anxiety symptoms.

INTRODUCTION

In most agricultural settings in the developing world, there is often limited contemporary information on the location of agricultural crops, the type of crop produced or whether pesticides are used. Considering that agricultural use of pesticides is a key source of pesticide exposure to inhabitants in such settings, this limited information limits the assessment of sources of pesticide exposure and related health effects of such exposures. Due to its favorable climate and demand for cut flowers, the Ecuadorian Andes region has had an exponential increase in its floriculture industry since its inception in 1983, leading to an annual value of cut flower exports of $835 million in 2017.[1,2] The Pedro Moncayo region is one of country's epicenters of rose production, which are grown in greenhouses.[3,4] Individuals living in agricultural areas are at higher risk of secondary pesticide exposure, through pathways such as pesticide drift, take-home exposure from household members who have direct contact with pesticides (para-occupational exposure), and residual contact exposure through surfaces and food.[5] Following pesticide application, indirect (secondary) pesticide exposure occurs via pesticide drift which decays with distance.[6]

To quantify secondary exposure, researchers have used pesticide use reporting (PUR) data to obtain density of pesticides applied in close proximity to homes.[7–9] Ecuador, and most agricultural areas worldwide, lacks PUR policies, thus using a proxy measure like distance to pesticide spray sites, or surface area of crops near the home, allows researchers to assess approximate exposure to pesticides in agricultural settings. In a review of 98 studies about pesticide exposure or health consequences of pesticide exposure, 25.5% of studies used surface area of crops within home buffer regions, while 7.1% of studies used residential distance from crops as their exposure constructs.[10] Surface area of agriculture within different buffer regions better measures agricultural density within selected buffer regions. While home distance to agriculture describes how close the nearest agricultural plot is. The two measures are related yet capture different levels of potential exposure; using both constructs can be a more accurate exposure proxy.

In a preliminary study of adolescents who lived in Pedro Moncayo, Ecuador (Chronister, under review), adolescents who lived farther from floricultural greenhouses did not have decreased concentrations of all urinary pesticide metabolites measured as hypothesized. For instance, while there were negative associations between increased residential distance to floricultural greenhousewith para-nitrophenol (PNP; a metabolite for the organophosphate parathion) concentrations for participants who lived within 200m to the nearest floricultural greenhouse, there werepositive associations for those living farther than 200m [11]. Furthermore, per a 50% increase of distance to floriculture greenhouses, there was a 2.06% (95%CI: 0.29%, 3.87%) increase of 3,5,6-Trichloro-2-pyridinol (TCPy; organophosphate) concentration [11]. Although there is a high prevalence of floriculture in this region, other types of agriculture are present including, but are not limited to corn, potatoes, broad beans, and alfalfa[12], and these crops likely explain the positive associations between some pesticide metabolites and distance to floricultural crops. In 2008, over 58.1% of Pedro Moncayo land was used for agriculture or floriculture.[12] While in 2020, it was identified that Pedro Moncayo was the 6th largest agricultural producer.

Using data collected in The Study of Secondary Exposures to Pesticides among Children and Adolescents (ESPINA), in 2008 2.01% of land in Pedro Moncayo was composed of floricultural greenhouses. The presence of floriculture doubled in 2016, as 4.58% of land was used for floriculture. Assuming agricultural land use at least remained stable from 2008 to 2016, potentially 53.8% of the land in this region could be used for agriculture. Non-floricultural agriculture (agriculture) is characterized as open-air agriculture, which can potentially lead to greater dispersion of pesticides through drift. Thus, it is possible that secondary pesticide exposure is also being influenced by an individual's proximity to agriculture. Pesticide exposure may also be associated with internalizing disorders, such as depression and anxiety[11,13]. Given preliminary evidence in the ESPINA cohort for the potential influence of pesticide exposure on mental health, it is important to characterize the association in their young adulthood.

The completion of project aims will be facilitated by access to publicly accessible Sentinel-2 imagery, privately accessible Planet imagery, and data collected in the ESPINA study. ESPINA is a longitudinal cohort which was established in 2008, and has seven follow up in person follow-up visits between 2008 and July 2024: April 2016 (Spring 2016), July to October 2016 (Summer 2016), July to September 2022 (Summer 2022), January to February 2023 (Winter 2023), July 2023 (Summer 2023), January to February 2024 (Winter 2024), and June to July 2024 (Summer 2024). Additional ecological momentary cognitive assessments captured using mobile phones have occurred for a subset of ESPINA participants outside of the follow-up periods mentioned. For this study we used data from the July to August 2022 assessment when pesticide metabolites were collected. Pesticide metabolite data at this time are not yet available for the 2023 and 2024 examinations. Therefore, Chapter 2 and Chapter 3 analysis are cross-sectional. Missing covariate data for some participants was imputed using Winter 2024 assessment data.

The following outlines the three research aims of the dissertation (Figure 0.1.):

Aim 1 (Chapter 1): Using Manifold Learning and the Segment Anything Model to identify small- and large-scale agriculture in an Equatorial Agricultural Community.

Aim 2 (Chapter 2): Identify whether home distance to the nearest agriculture field, or agricultural field surface area near homes, are associated with urinary metabolite concentrations of organophosphate, pyrethroid, and herbicide pesticides amongst Ecuadorian adolescents and adults.

Aim 3 (Chapter 3)**:** Identify whether home distance to the nearest agricultural field, or agricultural field surface area near homes, are associated with depression and anxiety symptoms amongst Ecuadorian adolescents and adults.

Public Health Implications

The proposed study has important public health implications. Implementation of remote sensing techniques will improve mapping of agriculture, allow for prospective monitoring, and the methods could be transportable to other regions. Findings would allow us to circumvent limitations of short-term pesticide exposure quantification inherent to environmental health studies, by assessing whether home proximity to agricultural crops may be associated with urinary metabolites. While assessing whether there is an association between chronic pesticide exposure with depression and anxiety outcomes could inform future prevention studies.

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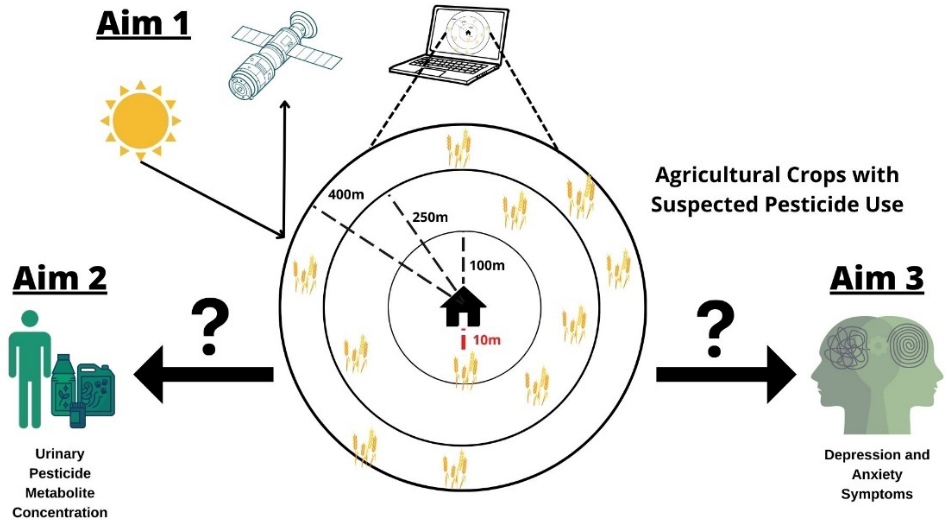


Figure 0.1. Visual abstract of the dissertation aims. Aim 1 is to use manifold learning and the segment anything model to identify small- and large-scale agriculture in an equatorial agricultural community using Sentinel-2 and PlanetScope satellite imagery. Aim 2 is to identify whether home distance to the nearest agriculture field, or agricultural field surface area near homes, are associated with urinary metabolite concentrations of organophosphate, pyrethroid, and herbicide pesticides amongst Ecuadorian adults. While Aim 3 is to identify whether home distance to the nearest agricultural field, or agricultural field surface area near homes, are associated with depression and anxiety symptoms amongst Ecuadorian adults.

Chapter 1 Using Manifold Learning and Segment Anything to identify small- and large-scale agriculture in an Equatorial Agricultural Community.

Abstract

Introduction: Located in the Ecuadorian Andes, Pedro Moncayo is known for smallholder farming and has frequent cloud cover, hindering usable Sentinel-2 imagery and at 10m resolution introduces mixed pixel issues. In other contexts, spectral mixture analysis (SMA), higher-resolution Planet images, and manifold learning have successfully classified agriculture, overcoming spectral index limitations. AI-powered object segmentation could enhance classification, its performance in this region is unknown.

Methods: Satellite imagery was obtained for Sentinel-2 T17NQA and T17NRA tiles from January 2021 to October 2022, and PlanetScope estimated vegetation index 2 (EVI2) images from January 2022 to October 2022. Sentinel-2 vegetation fraction (V) time series was created. Uniform Manifold Approximation and Project for Dimension Reduction (UMAP) was conducted on V (V-UMAP2) and EVI2 (EVI2-UMAP) time series. The Segment Anything Model (SAM) was conducted on the V, EVI-2, V-UMAP, and EVI2-UMAP time series to assess object segmentation effectiveness. Temporal endmembers (tEMs) of V-UMAP and EVI2-UMAP images were identified and used to unmix and create agricultural maps. Accuracy statistics were calculated using 2001 ground truth validation points throughout Pedro Moncayo

Results: The SAM generated more masks for Planet images compared to Sentinel-2 images but had large null regions. Pre-processing with UMAP improved mask generation, except for the large Sentinel-2 image. Four dominant endmembers were identified for the V-UMAP images, and separability of agriculture for EVI2-UMAP images was distinguishable in a subset of testing locations. Creating agricultural maps with the identified tEMS, the created agriculture maps using PlanetScope images provided better precision (76.8% vs 71.3%) and specificity

(93.2% vs 81.0%) but using Sentinel-2 images provided higher accuracy (62.0% vs 56.0%) and sensitivity (44.3% vs 20.9%) in Malchinguí. Prioritizing accuracy, an agricultural map using Sentinel-2 imagery was created with an accuracy of 72.57% and precision of 75.31%.

Conclusion: Sentinel-2 and Planet agricultural maps outperformed each other for different metrics. SAM showed moderate success in segmenting high-granularity images but struggled with lower granularity and larger study areas, but UMAP pre-processing enhanced mask generation. Despite these challenges, this is the first study to integrate manifold learning and SAM for agricultural characterization with moderate accuracy using Sentinel-2 and PlanetScope imagery.

Introduction

Pesticide use has surged since the 1950s, increasing the risk of pesticide exposure for agricultural communities, especially in Latin American countries like Ecuador. The greatest GDP contributing industries in Ecuador are agriculture, and pesticides regulation lags that which has been enacted United States and European countries [14]. The canton of Pedro Moncayo in Ecuador has an ideal climate for agricultural production due to its minimal seasonal variation in climactic factors such as temperature, precipitation levels, and day length, and is coupled with fertile soil that permits year-round planting of crops [15]. Ideal growing conditions coupled with the implementation of favorable policies promoting growth of this sector, have led to an increase of agricultural land use within the region [12,14]. Between 2000 and 2008, there was an estimated 17.1% growth of agricultural land use in Pedro Moncayo, which was driven by the expanded production of the production of flowers, vegetables, grains and other crops [12]. This growth has likely continued, given that the Ecuadorian government has implemented policies that support the agricultural industry to ensure its healthy growth and sustainability [16]. Agricultural production, for both smallholder and industrial farming, are known for diverse use of pesticides, putting communities in Pedro Moncayo potentially at risk for indirect exposure. A survey of 112 farmers in the Amazon basin revealed 99.1% use pesticides, with 47.3% applying them twice or more monthly[17]. Farmers used between 0 and 12 pesticides per farm, and the most common pesticides included paraquat, glyphosate, and malathion[17]. Another study in Carchi found 43 different fungicides and insecticides used on potato farms [18]. Similar patterns are observed in highland Ecuador, indicating widespread pesticide use and secondary exposure risks from off-target drift [19].

Given the dynamic growth of the agricultural sector in this region, and the potential risk of pesticide exposure to local communities, it is important to identify methods that can improve land use classification within Pedro Moncayo. Implementing remote sensing techniques to classify land cover both historically and prospectively allows us to circumvent challenges from land surveying techniques, which is time-and resource intensive [20,21]. Beginning in June of 2015, the Sentinel-2 satellite program has provided a free database of satellite images that can be leveraged to conduct land cover classification [22]. Sentinel-2 has moderate resolution (10m; 20 m for near infrared [NIR] and short-wave infrared [SWIR] bands), has a return rate of 5 days [23], and is run by the European Space Agency. Sentinel-2 imagery has been leveraged in multiple cases to classify land cover worldwide [24–26]. Agricultural characterization in Pedro Moncayo presents two main challenges: First, at 10m resolution most terrestrial pixels are spatially mixed. This is problematic given that the region has a high presence of small holder agriculture, classified as small-scale farming typically ten hectares of land or less. Second, Pedro Moncayo has frequent cloud cover which can limit usable images in this region. There are multiple potential techniques that can help improve agriculture characterization in Pedro Moncayo: incorporating higher spatial and temporal resolution satellite images, performing spectral and temporal mixture analysis, and implementing machine learning methods like manifold learning and object segmentation.

First, incorporation of PlanetScope images featuring high resolution could improve agricultural classification. Planet satellite imagery consists of a PlanetScope constellation of that has ~3.7m resolution [27], and has daily revisit times, outperforming Sentinel-2 for spatial and temporal resolution. Incorporation of the PlanetScope constellation has been shown to improve agricultural land cover classification in Africa [25] and India [28,29] compared to using Sentinel-2 data. Higher resolution may help reduce effects of mixed pixels at field edges, improving classification[30]. Meanwhile greater temporal resolution could increase the number of usable images to successfully classify temporal endmembers (tEMs).

As most of the terrestrial pixels are spatially mixed for Sentinel-2 images in this region, it makes it challenging to implement land use classification using indices like the normalized difference vegetation index (NDVI), enhanced vegetation index (EVI), and others. Implementation of spectral mixture analysis (SMA) in multispectral image analysis have demonstrated that most spatially mixed terrestrial pixels can be accurately modeled as linear combinations of rock and soil substrate (S), illuminated photosynthetic vegetation (V), non-illuminated/absorptive Dark (D) end members [31–33]. SMA helps to alleviate the mixed pixel problem for single image acquisitions, and uses the assumption that landscape comprises a small number of materials with distinct spectral signatures [34–36]. This method optimizes extraction of information from a multispectral image, by considering radiance or reflectance measured by each pixel as a linear combination of the radiance (or reflectance) of the spectral endmember materials, weighted with their fractional abundances [31]. SMA has accurately estimated vegetation cover (agricultural, forest, etc.), exceeding accuracy of spectral indices like NDVI in field validation exercises, while eliminating NDVI implementation issues from soil background and atmospheric effects [37]. Classifying these endmembers could allow us to identify agriculture.

Machine learning methods have become ever more popular for conducting multispectral image analysis, and manifold learning is increasingly used for remote sensing applications. As opposed to the linear dimensional reduction that is offered by principal component analysis [38], manifold learning conducts dimensional reduction in a non-linear way while preserving the connectivity structures of high dimensional datasets [39]. Manifold learning has been applied to multiple remote sensing applications, like multidecadal wetland loss[40], estimating soil nutrient levels [41], and characterizing urban land cover [42]. Pedro Moncayo has a high density of small holder agriculture complicating the dimensionality of observations. Implementing manifold learning, such as uniform manifold approximation and projection for dimension reduction (UMAP), may improve agricultural characterization in Pedro Moncayo.

Application of artificial intelligence to remote sensing provides an opportunity to improve upon traditional methods, especially related to object segmentation. Object based image analysis is a branch of Computer Vision whose analysis unit are objects as opposed to individual pixels [43], and have been used to classify agriculture especially for high resolution imagery [44]. The Segment Anything Model (SAM) is a recently developed visual segmentation tool by Meta AI, which was created to produce a precise and detailed segmentation masks based on user prompts. Trained using a dataset of 11 million images, the SAM large training database allows it to adapt to new image distributions and tasks without requiring additional samples [45]. As it uses a zero-shot learning, the model can process images that it has not previously encountered without initial training [46]. The SAM application in remote sensing of agriculture is nascent, but it has demonstrated similar performance to extensively trained object segmentation models to map smallholder agriculture [47], but has struggled with low resolution images [46–48]. The SAM, however, has not been applied to UMAP pre-processed remote sensing images.

This study will investigate a novel approach to characterizing agriculture, which will leverage SMA, manifold learning, and artificial intelligence-powered object segmentation of Sentinel-2 and PlanetScope images to classify agriculture in Pedro Moncayo, Moncayo Ecuador. Using these methods, we will address the following research questions:

1) How accurately does the Segment Anything Model effectively conduct object segmentation of satellite imagery in this setting? Secondarily, are there improvements in segmentation after pre-processing images with UMAP?
2) How accurately do Sentinel-2 and PlanetScope imagery map crop types in Pedro Moncayo, Ecuador? Secondarily, do maps created using PlanetScope imagery outperform those created using Sentinel-2 imagery based on accuracy, precision, sensitivity and specificity?
3) What is the extent of agricultural presence in Pedro Moncayo in 2022?

Methods

Region of Interest: Pedro Moncayo, Ecuador

Pedro Moncayo is a canton of province of Pichincha (Figure 1.1.), which ranges from 1730 to 4300 meters above sea level, has an average annual temperature of 13.7 C, with an annual rainfall of 400-1300 mm [49]. Pedro Moncayo consists of 5 parishes: Malchinguí, Tocachi, La Esperanza, Tabacundo, and Tupigachi (from West to East). In 2008 it was estimated that 58.1% of the territory was devoted to agriculture, while 30.6% of the land contains shrub and herbaceous vegetation [12,49]. The higher altitudinal zone (above 3300 m) is dominated by native ecosystems, represented by the paramo and highland montane forests [12]. The middle altitudinal area (2800-3300m) is predominantly used for agriculture and livestock, while the lower lands (sub 2800m) are characterized by a shrub dominated dry ecosystem [50]. Produce grown in the region include chia seeds, lettuce, chard, zucchinis, beans, broad beans, cauliflower, romaine lettuce, broccoli, leeks, corn, beets, garlic, radishes, carrots, onions, cilantro, and parsley[51]. Fruits that are grown include bananas (oritos), taxo, naranjilla, blackberry, and strawberry. Different grains that are grown include corn, wheat, barley, and 7 grain flour [51].

Sentinel-2 and Planet Imagery

Sentinel-2 is a constellation of two satellites (launch dates of Sentinel-2A: June 23, 2015 and Sentinel-2B: March 7, 2017), each with 13 spectral bands and 10m resolution, and a 5-10 day revisit time [22,23]. Tiles T17NQA (Path 43, Rows 1-16) and T17NRA (Path 43, Rows 3-31) cover the region of interest, and were collected for the study period (January 1, 2021, to October 31, 2022) from the U.S. Geological Survey's EarthExplorer data portal (USGS; earthexplorer.usgs.gov). All images were visually inspected, and only images without visible cloud coverage were included. A total of 10 and 11 images were included for T17NQA and T17NRA, respectively (Supplemental Table 1.1).

Due to the high altitude and annual rain coverage in Pedro Moncayo, the high cloud coverage of this region limited usable Sentinel-2 images. Planet satellite imagery (planet.com), consisting of the PlanetScope constellation of 430+ Dove and SuperDove Satellites, is high resolution (~3.7 m) and has daily return rates [27]. The Dove-C sensors provide four bands (blue, gree, red, and NIR) while the Dove-R has eight bands (red edge, red, green, green I, yellow, blue, coastal blue and NIR) and has daily revisit times [52]. The higher spatial and temporal resolution of PlanetScope has the possiblity to improve agricultural mapping, especially since it is expected to have a large group of small-holder agriculture. We obtained 2 band enhanced vegetation index 2 (EVI2) products using Dove-C PlanetScope imagery from January 1, 2022 to October 31, 2022 that covered a majority of the five parishes, with the exception of Tocachi, which was divided into a Northern and Southern Region (Supplemental Figure 1.1.). Images were visually inspected to remove all bands with visible cloud cover in that parish. We included 14 images for Malchinguí, 13 images for Tocachi North, 14 images for Tocachi South, 17 images for La Esperanza, 13 images for Tabacundo, and 10 for Tupigachi (Supplemental Table 1.1).

Image Pre-Processing

Instead of spectral unmixing for the Planet images, we obtained 2-band enhanced vegetation index (EVI2) images from Planet (planet.com). Vegetation indices (VIs) capture the health of vegetation by utilizing formulas or scaling changes that incorporate reflectance values from various wavelengths to determine plant conditions [53]. VI can be leveraged to map land cover and land use changes [24,54]. EVI2 is calculated without using the blue band [55]and has been found to perform as well as the EVI [56]. The EVI2 PlanetScope time series have shown strong agreement to Sentinel-2 EVI2 images [54].

Atmospheric correction using ACOLITE was conducted for Sentinel-2 images. Atmospheric correction is essential given the frequency of significant atmospheric variability in the Pedro Moncayo region. ACOLITE, an open-source atmospheric correction algorithm developed by the Royal Belgian Institute of Natural Sciences (RBINS), is compatible with Sentinel-2 (A/B) sensors, is coded in Python 3, and uses the dark spectral fit (DSF) method [57–59]. Atmospheric correction involves separating the top-of-atmosphere (TOA) observation into atmospheric and surface signals to retrieve surface reflectance (ρs). The DSF algorithm assumes atmospheric homogeneity and the presence of zero reflectance pixels in at least one band, uses the lowest TOA reflectance offset by a linear regression through the darkest pixels to construct the dark spectrum (ρ_{dark}). This dark spectrum helps estimate the atmospheric path reflectance (ρ_{path}) by fitting it to aerosol models, ultimately selecting the model with the lowest root mean squared differences. A more detailed explanation has previously been published [58–61].

Spectral Mixture Analysis

At 10m resolution, most terrestrial pixels are spatially mixed making it challenging to implement land use classification indices like the NDVI, EVI, and others. SMA is an approach to resolve the mixed pixel problem by assuming that landscapes are comprised of a small number of materials that can be differentiated using distinct spectral signatures [34–36]. Previously published studies have shown that spatially mixed terrestrial pixels can be accurately represented as linear combinations of rock and soil substrate (S), illuminated photosynthetic vegetation (V), non-illuminated/absorptive Dark (D) end members [31–33]. This method optimizes extraction of information from a multispectral image, by considering radiance or reflectance measured by each pixel as a linear combination of the radiance (or reflectance) of the spectral endmember materials, weighted with their fractional abundances [31]. SMA using S, V, and D endmembers has demonstrated superior accuracy in estimating vegetation cover, like agriculture, exceeding accuracy of spectral indices, while eliminating common errors caused by soil background and atmospheric effects when using spectral errors [37]. Subpixel vegetation fractions are estimated for all products by inversion of a linear spectral mixture model that identifies unique ground components using standardized spectral endmembers[62]. Linear spectral unmixing provides accurate, S,V, and D targets. The use of the three endmembers (S, V, and D), provides physically based estimates of the three most spectrally and functionally distinct types of land cover [40,63]. Standardized global endmembers were used to SMA, which were created using data from the 2013 underflight of Landsat 7 and 8 [37].

For all cloud-free Sentinel-2 images, we applied a linear mixing equation to represent the reflectance of a single pixel at each wavelength i (Equation 1), where S is for substrate, V is for vegetation, and D is for dark.

Equation 1 $$Reflectance_{\mu} = f_S E_{S\gamma i} + f_V E_{V\gamma i} + f_D E_{D\gamma i} + e$$

In the linear mixing equation (eq. 1) the fractional area coverage is represented by *fs, fv,* and *fd*, and their reflectance at each wavelength is *Es, Ev*, and *Ed,* respectively for S, V, and D. The remaining error (e) is the residual contribution that was not accounted for, otherwise known as the model misfit.[34] For Sentinel-2 images, a system of 11 linear equations, one for each band, are inverted to estimate the fractional area for the S, V, and D endmembers for all the pixels. Lastly, a unit sum constraint was applied so that fraction values range from 0% to 100%. The endmembers used were obtained from standardized endmembers that were gathered from a diverse global image mosaic which encompassed a wide range of biogeophysical conditions [37].

Temporal Mixture Analysis

For this study area, we expect agriculture to be separable from naturally occurring vegetation based on differences in timing of green-up (period of increased growing) and senescence (periods of decreased growing), relative to natural evergreen and deciduous plants. These differences can be determined using temporal mixture analysis (TMA), which supplements spectral data with multi-temporal data. TMA combines all pixels into a linear combination of endmembers, known as temporal endmembers (tEM), which represent observed variance in changes in spectral data over time. These patterns can be leveraged to identify unique tEMS for unique land cover classifications (e.g., agriculture, water, buildings). The transformed time series will then be examined in the UMAP feature space (see below), where the most statistically extreme time series occupy apexes of the data cluster and are referred to as temporal endmembers (tEMs) [31]. Edges connecting apexes correspond to binary mixtures, and pixels on the interior of the point cloud correspond to more complex mixtures of 3 or more tEMs. In the modeling phase, the tEMs are used as the basis vectors for a linear mixture model which represents every pixel time series as a linear combination of the tEMs (plus error). By representing the full space of temporal phenologies as combinations of the most statistically distinct tEMs, the model eliminates the need to make assumptions about the phenologies present in the data.[31]

Uniform Manifold Approximation and Project (UMAP) for Dimension Reduction

UMAP was conducted on all of the Sentinel-2 Vegetation fraction and PlanetScope EVI2 time series images. UMAP is an algorithm for non-linear dimension reduction [64], by mathematically assuming the Sentinel-2 or PlanetScope spectra are uniformly distributed on a locally connected Riemannian manifold using a locally constant Riemannian metric. The UMAP computations were performed using the open source umap-learn python package (https://umap-learn.readthe docs.io/en/latest/). The umap-learn package has tunable parameters including the number of dimensions of the low-D embedding space (n_components), the size of the local neighborhood used when learning the manifold structure of the data (n_neighbors), the limit of how closely points may be spaced in the output space (n_dist), and the distance metric in input space (min_dist) [39,64]. Variations of these parameters were explored, and the best performing parameters were setting n_components to 3, n_neighbors to 50, min_dist to 0.1, and the metric to Euclidean.

Object Segmentation using the Segment Anything Model (SAM)

Object segmentation is a category of artificial intelligence called computer vision which groups objects, or parts of objects, which can be identified in an image. In classic models, this is normally accomplished by creating an object classifier and anticipated shape distribution from manually annotated training images [65]. Unlike classic models, the Segment Anything project from Meta AI has developed a SAM which is a segmentation system that can be prompted to identify new objects and images without requiring further training [45]. The SAM was built using the largest segmentation dataset that consisted of over 1.1 billion masks on 11 million separate images [45]. To our knowledge, the SAM was not constructed using satellite imagery, thus, it is unknown how it will perform on Planet and Sentinel-2 images. The SAM is able to generate masks, which are objects identified by the model, for all actual objects in an image. For example, if applied to an image of a face, an eye would be properly detected by the SAM if an outputted mask covers the full extent of the eye on the image, which would be considered to be an object of the image. In another study mapping smallholder agriculture field boundaries, the SAM correctly identified about 58% of field boundaries, which was comparable to similar models that required extensive training [47]. There are multiple parameters that can be set for the SAM including the type of checkpoint, the mask (segmentation), points per side (points_per_side), the model's prediction for the quality of the mask (predicted_iou_thresh), mask quality threshold (stability_score_thresh). The parameters that were used for the SAM was 32 points_per_side, 0.86 pred_iou_thresh, and 92 stability_score_thresh. The Vit-H SAM checkpoint as used.

The SAM was conducted on two sets of images, those that did or did not have UMAP pre-processing. Each set consisted of the four images, a large sentinel tile and sub-region within the tile, and a large PlanetScope image, and a sub-region within the image, totaling 8 images. Images that were not pre-processed with UMAP were single band Sentinel-2 vegetation fraction images or EVI2 PlanetScope images. For the second set of images, UMAP pre-processing was conducted on Sentinel-2 vegetation fraction or PlanetScope EVI2 time series. SAM was applied to both sets of images, and the resulting masks and mask counts were output.

Object Segmentation Validation

To validate performance between the images that were and were not pre-processed with UMAP, between satellites, and between image size for the same satellite, the following procedures were done. The masks were visually inspected to determine effectiveness of the object segmentation by determining coverage of the masks over the sample location, and whether polygons seemed to estimate the plots of land in the image. The quantity of masks were calculated, where higher mask generation was classified as having better performance.

Field Validation

To quantify the accuracy of the remotely sensed agricultural maps, ground truth validation photos were taken in Pedro Moncayo, Ecuador from July 1, 2022, to July 31, 2022. A subset of the validation photo locations were chosen *a priori* based on initial land classification models using the methods described above, for Sentinel-2 images from January 1st to June 30th, 2021. Regions were targeted for field sampling based on their observed spatiotemporal variability in the 2021 satellite image time series. Additional points were also pre-identified from the visual inspection of the ArcGIS Pro basemap in suspected areas of agriculture, bare land, and natural vegetation coverage. At each location, an image of a compass was taken to identify the direction in which the photo was taken, then a ground-based photo of the land cover at the site. All images were collected using a Samsung S20 device, using the Pro capture features, with geotagging enabled for each image. While collecting images, GPS logger (version 3.2.1, https://wwww.basicairdata.eu) also tracked the investigator's movement during data collection. If any photos lacked geotags, they were applied with GPS coordinates captured using GPS Logger.

A total of 2598 images were taken, and after removing duplicate images of the same location, 2001 unique land cover validation points were identified with the following methods

(Figure 1.1.). Field photos were visualized inspected to identify land cover types into categories that were determined *a priori*: Agriculture, Floriculture, Natural Vegetation, Bare Soil, and Built (Figure 1.2.). Upon inspection of images, additional categories were created such as Corn, Intermixed Agriculture, or potatoes. Intermixed agriculture were plots of land that had evidence of agriculture (e.g., harvested corn) but might also have natural vegetation coverage. Sample images for each land use classification can be found in Supplemental Figure 1.2. For each image, additional validation points were created if multiple land cover types could be visualized. Once image classification was completed, there were a total of 2001 validation locations. The ground truth validation points were used for two purposes: to classify SAM masks to identify tEMs for each landcover classification, and to calculate the accuracy statistics for generated agricultural masks.

First, the SAM masks were overlayed with their corresponding UMAP images. A total of 9 regions of interest were selected across Pedro Moncayo that had a cluster of validation points that represented different land use classifications. For each region of interest, masks that intersected the validation point were classified as that land type. For example, a mask was labeled as agriculture if it intersected a validation point labeled as agriculture). The pixels of each classified mask was then visualized on the 3-D UMAP feature space to identify if there was clustering for similar land cover classifications, and a time series of the mean vegetation fractions for each land cover type was calculated and visualized on a scatterplot. tEMs for each land cover classification was then identified and used to unmix the vegetation fraction time series images to create the agriculture image using the PlanetScope images.

For validation purposes, agriculture validation points included points labeled as agriculture, corn, potatoes, or intermixed agriculture. While validation points that were labeled as any other landcover were considered not to be agriculture. Agriculture maps that were created using the Planet and Sentinel-2 images in Malchinguí and were compared to determine which performed best. This was done by outputting the agriculture maps using the aforementioned methods. The validation points were overlaid with the Sentinel-2 and PlanetScope agriculture maps where each polygon was an agriculture field. Counts of validation points that intersected agriculture polygons were determined. Agriculture points that intersected the polygons were labeled as true positives (TP), while any that did not intersect the polygon were false negatives (FN). Not agriculture points that intersected the polygons were labeled as false positives (FP), while those that did not intersect the polygon were labeled as true negatives (TN). Sensitivity, specificity, accuracy, and precision of the maps were then calculated using the following equations which have previously been published [66].

Equation 2 $$Sensitivity = \frac{TP}{TP+FN}$$

Equation 3 $$Specificity = \frac{TP}{TP+FN}$$

Equation 4 $$Accuracy = \frac{TP+TN}{Total\ Validation\ Points}$$

Equation 5 $$Precision = \frac{TP}{TP+FP}$$

Programs used for this study include Python 3, Bash 3.2.48, and ENVI classic 5.6.3 (Exelis Visual Information Solutions, Boulder, Colorado). Scatterplots were created using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All maps were visualized using ArcGIS Pro 3.0.0 (ESRI Inc.).

Results

Spectral unmixing of the Sentinel-2 images

A visualization of the spectral mixture fractions using S, V, and D endmembers can be found in Figure 1.3. for a mosaic of T17NQA and T17NRA images from August 4, 2021, where

Red shows the Substrate fractions, Green shows the Vegetation fractions, and Blue shows the Dark fractions. If the pixel shows a mixture of these fractions is visualized from the mixture of their corresponding colors and can be estimated using the color triangle. The mean substrate pixel cover between January 2021 and October 2022 peaks in October and June for the T17NQA, and just for October in T17NRA (Figure 1.3.b). For the mean vegetation pixel cover percentage (Figure 1.3.c), an annual trend was observed where the mean pixel cover peaked around April in 2021 and 2022 and was lowest between mid-July and October. Compared to the vegetation and substrate fraction time series, the dark pixel cover had the highest proportion, ranging from 53% to 72% of all pixel cover (Figure 1.3.d). A general decrease of the Dark pixel cover could be observed from July 2021 to October 2022. Linear regression did not find statistically significant changes in mean substrate, vegetation, nor dark pixel cover in this study region for the assessed time period (January 2021 to October 2022).

The SAM was applied to Sentinel-2 and PlanetScope images that were one band vegetation fractions (Supplemental Figure 1.3.) or were pre-processed with UMAP (3-bands) to assess its performance for satellite images (Figure 1.4.). Compared to using the SAM on single band images of vegetation fractions, pre-processing the images with UMAP improved mask generation with the exception of the Sentinel-2 T17NQA tile (71-masks [one band] versus 55 masks [three band UMAP]). Although more masks were generated for the Sentinel-2 T17NQA one band image without UMAP pre-processing, both versions failed to differentiate a majority of land plots.

Focusing on the UMAP pre-processed images (Figure 1.4.), when the SAM was applied to the Sentinel-2 T17NQA tile 55 masks were generated, however, there was a lack of land plot differentiation. For the red square region (Figure 1.4.b), 291 masks were identified. The red square region of the Sentinel-2 T17NQA image has a known industrial agriculture plot at its center (Figure 1.4.b), which was identified as several objects by the SAM. There was a lack of plot differentiation for the western half of the image, despite evidence of distinct land plots through visual inspection of the UMAP with SAM image. The number of masks created was higher for the Planet imagery than the Sentinel-2 T17NQA images. A total of 422 masks were generated for the PlanetScope Malchinguí region (Figure 1.4.c), while 397 masks were generated for the yellow square region (Figure 1.4.d). There were larger pockets of null values (black areas), and less differentiation of land parcels were observed for the full Malchinguí map compared to the yellow region. Based on the SAM performance, it was decided to only use the SAM on small regions like the Planet Regions of Interest but not larger regions, like the T17NQA or T17NRA tiles.

Nonlinear dimensionality reduction with UMAP was used to identify spatiotemporal patterns of different land covers (Figure 1.6.). SAM masks were labeled as their corresponding land cover based on which validation point it intersected. The pixels for the labeled masks were visualized on the UMAP feature space, and the mean pixel values were visualized by time for each ROI. In the UMAP feature space, distinct clustering patterns for agriculture were observable for ROI 1 through 5. Looking at the scatterplots, the mean EVI2 for agriculture had a bell curve shape for ROI1, appeared to decrease overtime in ROI2 and ROI3 but had two peaks for ROI4 and ROI5. ROI6 through ROI9 had less observable differentiation of agriculture from all of the other land type classifications. In particular, floricultural pixels overlapped both natural vegetation and agriculture in ROI6. This region was particularly chosen for having a high presence of floricultural greenhouses, thereby providing an example of how such structures could be differentiated from agriculture. Despite floriculture generally having the lowest mean EVI2 for the other ROIs, its values were higher than bare land and corn in ROI6. The distribution of the pixels within the UMAP feature space for ROI2, ROI3, and ROI5 demonstrate that there may be a higher variety of distinct land cover or vegetation types compared to the other ROI regions that have C-shapes in the UMAP feature space. This is because distinct vegetation tEMS identified using the UMAP will demonstrate clustering, or separation from the remaining group of pixels.

Endmembers were identified using UMAP for the Sentinel-2. As the SAM did not effectively create a sufficient number of masks for larger imagery (Figure 1.4.a), it was not applied to the T17NQA nor T17NRA UMAP images. Manual exploration of the UMAP feature space identified four tEMs (Figure 1.7.d and e) that covered a majority of the map (Figure 1.7.a), classified as having vegetation fraction time series that were generally always high (green), had a mid-peak (cyan), had a mid-low peak (purple), and was always low (red) (Figure 1.7.b).

Validation of Agriculture maps

Agriculture maps were created for Malchinguí using the PlanetScope images and Sentinel-2 images (Figure 1.8.) For the PlanetScope images, endmembers used to unmix the imagery were those identified in ROI5 (agriculture, corn, intermixed vegetation, and floriculture) (Figure 1.6.f), and the natural vegetation endmember from ROI2 (Figure 1.6.c). For the Sentinel-2 images, the four endmembers identified in Figure 1.7.b were used to unmix the pixels. When unmixed, the model misfit values were satisfactory for PlanetScope and Sentinel-2 maps. For PlanetScope, 97% of the pixels had root mean square errors (RMSE)<0.05, while 99% of pixels had RMSEs<0.06 for the Planet imagery. For Sentinel-2, 90% of pixels had RMSEs<0.056 while 99% of pixels had RMSEs<0.10. Using a total of 490 ground truth validation points in Malchinguí, it was determined that the Planet and Sentinel-2 maps outperformed each other for different indicators. The Planet map had higher precision (76.8% vs 71.3%), and specificity

(93.2% vs 81.0%) than Sentinel-2 maps. The Sentinel-2 agriculture map on the other hand had higher accuracy (62.0% vs 56.0%) and sensitivity (44.3% vs 20.9%). For the purposes of the map, it was decided to proceed with making the full agricultural map using the Sentinel-2 images, as it had higher accuracy and sensitivity, thus would have improvements on identifying agriculture true positives.

Using the unmixed Sentinel-2 images, an agriculture map was output for the full Pedro Moncayo region (Figure 1.9.). The map showed that 18.9% of Pedro Moncayo consisted of agriculture. Relative to the total surface area by parish, agriculture accounted for 15.4% in Malchingui, 15.8% in Tocachi, 14.7% in La Esperanza, 22.6% in Tabacundo, and 30.1% in Tupigachi. Using 2001 validation points, the accuracy of our method across all of the Pedro Moncayo region was 72.57%, precision was 75.31%, sensitivity was 51.10%, and specificity was 88.00%.

Discussion

This study explored the application of manifold learning (UMAP) and object segmentation (SAM) on Sentinel-2 V fraction time series and PlanetScope EVI2 time series to identify agriculture in Pedro Moncayo, Ecuador. UMAP was able to find distinct clusters of vegetation and EVI2 pixels for both sensors included, which demonstrated its success in differentiating between types of agriculture. SAM was found to have moderate success in object segmentation for images with higher granularity and smaller study sizes but had no success in object segmentation for lower granularity and larger study sizes. We found that creating agriculture maps using PlanetScope images provided better precision (76.8%) and specificity (93.2%) but using Sentinel-2 images provided higher accuracy (62.0%) and sensitivity (44.3%) in Malchinguí. Using T17NQA and T17NRA Sentinel-2 tiles, we were able to produce a map of agriculture in Pedro Moncayo that had an accuracy of 72.57% and precision of 75.31%. To our knowledge, this is the first study that combined manifold learning and SAM object segmentation to characterize agriculture using Sentinel-2 and PlanetScope imagery.

Comparison of agriculture characterization using PlanetScope versus Sentinel-2

PlanetScope (Figure 1.7.a) and Sentinel-2 (Figure 1.7.b) imagery characterized agriculture in Pedro Moncayo with moderate success, where neither of the models outperformed the other for all of our performance metrics (accuracy, precision, sensitivity, specificity). Although there is evidence of industrial agriculture in this region as observed in Figure 1.4.b, we anticipated that a majority of this region would consist of smallholder farming; thus, it was anticipated that PlanetScope maps would have the best performance metrics. This expectation derives from other studies which have found that PlanetScope imagery helped classify agriculture for small farms (<600 m^2) with ~85% accuracy in India[28] , 57.3%-60.9% in Ghana[67], 76.0%-84.12% in Malawi [25], and 69.7%-85.3% in South Sudan[67]. One reason our Planet map did not perform as well as the Sentinel-2 may be that we did not differentiate agricultural crop types outside of corn and potatotes. In the UMAP feature spaces for the PlanetScope ROIs, the shape of the pixel distributions for ROI2 (Figure 1.5.c) and ROI3 (Figure 1.5.d) suggests the presence of additional agricultural crops that are not accounted for using the land classification types that we included. In the ground truth images obtained for this study, common crops present in this region outside of corn included alfalfa, sweet peas, and wheat. These crops may have distinct green-up and senescence patterns that might have been unobservable when all agriculture was aggregated together. This may explain why we observed low sensitivity for the PlanetScope images (20.9%). The pixel distributions in the UMAP space for other ROIs in Pedro Moncayo, however, did not have as distinct clusters compared to ROI2 and ROI3. Given the variance observed in this region, it is possible that characterization of agriculture using PlanetScope in this region should be done for regions with comparable sizes to the ROIs instead of by parish or by canton. Likewise, other studies have found a 4%-10% improvement in accuracy when PlanetScope and Sentinel-2 data were combined [25,28,67]. It is possible that the accuracies of our maps would have similar improvements if we combined imagery from both sensors.

Characterization of Agriculture of Pedro Moncayo

The final agricultural map created using Sentinel-2 imagery had 72.57% accuracy, and 75.31% precision. Despite not characterizing major agricultural crops, the accuracy observed in our map outperforms maps created in Ghana and South Sudan [67]. It also had higher accuracy than a map of maize and rice in southern Ecuador using MODIS imagery (56.06%) [68]. The map underperformed compared to a study which mapped cropland in the coastal (77.6-78.3%), Andes (84.4%-86.1%), Amazon (97.1%-97.5%), and country (83.2%-84.3%) regions of Ecuador [69]. This study used a time series consisting of Landsat 7 and 8 images over an 8-year period. The longer time period of satellite data in that study might have improved the classification of tEMs, whereas as we only used a 1-year distribution for PlanetScope and 2-year distribution for Sentinel-2.

This analysis found that agriculture consisted of 18.9% of Pedro Moncayo surface area, with the greatest presence observed in Tupigachi (30.1%), while the lowest proportion was in La Esperanza (14.7%). In 2008, it was estimated that 58.1% of Pedro Moncayo land was used for agriculture or floriculture[12], of which 2.01% in 2008 was composed of floriculture, which increased to 4.58% in 2016 [70,71]. Assuming that agriculture in the region has remained relatively constant, approximately 53.52% of Pedro Moncayo should consist of agricultural land. The proportion of land cover does align with other estimations of agriculture land cover in this region of Ecuador in other studies. Our estimation of agriculture does align with an analysis led by Ochoa-Brito et al that estimated cropland covered 17.9% of the Ecuadorian Andes in 2016 using Landsat 7 and 8 NDVI time series [69]. There was also misalignment between government statistics and their estimation of agriculture, even in regions where maps had 97% accuracy [69]. It is possible that government estimates include pastureland in their estimates of agricultural land use, which would augment the surface areas they calculated. Pastureland was classified as natural vegetation in this study. More details on how the Ecuadorian government estimates agricultural land in this region would improve understanding of the true agricultural coverage.

UMAP for modeling fractional endmember time series

Applying UMAP as a pre-processing step allowed us to visualize clusters of distinct. land covers that would not have been as readily distinguishable otherwise. Implementation of UMAP in joint characterization has improved land cover transition modeling in a variety of complex topographies [39], improved classification of soil nutrient levels[41], and improved quality of agricultural classification[72], demonstrating its effectiveness in spectral image analysis to classify land cover or other land attributes. Identification of meaningful pixel clusters were identified manually, therefore incorporating methods to implement unsupervised or supervised identification of clusters in the UMAP feature space could improve applicability of this method for spectral image analysis.

Efficacy of implementing the Segment Anything Model for Object Segmentation

Based on our findings, the SAM model proved to be a moderately suitable tool when using satellite images of higher granularity and resolution improve its performance. This study demonstrated better performance for smaller regions within the same satellite images (e.g., Sentinel 2 T17NQA tile versus red square; Figure 1.4.a and b), and better performance for higher spatial resolution images (e.g., Sentinel-2 versus Planet; Figure 1.4.). Higher spatial resolution images had better performance when looking at smaller regions, evidenced by comparing the red and yellow square regions (Figure 1.4. b and d). Compared to the Sentinel-2 ROI (red square), 106 more masks were generated for the Planet ROI 1 (yellow square). In this study, we applied uniform SAM parameters across all presented imagery to understand its performance on satellite imagery. Although it is plausible that fine-tuning SAM parameters could enhance mask generation for larger images, such as Sentinel-2 tiles, our testing of multiple parameter variations (data not shown) yielded negligible improvements in the generated masks. The exploration of parameters was not exhaustive, however, due to the processing time of running the SAM that ranged from 15 to 30 minutes for each image. A similar trend where SAM performance was improved with smaller images and higher granularity was observed when applying the model to map smallholder farming in India [47].

Using UMAP to pre-process the images improved SAM mask generation, compared to using a vegetation fraction Sentinel-2 or EVI2 Planet 1-band image. Caution is advised when using the SAM for remote sensing applications. Although higher resolutions improved mask generation, there were still numerous plots of land with null mask generation, and some masks appeared to merge distinct plots of land. For this reason, the SAM results were only used for validation purposes for the PlanetScope imagery but was not used to generate the final agricultural maps. The SAM model was trained on a dataset of 11 million images, but to our knowledge, this training did not include satellite imagery. Within computer vision, the training dataset significantly influences the model's applicability to real-world datasets. These findings are aligned with other studies that find that the SAM does not perform well in agricultural image segmentation tasks, which may be due to low contrast between the target and background, and uneven illumination which reduce the image quality and clarity [48]. We found that using UMAP images versus raw vegetation fraction images improved mask generation demonstrating that pre-processing satellite images may improve segmentation using the SAM. Although there is an improvement in performance, pre-processing with UMAP does not overcome barriers observed in less granular images. Agricultural SAM adapters have improved agricultural segmentation tasks [48] but were not explored in this analysis. Further investigation into the SAM model's effectiveness is warranted to better understand its efficacy and feasibility for remote sensing applications.

Strengths and Limitations

One strength of this study is that we included ground truth images that were captured in this image, thus we were not reliant on location tags created from basemap visualization methods. This helps improve our classification of land types, especially for classifications that would have been difficult to differentiate based on satellite images of the region (e.g., bare land versus potatoes). However, it is still possible that there was misclassification of the images obtained. Limitations of this study include the decision to classify overall agriculture and did not differentiate for specific crop types outside of corn and potatoes, which may have affected our accuracy. Additionally, based on the UMAP feature space observed for all the ROIs, there seemed to be clustering of multiple land cover types which indicates that if we want improve precision in agriculture identification, classification should be done in regions smaller than parishes.

Conclusion

This study explored the application of manifold learning (UMAP) and object segmentation (SAM) on Sentinel-2 V fraction time series and PlanetScope EVI2 time series to identify agriculture in the Andean community of Pedro Moncayo, Ecuador. PlanetScope images provided better precision (76.8%) and specificity (93.2%), while Sentinel-2 images offered higher accuracy (62.0%) and sensitivity (44.3%) in Malchinguí. The combination of T17NQA and T17NRA Sentinel-2 tiles yielded an agricultural map for the entirety of Pedro Moncayo with 72.57% accuracy and 75.31% precision. UMAP successfully differentiated vegetation clusters, while SAM showed moderate success in segmenting high-granularity images but struggled with lower granularity and larger study areas. To our knowledge, this study is the first to integrate manifold learning and SAM for agricultural characterization using Sentinel-2 and PlanetScope imagery. The findings highlight the need for further method development and parameter optimization to enhance the efficacy of these models in remote sensing applications.

Acknowledgements

Chapter 1, in part, is currently being prepared for submission for publication of the material. Briana N.C. Chronister; Sarai Reyes; Franklin De La Cruz; Dolores Lopez-Paredes; Jose R. Suarez-Lopez; and Daniel Sousa. *Using manifold learning and segment anything to identify small- and large-scale agriculture in an equatorial agricultural community.* The dissertation author was the primary investigator and author of this paper.

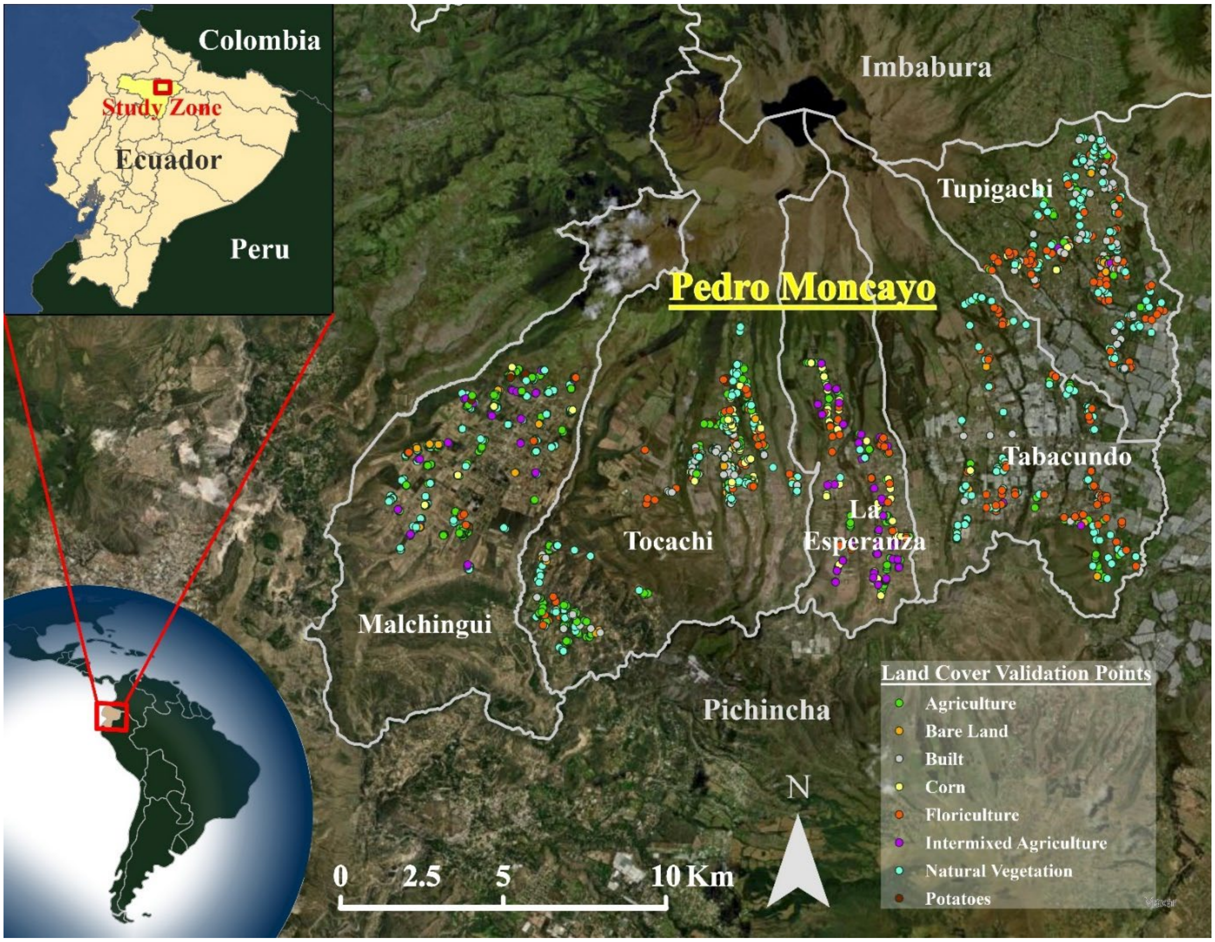


Figure 1.1. Index Map. Pedro Moncayo Canton (White outlined region) is located in northern Ecuador, within the Pichincha province. Pedro Moncayo is located just south of the Imbabura province. The 2001 land cover validation points are displayed. Image source: ArcGIS basemap (true color).

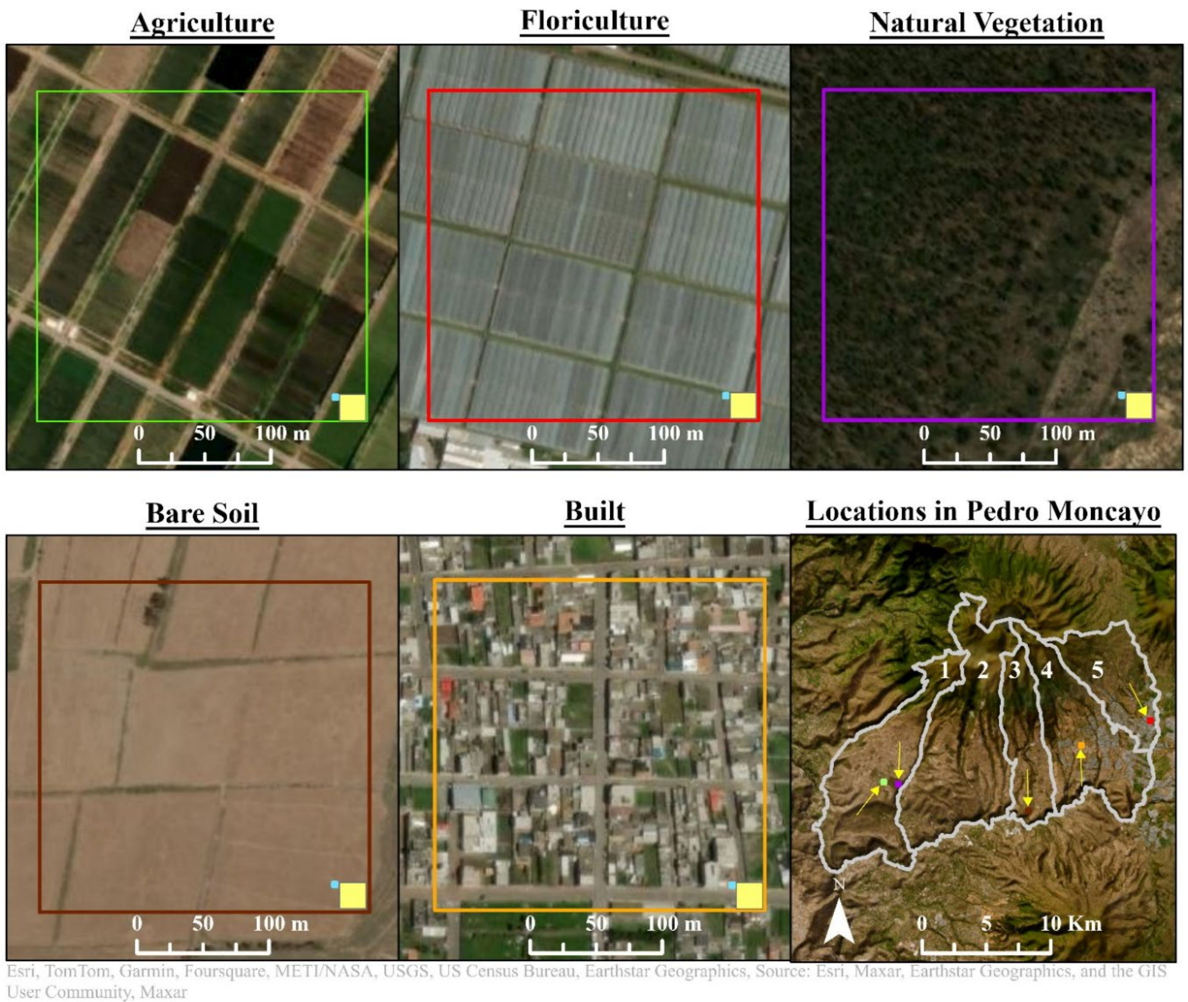


Figure 1.2. Selected land cover types (250m by 250m squares), and their locations in Pedro Moncayo, Ecuador. The yellow square represents Sentinel-2 resolution (20m by 20m) while the light blue square represents Planet satellite resolution (3m by 3m). 1=Malchingui, 2= Tocachi, 3=La Esperanza, 4=Tabacundo, 5=Tupigachi. Image source: ArcGIS basemap (true color).

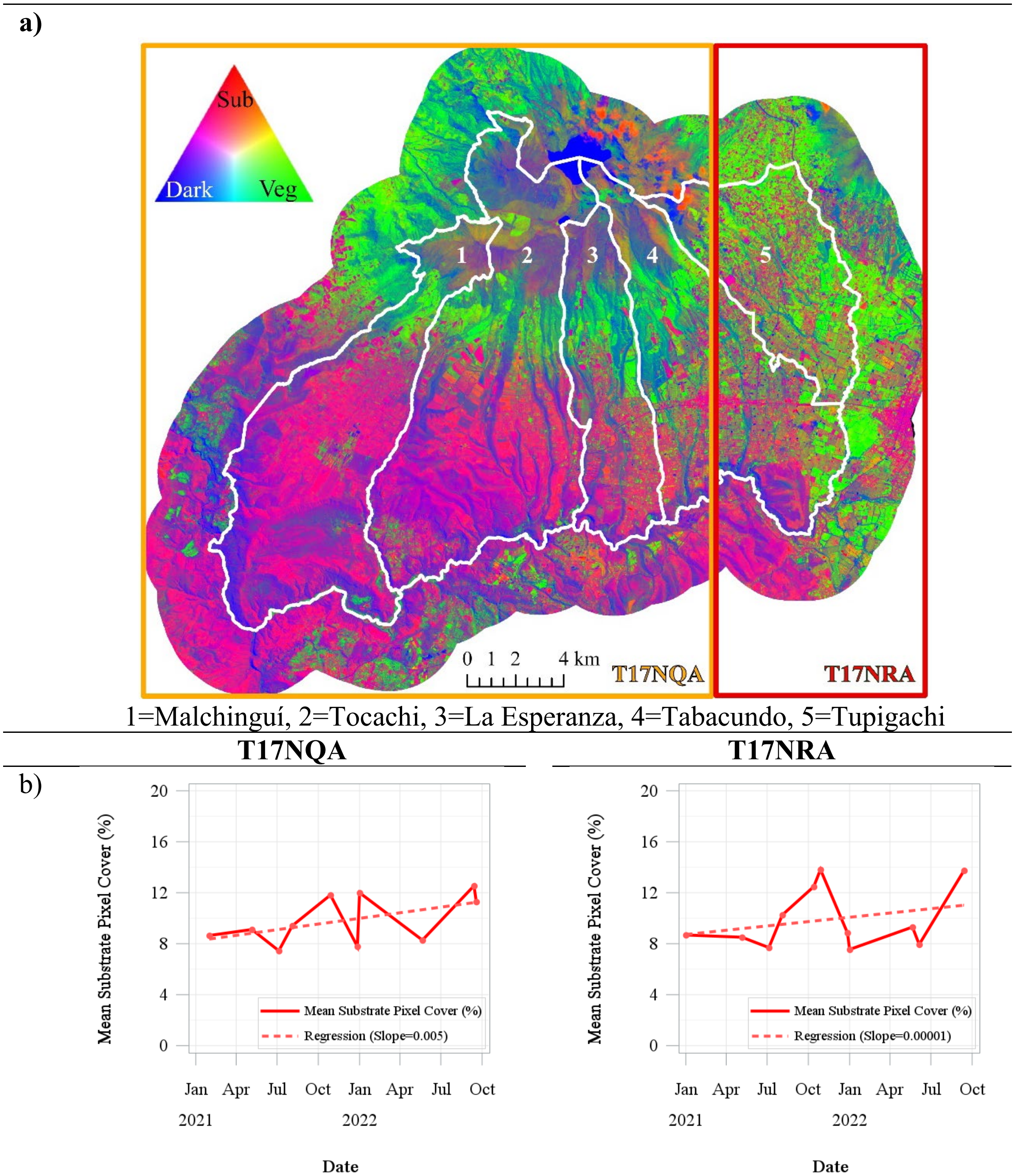


Figure 1.3. a) Spectral mixture fractions using local endmembers (R/G/B= Substrate/Vegetation/Darks), (stretch values: Substrate: [0.01- 0.23], Vegetation:[-0.01 - 0.39], Dark: [0.40-0.96]). The region displays a mosaic of two Sentinel-2 tiles from August 4, 2021, T17NQA (left) and T17NRA (right). b-d) Study area means pixel measures of endmember fraction change over time. The time series of study area spatial mean Substrate (b), vegetation (c), and dark (d) fractions for the Pedro Moncayo Canton 3km buffer region for both T17NQA and T17NRA for the duration of the study period. The mean substrate pixels slightly increased, while the mean vegetation and dark pixels slightly decreased for both tiles but were not statistically significant (p=0.10-0.83) based on linear regressions.

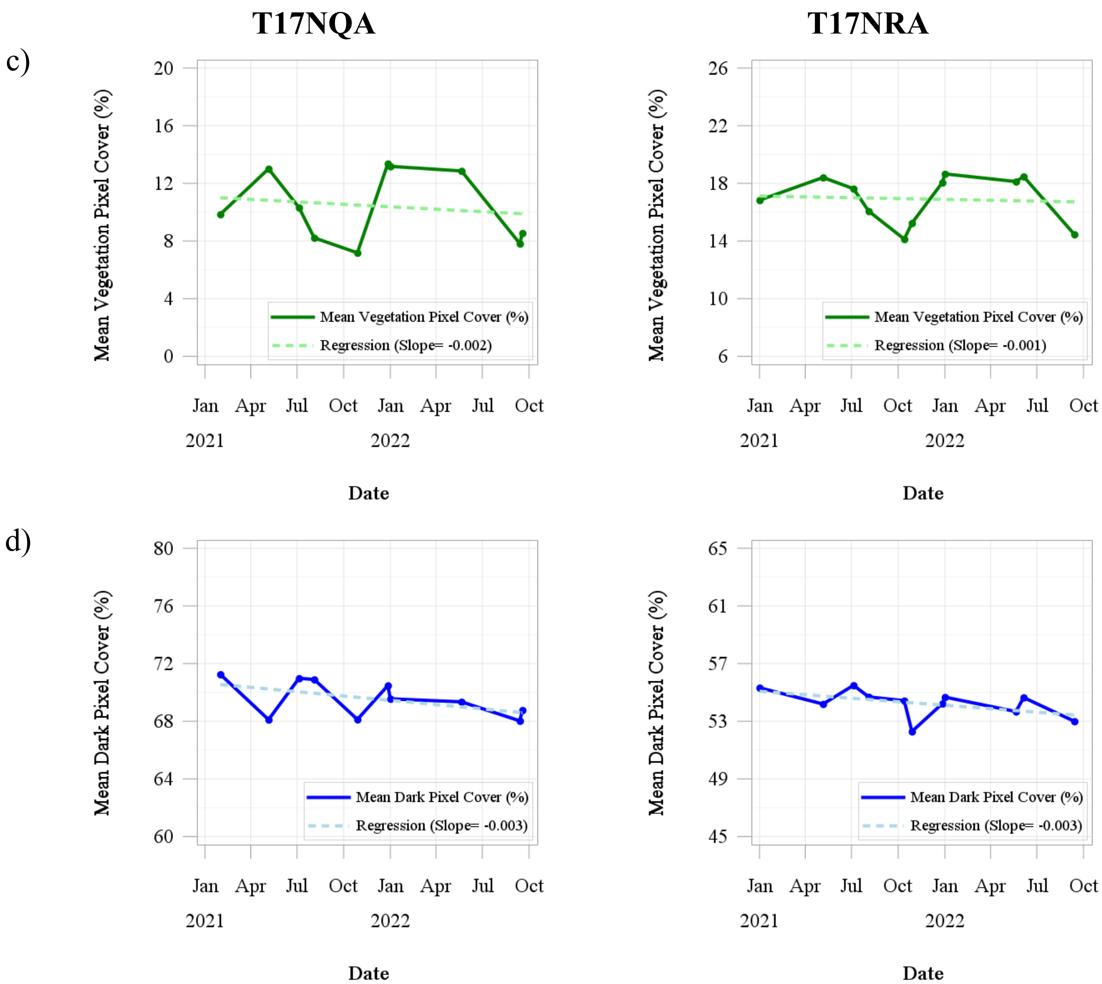
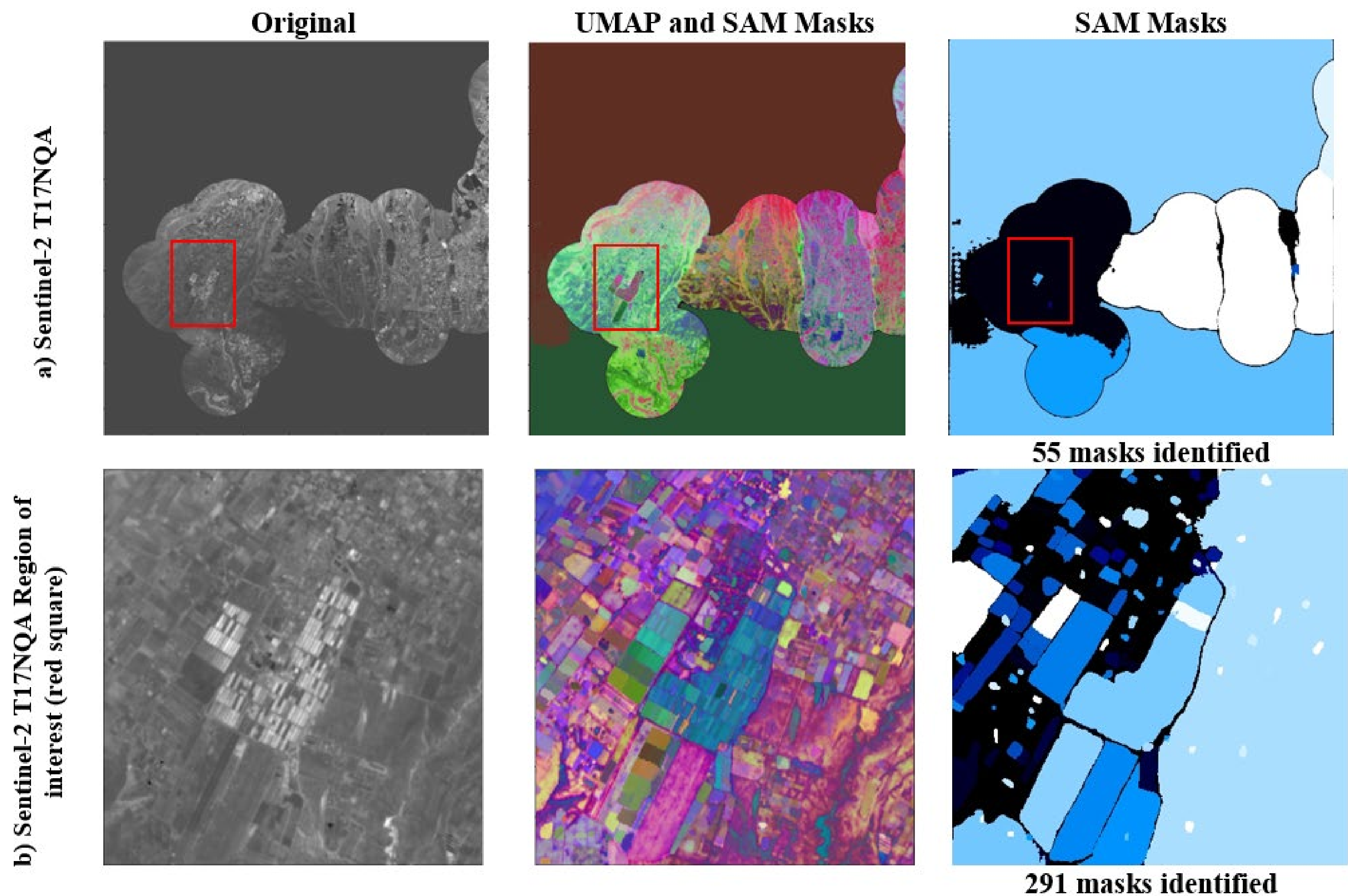


Figure 1.3. continued a) Spectral mixture fractions using local endmembers (R/G/B= Substrate/Vegetation/Darks), (stretch values: Substrate: [0.01- 0.23], Vegetation:[-0.01 - 0.39], Dark: [0.40-0.96]). The region displays a mosaic of two Sentinel-2 tiles from August 4, 2021, T17NQA (left) and T17NRA (right). b-d) Study area means pixel measures of endmember fraction change over time. The time series of study area spatial mean Substrate (b), vegetation (c), and dark (d) fractions for the Pedro Moncayo Canton 3km buffer region for both T17NQA and T17NRA for the duration of the study period. The mean substrate pixels slightly increased, while the mean vegetation and dark pixels slightly decreased for both tiles but were not statistically significant (p=0.10-0.83) based on linear regressions.

Figure 1.4. Application of the Segment Anything Model (SAM) on Sentinel-2 T17NQA and Planet images. Object segmentation was conducted using the SAM with default automatic mask generation parameters, which were found to be the most effective (points per side=32, prediction quality measure of 0.86, and stability score of 0.92). Segment anything demonstrated reduced capabilities for larger regions of interest (S2a), versus using smaller regions of interest (S2b) for object differentiation. Masks colors were automatically generated, and different colors indicates unique masks.


Original
UMAP and SAM Masks
SAM Masks
a) Sentinel-2 T17NQA
55 masks identified
b) Sentinel-2 T17NQA Region of interest (red square)
291 masks identified

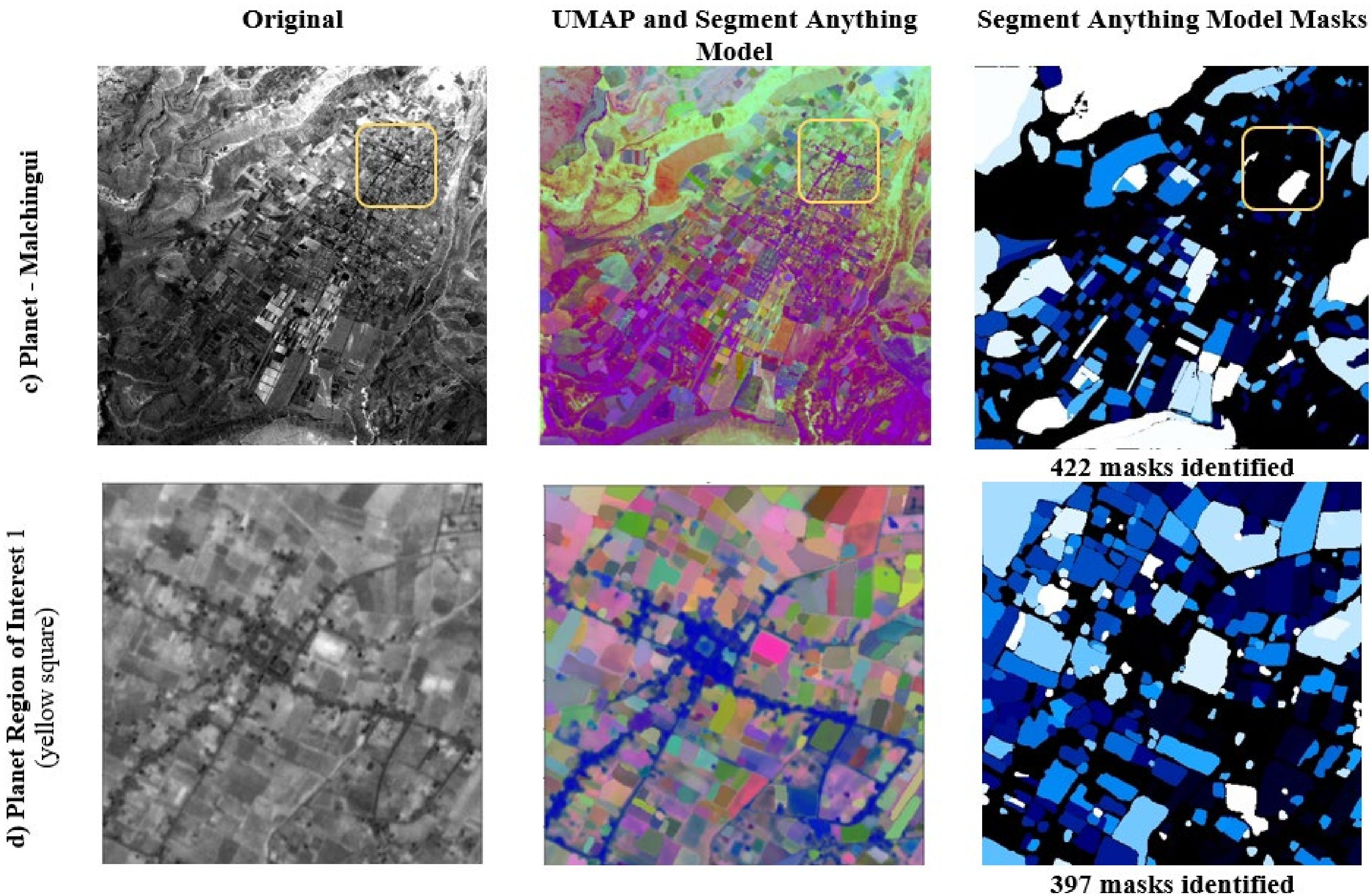
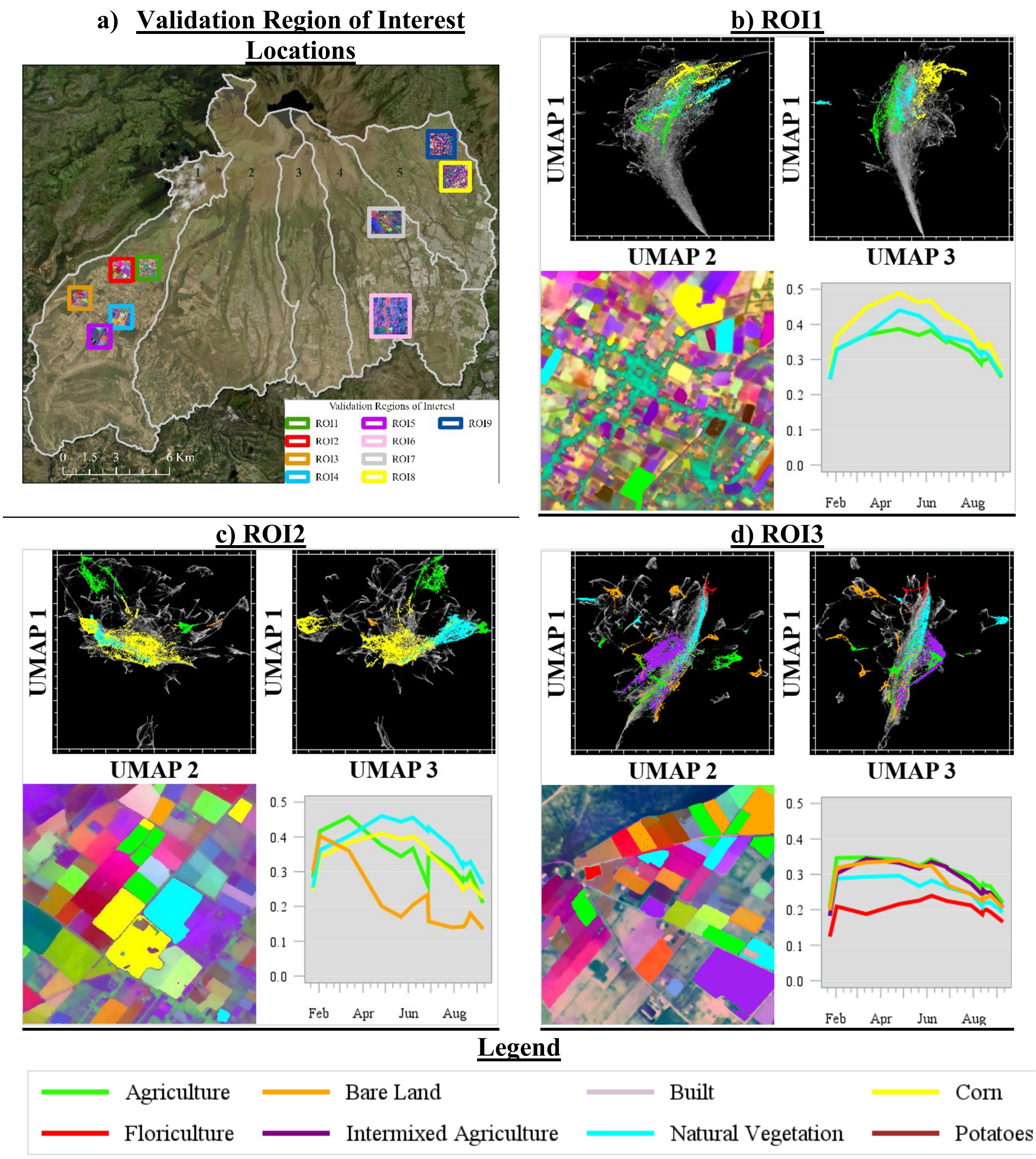


Figure 1.5. continued. Application of the Segment Anything Model (SAM) on Sentinel-2 T17NQA and Planet images.

Figure 1.6. Nonlinear dimensionality reduction with UMAP identifies spatiotemporal patterns using Planet imagery seen with scatterplots of mean enhanced vegetation index 2 (EVI2) values by land cover type. Localized, statistically distinct temporal patterns are evident in the validation ROIs. For each validation region, polygons obtained from the Segment Anything Model outputs were classified using validation locations. Distinct clustering patterns can be observed particularly for ROI1, ROI2, ROI3, ROI4, and ROI5. Certain regions, such as, ROI6, ROI7, ROI8, and ROI9 did not have distinct separation between agriculture and other classifications.



1=Malchinguí, 2=Tocachi, 3=La Esperanza, 4=Tabacundo, 5=Tupigachi

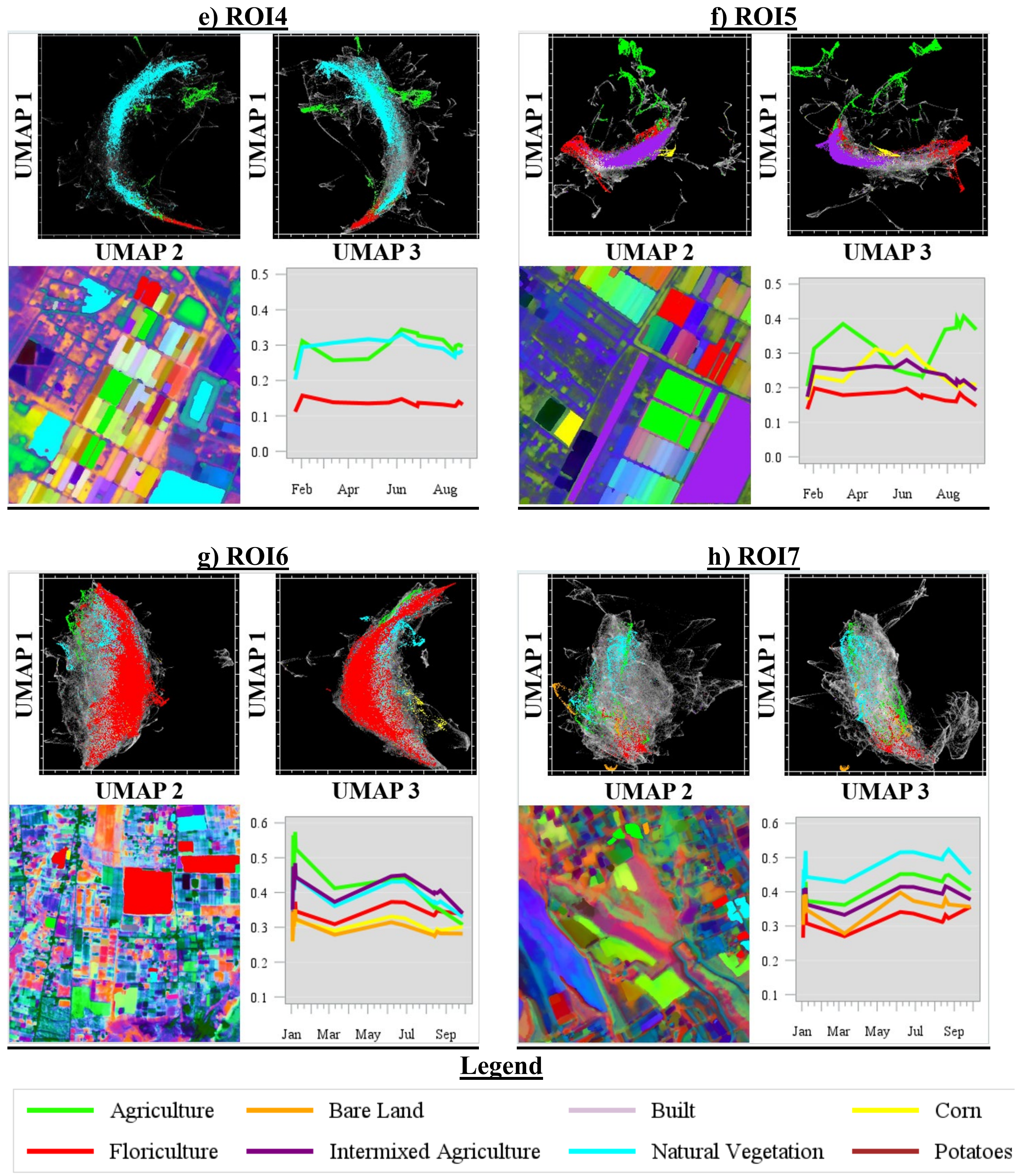


Figure 1.6. continued. Nonlinear dimensionality reduction with UMAP identifies spatiotemporal patterns using Planet imagery seen with scatterplots of mean enhanced vegetation index 2 (EVI2) values by land cover type.

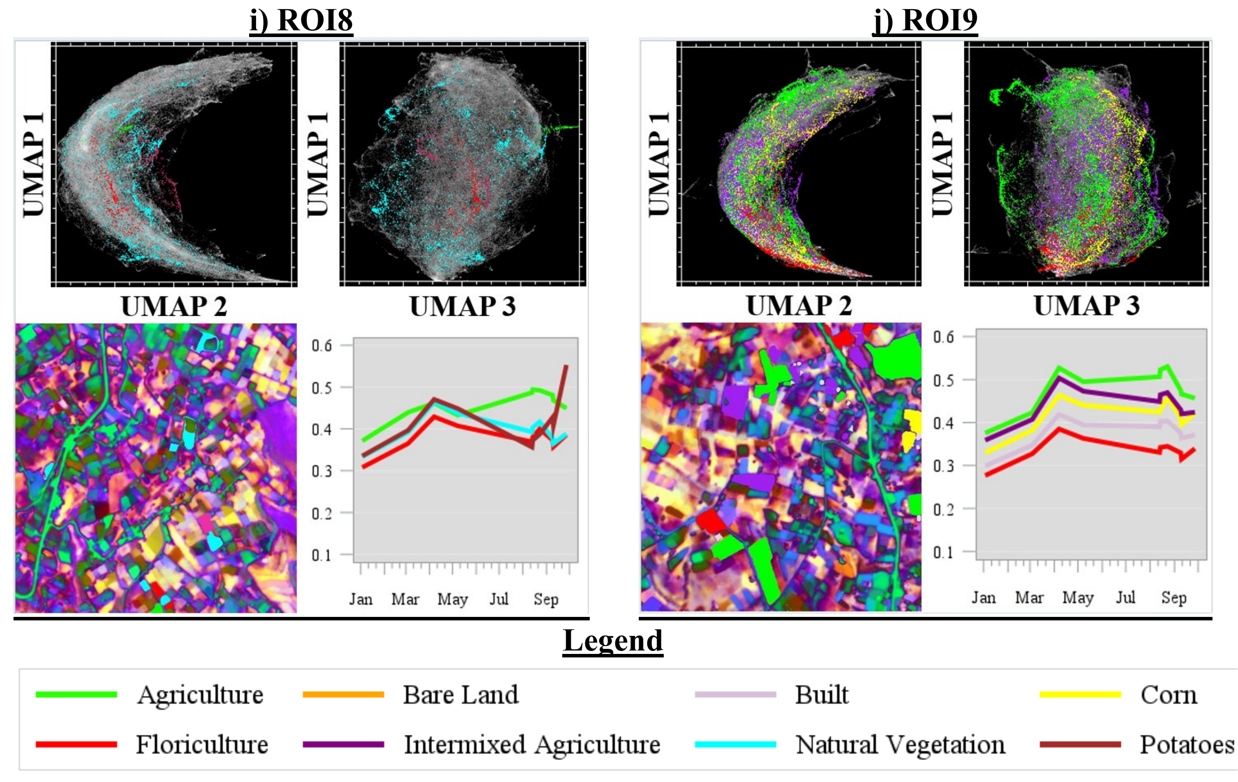
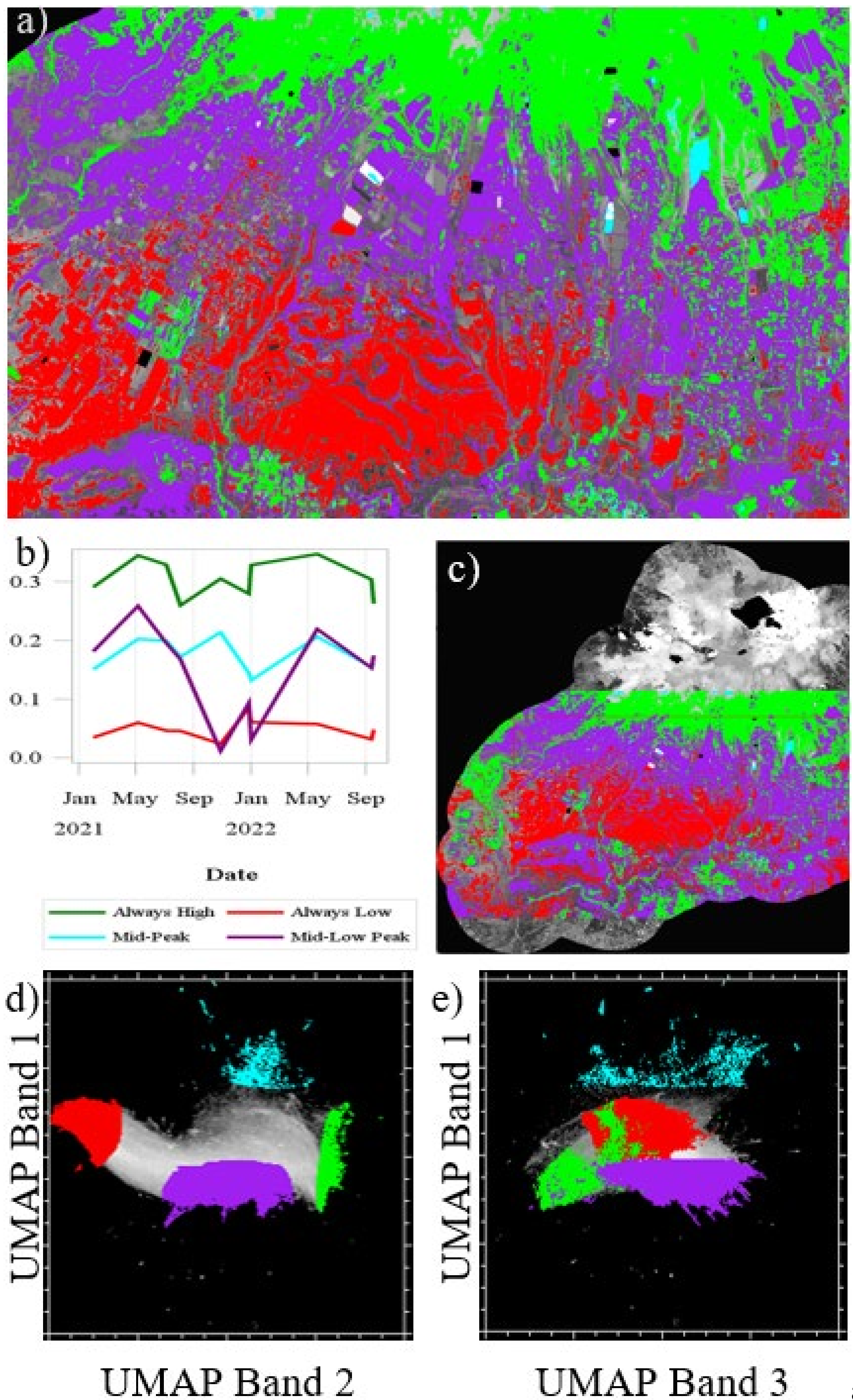
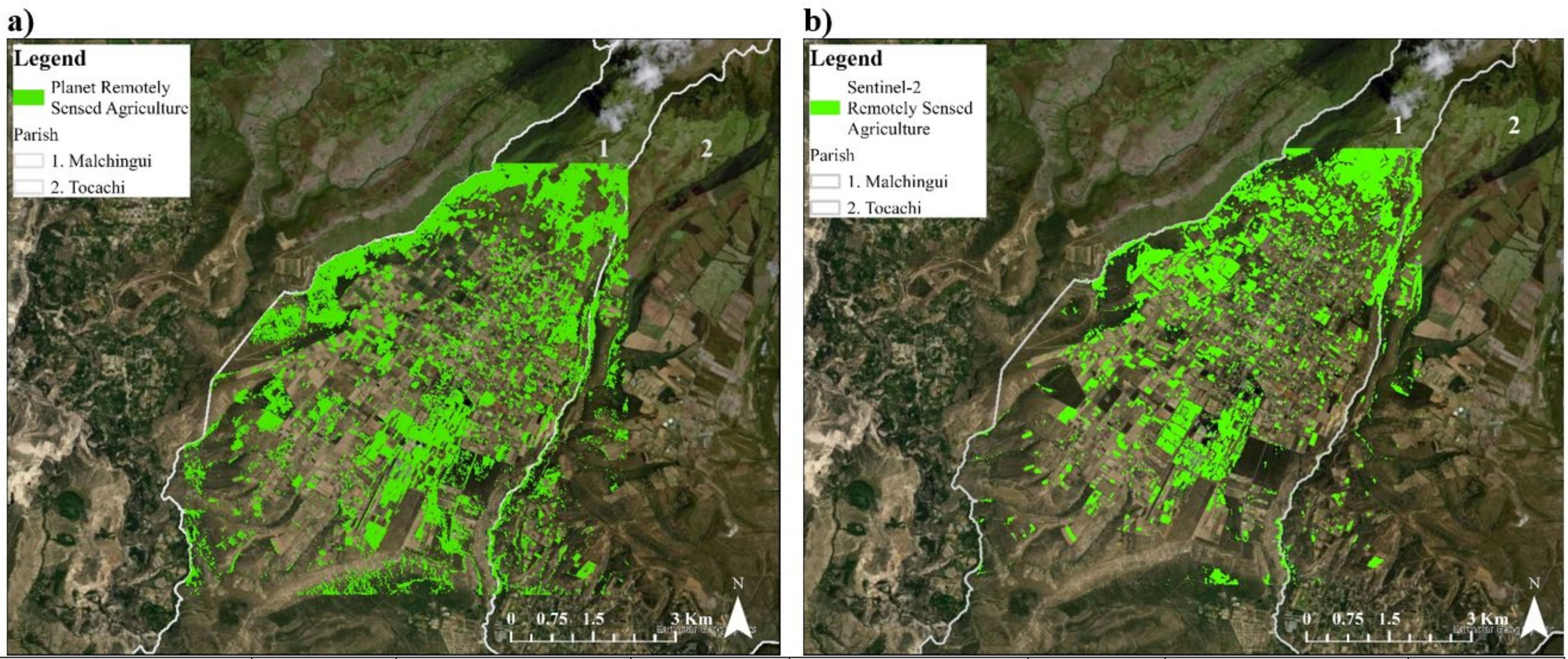


Figure 1.6. continued. Nonlinear dimensionality reduction with UMAP identifies spatiotemporal patterns using Planet imagery seen with scatterplots of mean enhanced vegetation index 2 (EVI2) values by land cover type.



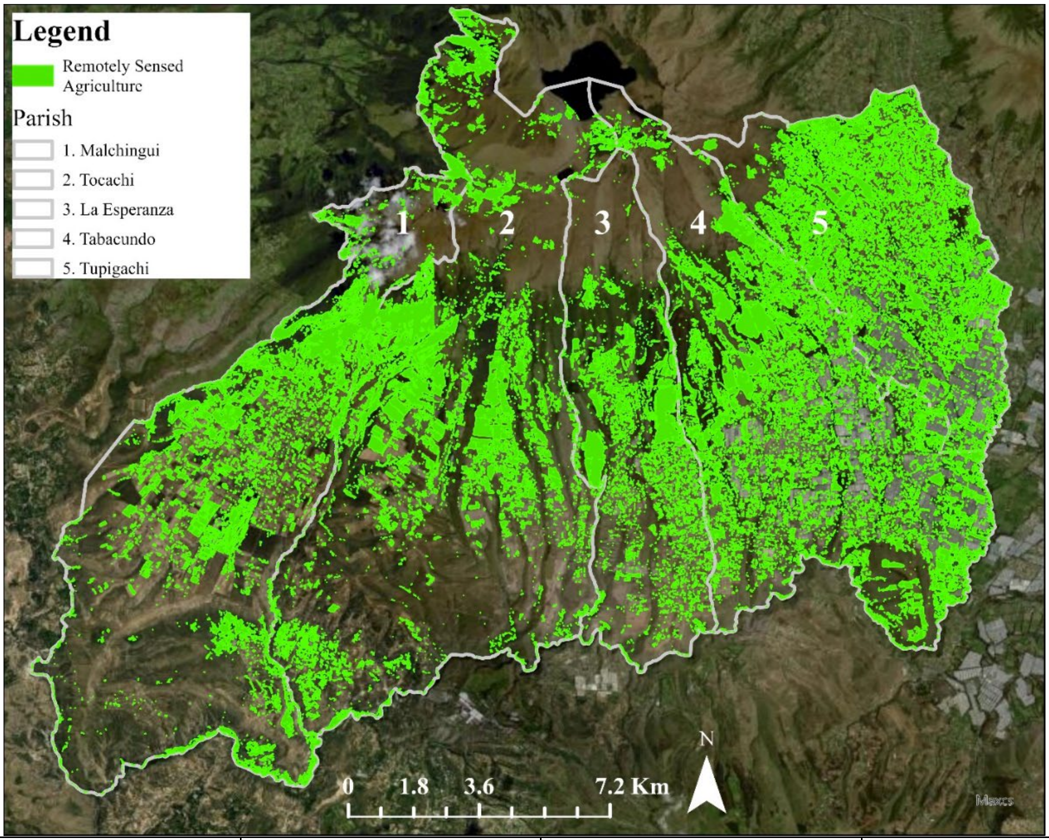
agr

Figure 1.7. Nonlinear dimensionality reduction with UMAP Identified four distinct spatiotemporal patterns using Sentinel-2 T17NQA time series images of the vegetation fraction, demonstrated on the map (a) and scatter plot (b). Green and cyan clusters were identified to be agricultural land types. Purple clusters were found to be a mixture of agriculture types. While the red cluster was indicative of bare land, floriculture, and natural vegetation.



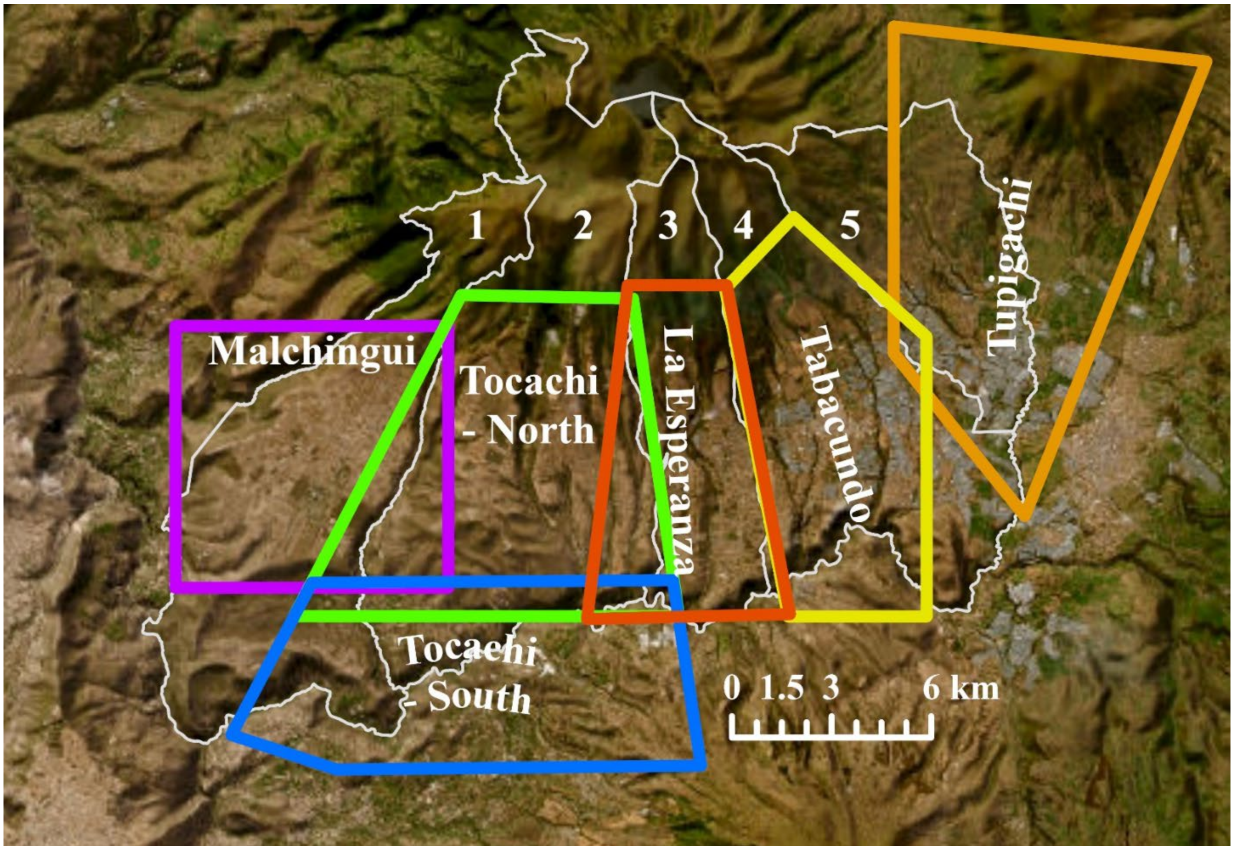
True Positives	53	**False Negatives**	200	**True Positives**	112	**False Negatives**	141
False Positives	16	**True Negatives**	221	**False Positives**	45	**True Negatives**	191
Accuracy	56.0%	**Precision**	76.8%	**Accuracy**	62.0%	**Precision**	71.3%
Sensitivity	20.9%	**Specificity**	93.2%	**Sensitivity**	44.3%	**Specificity**	81.0%

Figure 1.8. A remotely sensed agricultural map was created in Malchingui to compare using maps created using Planet and Sentinel-2 Imagery. When unmixed, model misfit was satisfactory for Sentinel-2 and PlanetScope images. For PlanetScope, 97% of pixels had a RMSE <0.05, while 99% of pixels had RMSEs<0.06. For Sentinel-2, 90% of pixels had an RMSE<0.05, while 99% of pixels had a RMSEs<0.10. Accuracy statistics were estimated Using 490 ground truth validation and found that Planet imagery had lower accuracy (56.0% versus 62.0%) and sensitivity (20.9% versus 44.3%) but had higher precision (76.8% versus 71.3%) and specificity (93.2% vs 81.0%).



True Positives	427	**False Negatives**	409
False Positives	140	**True Negatives**	1025
Accuracy	72.57%	**Precision**	75.31%
Sensitivity	51.1%	**Specificity**	88.0%

Figure 1.9. Final remotely sensed agricultural map within Pedro Moncayo. Using an unmixed time series of the vegetation fraction for T17NQA and T17NRA images, Agricultural landcover was identified as a mixture of the four endmembers identified in Figure 1.7. Using the ground truth images, the map was found to have an accuracy rate of 72.57% and precision of 75.31%. Agriculture coverage covers 18.9% of Pedro Moncayo. By parish, agricultural surface area coverage was 14.7% of La Esperanza, 15.4% of Malchinguí, 22.6% of Tabacundo, 15.8% of Tocachi, and 30.1% of Tupigachi.



Supplemental Figure 1.1. Coverage of Pedro Moncayo by PlanetScope Images. Each colored polygon represents the coverage region for each group of acquired Planet Images and are named after the parish they predominantly cover: Malchinguí, Tocachi North, Tocachi South, La Esperanza, Tabacundo, and Tupigachi. Distinctly, the numbers coincide with the parishes of Malchinguí (1), Tocachi (2), La Esperanza (3), Tabacundo (4), and Tupigachi (5).

a) Agriculture

Land parcels that had evidence of crop growth including grains, soybeans, sweet peas, strawberries, or others. Common features include organization of plants in linear rows, recently harvested grains, or evidence of cultivation, and general lack of weeds within the land parcel.

Supplemental Figure 1.2. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture.

b) Natural Vegetation

Description: Vegetation that had evidence that it was not planted by individuals, indicated by lush or dense distribution of plants, and were not identified as grains such as wheat. Common plants observed were grasses, weeds, or native flora. Pastureland was also classified as natural vegetation.

Supplementary Figure 1.2. continued. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture.

c) Corn

Fields that had evidence of corn grown, indicative of their long and thick stalks, with heights of 4-10 ft, and long narrow blade like leaves. A majority of fields were already harvested; thus, corn stalks were a golden color, with no fruit.

Supplementary Figure 1.2. continued. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture.

(d) Intermixed Agriculture

Parcels of land that had evidence of agricultural activities, whether it was corn growing, materials used for agricultural activity (e.g., black plastic rows used for strawberries) but were inactive and covered in natural vegetation. This was commonly seen as grasses, native plants, or weeds.

Supplementary Figure 1.2. continued. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture.

(e) Bare Land

Land parcels that were composed of dry dirt. Some parcels had sparse plants grown throughout the plot but were ~90% just dirt.

(f) Potatoes

These plots resembled bare land but had evidence of being tilled recently and had evidence of having irrigation of some type. The time period is when potatoes are planted, thus the crop cannot be seen from the surface. Local farmers confirmed a subset of potato fields, including the one below.

Supplementary Figure 1.2. continued. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture.

g) Built

Any images that showed buildings were classified as built. This included homes, business buildings, or agricultural sheds. In general, most of the buildings were made of concrete in this region, which variations in roof types. This included exposed concrete, to tiled roofs.

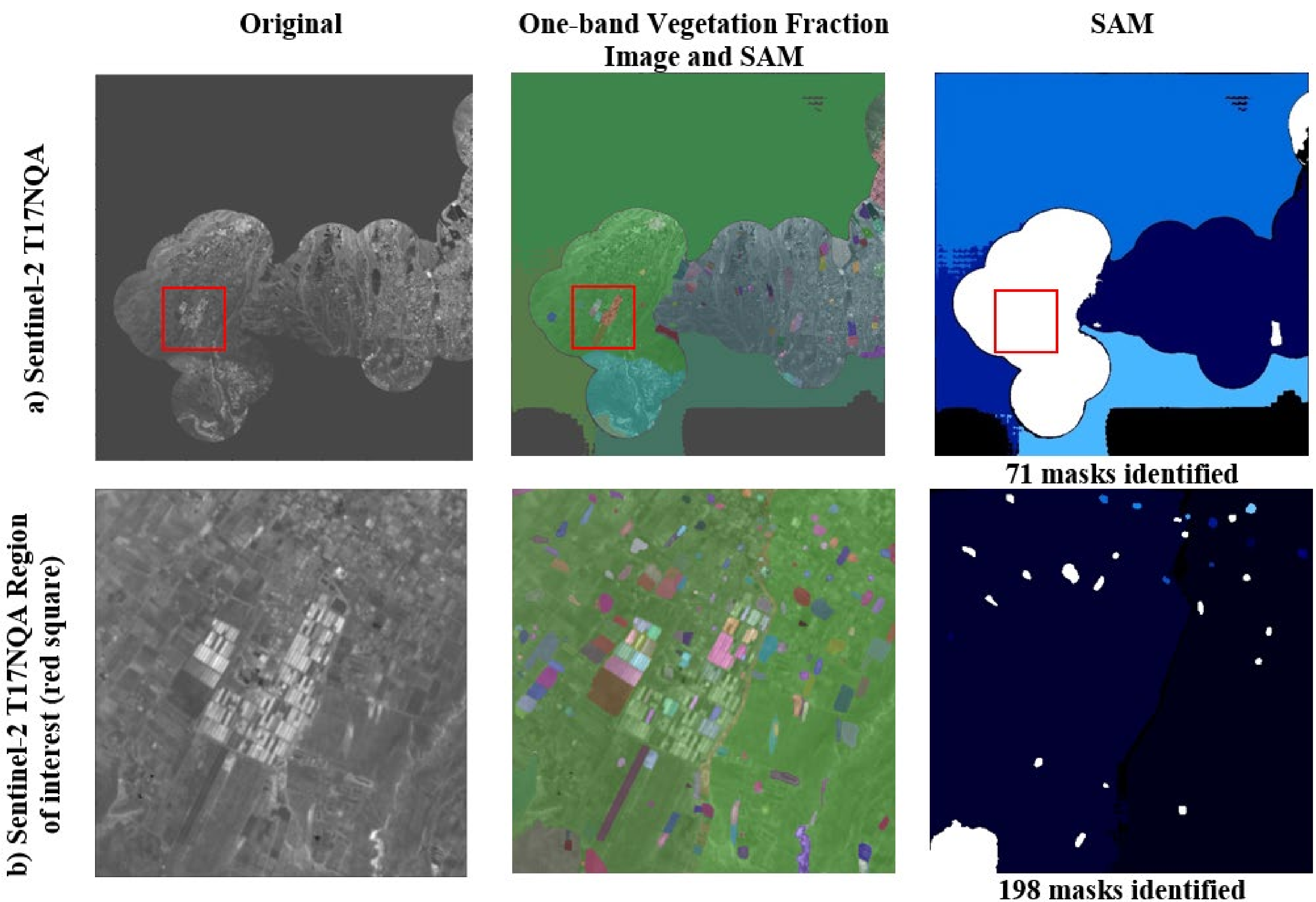
Supplementary Figure 1.2. continued. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture.

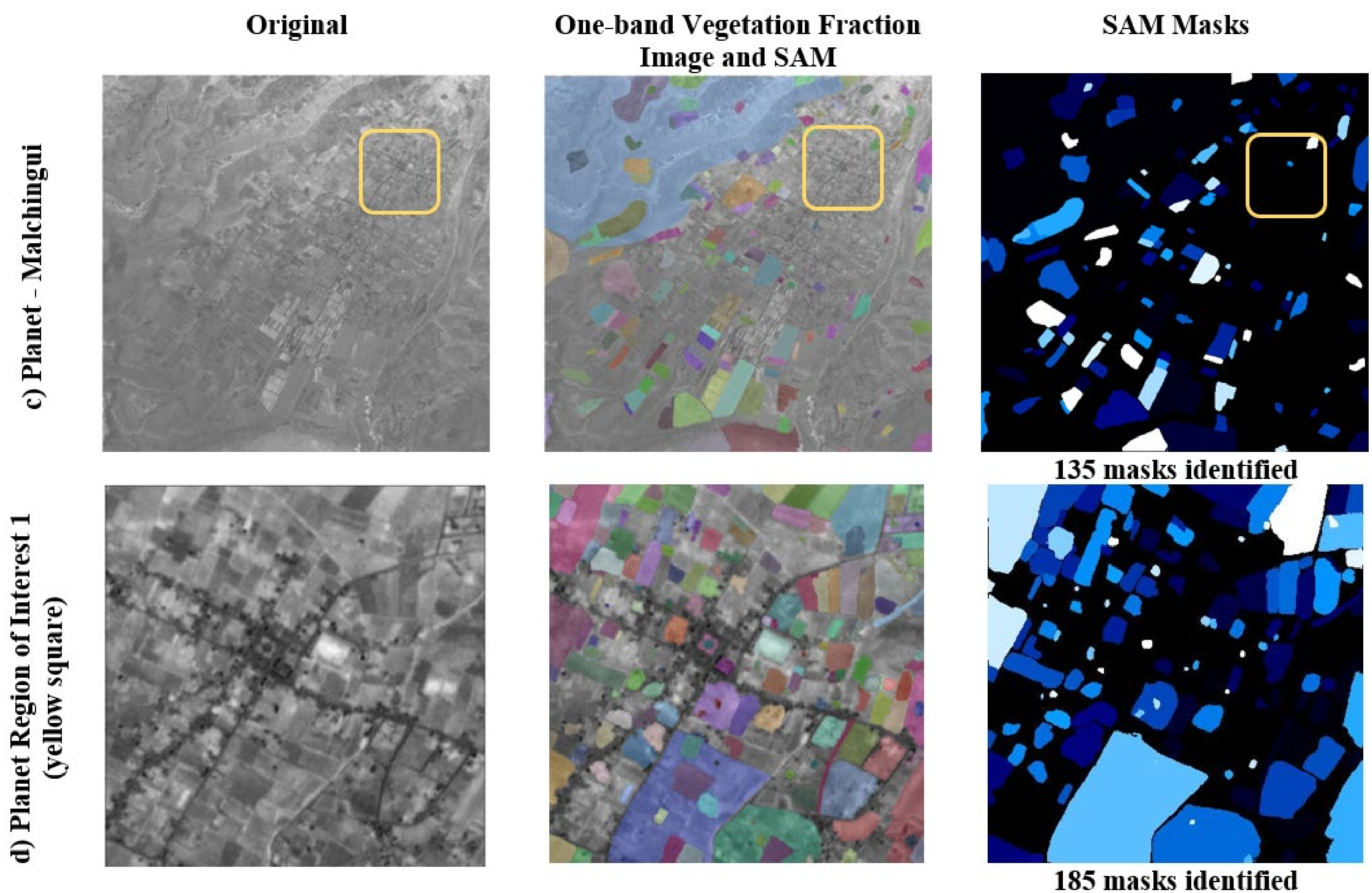
h) Floriculture

All greenhouses in this region were classified as being floriculture, given the high prevalence of floriculture in this region. All greenhouses are white and are made of plastic material.

Supplementary Figure 1.2. continued. Sample ground truth images for (a) agriculture, (b) natural vegetation, (c) corn, (d) Intermixed agriculture, (e) Bare Land, (f) potatoes, and (g) built, and (h) floriculture, and descriptions of how they were classified.

Supplemental Figure 1.3. Application of the Segment Anything Model (SAM) on one band Sentinel-2 T17NQA and Planet images. Object segmentation was conducted using default automatic mask generation parameters for the SAM, which were found to be the most effective (points per side=32, prediction quality measure of 0.86, and stability score of 0.92). The images displayed are the original vegetation fraction time series images, the UMAP images with overlaid SAM masks, and the SAM masks themselves (stretch: White to Blue). Each mask is given an identifying number, and the presented image has a stretch of white (lowest identification number) to blue (highest identification number), and black means no masks were identified in that region. Segment anything demonstrated reduced capabilities for larger regions of interest (a), versus using smaller regions of interest (b) for object differentiation based on the generated mask count.


Original
One-band Vegetation Fraction Image and SAM
SAM
a) Sentinel-2 T17NQA
b) Sentinel-2 T17NQA Region of interest (red square)
71 masks identified
198 masks identified



Supplemental Figure 1.4. continued. Application of the Segment Anything Model (SAM) on one band Sentinel-2 T17NQA and Planet images.

Supplemental Table 1.1. Image Acquisition dates for Sentinel-2 and PlanetScope imagery that were used in the analysis.

	Sentinel-2 Image Acquisition Dates		PlanetScope Image Acquisition Dates					
Image	T17NQA	T17NRA	Malchingui	Tocachi - North	Tocachi - South	La Esperanza	Tabacundo	Tupigachi
1	1/31/2021	1/1/2021	1/24/2022	1/7/2022	1/8/2022	1/3/2022	1/3/2022	1/3/2022
2	5/6/2021	5/6/2021	2/2/2022	5/22/2022	1/8/2022	1/7/2022	1/4/2022	3/4/2022
3	7/5/2021	5/21/2022	3/13/2022	6/27/2022	3/10/2022	1/8/2022	1/5/2022	4/7/2022
4	8/4/2021	7/5/2021	4/26/2022	6/28/2022	4/26/2022	3/10/2022	1/7/2022	5/8/2022
5	10/28/2021	8/4/2021	5/22/2022	7/29/2022	5/22/2022	4/26/2022	1/8/2022	8/13/2022
6	12/27/2021	10/13/2021	6/7/2022	8/13/2022	7/29/2022	5/22/2022	3/10/2022	8/14/2022
7	1/1/2022	10/28/2021	6/27/2022	8/13/2022	8/13/2022	6/7/2022	6/7/2022	8/23/2022
8	5/21/2022	12/27/2021	6/28/2022	8/18/2022	8/16/2022	6/28/2022	6/28/2022	9/9/2022
9	9/13/2022	1/1/2022	7/29/2022	9/9/2022	8/23/2022	7/29/2022	8/13/2022	9/10/2022
10	9/18/2022	6/5/2022	8/13/2022	9/12/2022	9/9/2022	8/13/2022	8/14/2022	9/27/2022
11		9/13/2022	8/14/2022	9/13/2022	9/18/2022	8/16/2022	8/18/2022	
12			8/18/2022	9/23/2022	9/22/2022	8/18/2022	8/23/2022	
13			8/23/2022	9/27/2022	9/27/2022	8/23/2022	9/27/2022	
14			9/9/2022		9/30/2022	9/9/2022		
15						9/18/2022		
16						9/22/2022		
17						9/27/2022		

Chapter 2 Home distance to Agriculture and Organophosphate, Pyrethroid, and Herbicide Urinary Metabolite Concentration in Ecuadorian Adolescents and Young Adults

Abstract

Introduction: Pesticide drift, known as off-target movement of pesticides, is a major cause of pesticide exposure in agricultural communities including Pedro Moncayo, Ecuador. As pesticide exposure in agriculture puts communities at risk, characterizing the extent of pesticide drift is crucial to create targeted public health interventions aiming at reducing exposures.

Methods: 500 adults (16-25, 49.6% male) living in Pedro Moncayo, Ecuador were assessed in 2022. Urinary concentrations of organophosphate, pyrethroid, and herbicide pesticide biomarkers were measured using mass-spectrometry. Home distance to the nearest agricultural plot (home-ag distance) and surface area of agriculture (home-ag SA) were calculated. Generalized estimating equations (GEE) estimated associations between home-ag distance and home-ag SA with gravity-adjusted metabolite concentration, adjusting for demographic, socioeconomic, anthropometric, and alternative pesticide exposure pathways. Odds ratios of having detectable metabolite concentrations was conducted using logistic regression and geospatially weighted regression (GWR) was conducted, adjusting for similar covariates. Effect modification by sex was evaluated.

Results: A 1% increase in home-ag distance was negatively associated with 2,4-dichlorophenoxyacetic acid (2,4-D) concentration in males (β=-8.21% [-13.27%, -2.86%]), but positively associated with 3-phenoxybenzoic acid (3-PBA) concentration (β=4.38% [0.28%, 8.65%]) for the overall cohort. A 1% increase in home-ag SA for a 50m (home-ag SA_{50m}) buffer was associated with 103.7% higher 2,4-D concentration, which was greater in males (β=288.86%

[44.46%, 946.78%]) than females (β=1.03% [-60.51%, 158.48%]). In women, a 1% increase in home-ag SA_{150m} was associated with lower 3,5,6-Trichloro-2-pyridinol (TCPY) concentration (β=-0.13% [-0.25, -0.01]). Negative associations were observed between home-ag SA_{100m} with *para*-nitrophenol (PNP) (β=-14.29 (-24.18, -3.10]), which weakened with greater buffer sizes. A $1000m^2$ increase of home-ag SA_{50m} had 33% higher odds of having detectable malathion dicarboxylic acid (MDA). GWR identified that home-ag SA_{50m} had the strongest positive associations with 2,4-D and negative associations with 3-PBA in southern Malchinguí.

Conclusions: We observed associations between home-ag distance and home-ag SA with organophosphate, pyrethroid, and herbicide concentration, with some effect modification by sex. The findings suggest that 2,4-D and MDA exposures stem from agricultural sources, but not for PNP, TCPY, and 3-PBA. Future studies should incorporate participant movement patterns and map unique crop types to improve pesticide drift characterization.

Introduction

Off-target pesticide drift of pesticides to nearby homes is a major cause of pesticide exposure in agricultural communities as volatilization can occur for up to 90% of crop application doses [73]. Exposure from pesticide drift has been linked to acute pesticide illnesses, such as pesticide poisonings, in other countries. For example, from 1998 to 2006 it was estimated that off-target drift led to 2,945 pesticide poisoning cases of individuals who lived within 1.4 km of agriculture in 11 states within the United States.[74] In Ecuador from 2001 to 2007, the *Instituto Nacional de Estadisticas y* Censos (INEC; National Institute of Statistics and Census) reported a pesticide poisoning incidence of 25.89 per 10,000, primarily stemming from organophosphate and carbamate insecticides, and had a high burden in adolescents and young adults (15-25 years) [75]. The pesticide poisonings incidence rate in Ecuador was 14.2 times higher than annual incidence rates of developing countries (1.82 per 10,000) [76]. Living in close proximity to agricultural sites has been linked to increased urinary metabolite concentrations, and higher rates of suspected health consequences of pesticide exposure in other populations [7,77–79]. In Pedro Moncayo, we previously found that children living within 275m of greenhouse floricultural crops had lower concentrations of acetylcholinesterase (AChE) activity, reflecting greater exposure to cholinesterase inhibitor pesticides [80]. Within the same cohort of adolescents who lived in Pedro Moncayo, Ecuador, adolescents who lived farther from floricultural greenhouses did not have decreased concentrations of all urinary pesticide metabolites measured as hypothesized. For instance, while there were negative associations between increased residential distance to floricultural greenhouse with para-nitrophenol (PNP; a metabolite for the organophosphate parathion) concentrations for participants who lived within 200m to the nearest floricultural greenhouse, but there were positive associations for those living farther than 200m [11]. Furthermore, per a 50% increase of distance to floriculture greenhouses, there was a 2.06%

(95%CI: 0.29%, 3.87%) increase of 3,5,6-Trichloro-2-pyridinol (TCPy; organophosphate) concentration [11], suggesting that pesticide drift may be coming from non-floricultural sources. Yet, it is unknown whether open-air agriculture also contributes to pesticide exposure in young adults living in Pedro Moncayo, Ecuador.

Open-air agriculture, as opposed to greenhouse floriculture, potentially has higher dispersion of pesticides through drift as it lacks a barrier that can contain volatilized pesticides [74]. This puts adults living in agriculture communities at risk of exposure. Distance to pesticide spray sites can potentially be a strong determinant of pesticide exposure for individuals living in agricultural communities [81]. The extent of pesticide drift varies by pesticide application method, which ranges from manually carried hydraulic sprayers, power-operated hydraulic sprayers, and air-assisted sprayers [82]. Typical pesticide application methods used by Ecuadorian farmers include backpack sprayers, and although this leads to shorter off-target drift compared to other methods, it can still lead to widespread contamination of farm households.[83] The type of agriculture can also influence the extent of pesticide drift. Detectable air concentrations of pesticides have been observed within a range of 0 to 4828 kilometers (km) from open-air agriculture [74,84], and concentrations decay with -increasing distance [81]. Pesticide poisonings due to off target pesticide drift from open air agriculture have been reported in populations that lived within 1.6km of application sites [74].

As similar crop types attract similar pests, there may be overlap between the types of pesticides applied on similar crops. Herbicides, like glyphosate, targets weeds and other plants which makes them less ideal to be used in floriculture, as they can also lead to the destruction of the rose plants. They are more commonly used in agriculture, as they can be used as pre-harvest desiccant for crops like corn, wheat, and beans [85]. Pesticide usage patterns have been found to be similar across various crop types. Organophosphates and pyrethroids are insecticides, as they target insects using different mechanisms. Organophosphates inhibit the enzyme acetylcholinesterase (AChE) [86] while pyrethroids depolarizes voltage-gated sodium channels in neurons [87]. Pyrethroids composed about 17% of the market share of insecticides used between 2010 and 2015 [88]. Exposure to pesticides, like organophosphates, pyrethroids and herbicides, can have negative health consequences that can be both acute (irritation, fatigue, mood alterations) and long term (leukemia, hypertension, and diabetes) [89–93]. Due to the potential health risks of exposure, it is crucial to identify pathways for pesticide exposure within local contexts.

To assess indirect exposure to pesticides in agricultural communities, home distance to pesticide spray sites (agricultural crops), and surface area of agricultural crops near the home have been used to classify long-term exposure to pesticide exposure in other cohorts and are generally validated using pesticide use reporting (PUR) systems to obtain density of pesticides applied near homes [7–9]. Ecuador, like most low- and middle-income countries and many high-income countries, lacks PUR policies, which makes it more difficult to classify pesticide exposure from pesticide drift. Therefore, alternative methods of exposure classification from pesticide drift are needed in such areas. Residential distance to agriculture is a valuable construct of chronic pesticide exposure, particularly for populations living near agricultural crops. When PUR is not available, a method to validate geospatial proxies of pesticide exposure is to determine whether residential distance to agricultural fields, or surface area of agricultural fields near homes, are associated with increased urinary pesticide metabolite concentration. This study will use the agricultural map that was developed in Chapter 1, to determine whether agriculture in Pedro Moncayo is a source of para-occupational pesticide exposure in our cohort, while additionally validating distance as a proxy exposure variable for certain classifications of pesticides.

Methods

Participants

Established in 2008, the Secondary Exposures to Pesticides among Children and Adolescents (ESPINA) study is a prospective cohort study that examines the associations of subclinical pesticide exposure on human development. In 2008, 313 children (4-9 years) living in Pedro Moncayo were recruited either through the 2004 Survey of Access and Demand of Health Services (SADHS) (73%) or through community announcements (27%) [94]. In 2016, the cohort was expanded to 554 participants. Since 2008, there have been seven in-person follow-up assessments: spring (April) and summer (July-October) in 2016 [97], summer (July-September) of 2022, the winter (January-February) and summer (July) of 2023, and winter (January-February) and summer (June-July) of 2024 (Figure 2.1.). Participants completed thorough surveys for the summer 2016, summer of 2022, and winter 2024 assessments, while pesticide metabolite concentrations were completed for the summer 2016 and summer 2022 assessments by the time when we conducted the present analyses. This analysis focuses on the 2022 assessment, as this is the time point that has a map of agriculture (Chapter 1). A total of 505 participants were examined in 2022 and included in the present analysis.

Demographic and socioeconomic information was collected at the 2022 visit. Height was measured to the nearest 1mm, and weight was measured using a digital scale (Tanita 0108MC; Corporation of America, Arlington Heights, IL, USA) [95]. These two measures were used to calculate body mass index (BMI).

Imputation of missing variables

To maximize the sample size, imputation was conducted for frequency of pesticide use at home, cohabitation with a floricultural or agricultural worker, pesticide use at work, occupation, education level, and salary. 19 individuals did not report frequency of pesticide use at home. Values were imputed with reported pesticide use behaviors from the Winter 2024 assessment first (n=11), and the remaining observations were imputed with reported use for the summer 2016 assessment (n=8). For cohabitation with an agricultural or floricultural worker, 13 observations were imputed using data from the winter 2024 exam (n=8) or the summer 2016 exam (n=5). For pesticide use at work, we imputed occupation reported at the 2024 exam for 14 individuals, and 10 individuals were classified as "I don't know/prefer not to answer." For occupation in agriculture or floriculture, 8 people were imputed based on reported occupation for the winter 2024. At the winter 2024 assessment, individuals were asked what their occupation was between January to June 2023, and for July to December 2023. Occupation for the 2022 cross section was imputed using reported occupation from January to June 2023 first (n=7), occupation from July to December 2023 (n=1), and lastly five were imputed based on reported occupation of their parents in 2016 (2 agricultural or floricultural workers, 3 were not agricultural or floricultural workers). Participants' education level was imputed using levels reported in 2023 for 6 individuals. As education was reported as a categorical variable, 1 individual was imputed using the mode education in the parish that they resided (Tocachi). For household monthly salary, 11 observations were imputed using salary reported in 2023, and 10 were recategorized to "Prefer not to answer."

Metabolite Assays

Eight pesticiees or pesticide metabolites of insecticides and herbicides were measured. This included four organophosphate insecticide metabolites (2-isopropyl-4-methyl-6-

hydroxypyrimidine [OXY2], 3,5,6-Trichloro-2-pyridinol [TCPY], para-Nitrophenol [PNP], and malathion dicarboxylic acid [MDA]), three pyrethroid insecticide metabolites (3-phenoxybenzoic acid [3-PBA], 4-fluoro-3-phenoxybenzoic acid [4F-3PBA] and trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid [TCC]), and one herbicide (2,4-Dichlorophenoxyacetic acid [2,4-D]). Only 5 individuals had 4F-3PBA concentrations above the level of detection (LOD); hence, this metabolite was not included in the analysis.

Urinary concentrations of creatinine and pesticide biomarkers were measured in samples collected upon awakening from the July-September 2022 examination. Participants brought the urine samples collected soon after awakening to the examination site where they were aliquoted and frozen in coolers with dry ice. At the end of each day, samples were transported to Quito for storage at -70° C. Samples were then transported frozen to the University of California San Diego (UCSD) using a specialized courier, where the samples were kept at -80° C for long-term storage. Samples were then shipped frozen from the University of California San Diego (UCSD) to the National Center for Environmental Health, Division of Laboratory Sciences of the CDC (Atlanta, GA) for quantification of pesticides and pesticide metabolites. Online solid phase extraction high-performance liquid chromatography-isotope dilution-tandem mass spectrometry was used to quantify the urinary pesticide biomarkers [96]. More details regarding the measurement method been previously published [96]. Quality control/quality assurance protocols were followed to ensure data accuracy and reliability of the analytical measurements. All the study samples were re-extracted if quality control failed the statistical evaluation [97,98]. The LOD was 0.1 for TCPY, PNP, 3-PBA and OXY2, 0.15 for 2,4-D, 0.5 for MDA and 4F-3PBA, and 0.6 for TCC. Metabolite concentrations below the LOD were imputed using a constant (LOD/square root of 2). Observations that had interfering substances were not imputed. To assess the dilution of urine, urinary pesticide metabolite concentrations were adjusted for specific gravity (SG) (Equation 6) [99,100].

Equation 6 $Adjusted\ Concentration = Metabolite\ Concentaration \times \frac{SG_{mean}-1}{SG-1}$

For Equation 6, the SG_{mean} is the mean specific gravity of the cohort, while the SG is the specific gravity for the individual.

Agricultural proximity construct creation

ESPINA participants' home locations were obtained from the Community Information System (SILC), which is a geo-referenced information system developed by Fundación Cimas del Ecuador in collaboration with the Commonwealth of rural parishes of Pedro Moncayo County, which included active community involvement. Home locations were geolocated manually using GPS receivers. Agricultural fields were identified using methods reported in Chapter 1. In summary, spectral mixture analysis was conducted on Sentinel-2 T17NQA and T17NRA images from January 1, 2021, to October 31, 2022. A time-series of vegetation fraction images was created, and nonlinear dimensionality reduction with Uniform Manifold Approximation and Projection (UMAP) was identified. Clustering of distinct agricultural temporal end members (tEMs) was identified in the UMAP feature space manually. The tEMs were used to unmix the processed Sentinel-2 images, and an agricultural map was created that had 72.57% accuracy and 75.31% precision. Country-level, province-level, and county-level borders were provided by the World Bank [101]. All layers were reprojected to have the WGS 1984 UTM Zone 17S projection.

Two agricultural proximity constructs were created. The distance from the participants' home to the border of the nearest agricultural field (home-ag distance), and agricultural surface area for different radii (buffer sizes) around the participants home (home-ag SA). The buffer regions ranged from 50m (home-ag SA_{50m}) to 500m (home-ag SA_{500m}), by every 50 m. Both home-ag distance and home-ag SA were calculated in meters (m) and m^2 , respectively, and were converted to kilometers (km) and km^2. Similar studies have used buffer regions ranging from 0 to 8,000 meters [10]. Smaller buffers will be assessed first, as the primary pesticide application method used in this region use hand-sprayers which have shorter pesticide drift than aerial sprayers [82]. However, if no associations are discovered, larger buffer sizes will be assessed.

Statistical Analysis

This analysis included all individuals who participated in the summer 2022 follow-up assessment (n=505), provided their home address, had measurement for at least one urinary pesticide metabolite, and had no missing for any covariates after imputation. 500 individuals were included in this analysis, as one participant did not have urinary pesticide metabolites, one had missing information for the covariates, and three did not provide their home address (Figure 2.1.). Participant characteristics were calculated using means and standard deviations (SD) for normally distributed continuous data, median and interquartile ranges (IQR) for non-normally distributed variables and counts and column percentages for count. A p-value for difference (p-diff) for participant characteristics across a median split of home-ag SA_{50m} was calculated using an unadjusted linear regression.

Generalized Estimating Equations (GEE) were used to estimate the association between our two proximity constructs and urinary pesticide metabolite concentrations, with the exception of MDA as it was only detectable concentrations in 9.2% of the cohort. The proximity constructs and urinary pesticide metabolite concentrations were not normally distributed, and were natural log transformed (ln-transformed). Estimates were back transformed to determine the percent (%) difference in urinary pesticide metabolite concentration for a 1% increase in home-ag distance or home-ag SA. This was done by calculating 1.01 to the power of the coefficient, subtracting 1, and multiplying by 100. Two models were used. Model 1 covariates adjusted for age, BMI, gender (reference [ref]=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College-to-College Graduate). Our proximity constructs aim to estimate potential pesticide drift that is occurring; therefore, it is possible that alternative sources of pesticide exposure that are plausibly related to both proximity to agriculture and urinary pesticide metabolite concentrations, could confound this association. Some alternative pathways include para-occupational exposure (e.g., living with an agricultural worker) [94,102], occupational exposure[103], and pesticide use behaviors like residential use [104,105]. To account for these alternative exposure pathways, Model 2 adjusted for Model 1 covariates and living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), and frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always). If inclusion of the Model 2 variables led to a 10% change in any of the estimates compared to Model 1, then Model 2 covariates will be used for subsequent models.

The residuals for the GEE models assessing the association between home-ag distance, home-ag SA_{50m}, and home-ag SA_{100m} with metabolite concentration were output. Autocorrelation of the model residuals were assessed using the Global Moran's index (Moran's I). A statistically significant Global Moran's I indicate that there is spatial clustering of errors, a potential indicator for model misspecification [106]. Getis-Ord Gi* statistic was used to identify hot and cold spots within a 90% confidence interval; golden search was used to identify an ideal Euclidean distance band using the optimized hotspot analysis tool [107,108]. Compared to the standard hotspot analysis tool, the optimized version uses the false discovery rate (FDR) correction method that corrects for multiple testing and spatial dependence, lowering potential Type I error. To de-identify home locations of individuals, non-significant Gi* statistic points were masked, and the hot and cold spot point diameters were given a 1350 m diameter solely for visualization and reporting purposes.

To identify whether there is spatial variation between the association of home distance to nearest agricultural crop (exposure) and urinary metabolite concentrations (outcome), we conducted geographically weighted regression (GWR). The GWR model creates a separate regression equation for each home location, allowing the association to vary across the county and uses the golden search neighborhood selection method to identify the optimal distance band [109]. The GWR models assessed for a 1km increase in home-ag distance or a 1km^2 increase in home-ag SA for a 50m or 100m buffer and were adjusted for model 2 covariates. The GWR coefficients and pseudo t-values were mapped, and the points were given an 1350 km diameter to improve de-identification of participant's home locations.

Effect modification by sex was assessed by introducing an interaction term between home-ag distance, home-ag SA_{50m}, and home-ag SA_{100m} with sex in the GEE models for Model 1 and Model 2. If the interaction term was statistically significant ($p<0.05$), then the association was stratified by sex. Assessment of threshold effects was not assessed, as the mean home-ag distance of the participants was low (~19m). Other studies post-pesticide spraying have identified steep degradation of air contamination farther than 250m [81]. While in ESPINA, lower AChE activity was observed among children living within 275m of a floricultural greenhouse [80]. Neurobehavioral alterations in ESPINA were primarily observed within 100m of greenhouses [77]. All of the distance variables were within the smallest threshold observed in other studies.

Logistic regression models were run using Model 2 covariates to assess two outcomes for a SD increase in home-ag distance (km) or home-ag SA. First, for metabolites that had detectable concentrations under 50% (MDA, TCC, OXY2), odds of having detectable levels of pesticide metabolites were estimated (ref=having concentrations below the level of detection). Secondly, for metabolites that had detectable levels above 50% (PNP, TCPY, 2,4-D and 3-PBA), logistic regression estimated the odds of having concentrations that were in the upper median of the cohort (ref=concentrations in the lower median). The logistic regression models were stratified by sex if significant interaction terms were discovered (see above).

Statistical analysis was done using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and geospatial analysis was done using ArcGIS Pro 3.0.0 (ESRI Inc.).

Results

Participant characteristics were calculated for the overall group and stratified by a median split of agricultural surface area within a 50m buffer (Table 2.1). A total of 500 participants were included in the analysis, of which 50.40% of the population were females, 18.00% identified as Indigenous, 51.80% had a monthly household salary of less than $500 a month, and 46.20% of individuals were high school graduates (Table 2.1). The average age was 20.28 years, with an age range of 16 to 25. Most individuals lived with an agricultural or floricultural worker (73.20%) but did not work in agriculture or floriculture (71.60%) nor use pesticides at work (66.60%). Individuals who were in the lower median of home-ag SA_{50m} had a smaller proportion of Indigenous individuals (10.40% vs 25.60%, $p<0.0001$), had a higher proportion of individuals who do not work in agriculture or floriculture (77.60% vs 65.60%, $p=0.004$), and had higher 3-PBA concentrations (0.54 [0.35, 0.85] vs 0.49 [0.30, 0.76], $p=0.01$). Participant characteristics were also stratified by sex (Supplemental Table 2.1). Males were found to have lower BMI (23.04 [20.84, 24.70] versus 24.28 [22.10, 26.65], $p<0.0001$) and were less likely to have Some College-to-College Graduate education level (35.08% versus 41.67%, $p<0.07$), compared to females.

GEE was conducted to determine the percent difference in urinary pesticide metabolite concentration between a 1% increase in home-ag distance, or a 1% increase in home-ag SA for buffer sizes between 50m and 500m using Model 1 (Supplemental Table 2.2) and Model 2, which further adjusted for additional pesticide exposure constructs (Table 2.2). Comparing the estimates between Model 1 and Model 2 for the associations, it was confirmed that pesticide exposure constructs were confounding the associations as a ≥10% change for many of the estimates was observed between the models. Thus, the remaining results will focus on findings using Model 2. There was a positive association between home-ag distance and 3-PBA concentration ($\beta=4.38$ [0.28, 8.65]), indicating that the farther an individual lived from agriculture, the higher their 3-PBA concentrations (Table 2.2). No associations were observed for OXY2 nor TCC.

Significant sex interaction terms (gender*distance construct) were identified for 2,4-D with home-ag distance (Supplemental Table 2.3), for PNP with home-ag SA_{50m} (Supplemental Table 2.4), and TCPY with home-ag SA_{50m} and home-ag SA_{100m} (Supplemental Table 2.4) in the GEE models. Therefore, GEE models for PNP, 2,4-D, and TCPY were estimated for the overall cohort and stratified by sex. PNP was found to be negatively associated with home-ag SA for buffer sizes ranging from 50m to 500m (Table 2.3). The association weakened with greater surface areas and were strongest in men for 2,4-D (Table 2.3). A 1% increase in home distance from the nearest agricultural field was associated with a -8.21% [-13.27%, -2.86%] lower 2,4-D concentration in males, but the association was positive for females (2.93% [-2.82%, 9.02%]). This indicates that for men, living farther away from agricultural was associated with a decrease in 2,4-D concentration. Within a 50m buffer, a 1% increase in home-ag SA led to a 103.7% (1.35%, 309.38%) increase in 2,4-D concentration for the overall cohort, which strengthened for males (288.86% [44.46%, 946.78%]) but weakened for females (1.03% [-60.51%, 158.48%]). For TCPY (Table 2.4), a 1% increase in home-ag SA_{150m} of the participant's home was associated with a -0.13% (-0.25%, -0.01%) decrease in TCPY concentrations in females. This association strengthened in smaller buffer sizes like 100m (-17.17% [-32.22%, 1.21%]) and 50m (-28.62 [-66.77, 53.3]). Inversely, positive associations between agricultural surface area and TCPY were observed for men, albeit not statistically significant.

Table 2.5 shows the odds of having PNP or 2,4-D concentrations in the upper median of the observations, compared to those in the lower median, for a SD increase in home-ag distance. A SD increase in home-ag SA_{50m}, which is equivalent to a 0.001 km^2 increase in SA, was associated with an 18% reduction of odds for having PNP concentrations in the upper median of the cohort (OR=0.82 [0.67, 0.99]). The odds became more protective with increasing buffer sizes from 100m (OR=0.77 [0.63, 0.94]) to 500m (OR=0.73 [0.60, 0.91]). For all the buffer sizes, having a SD greater home-ag SA was more protective against having higher PNP concentrations in males, compared to females and the overall cohort. One SD of home-ag distance was equivalent to 16.86m. For 2,4-D, no associations were observed for the overall cohort. However, men who lived 16.86m farther from an agricultural crop had a 23% lower odds of having 2,4-D concentrations in the upper median (OR= 0.77 [0.59, 1.02]) compared to individuals who lived 16.86m closer. Similar associations were observed in the 50m buffer, as individuals with 0.001 km^2 higher home-ag SA_{50m} had 39% higher odds of having 2,4-D concentrations in the upper median, compared to individuals with 0.001 km^2 less home-ag SA_{50m}. Unlike the men, living closer to agriculture (OR=1.2 [0.91, 1.59]) or having more agricultural in surrounding buffers (OR_{100m}=0.76 [0.56, 1.03]) was protective against having 2,4-D concentration in the upper median for females.

MDA had a significant interaction between sex and distance (Supplemental Table 2.3), therefore the logistic regression models were run for the overall cohort and were stratified by sex (Table 2.6). Living a SD farther the nearest agricultural field led to a 41% reduction in odds of having detectable MDA concentrations (OR_{males}=0.59 [0.34, 1.02]), but there was a 23% increase of odds for females ($OR_{females}$=1.23 [0.8, 1.9]). Generally, having a SD higher home-ag SA increased the odds of having MDA concentrations above the LOD for men, which had the greatest odds within a 100m home buffer (OR_{males}=1.85 [1.13, 3.03]). Starting at a buffer region of 200m, the odds of having MDA concentrations above the LOD became protective for females but were not statistically significant ($OR_{females}$=0.89 [0.55, 1.44]). The logistic regression did not find associations for OXY2, 3-PBA, TCC, and TCPY (Supplemental Table 2.5 and Supplemental Table 2.6).

The Global Moran's index estimated spatial autocorrelation of residuals of the GEE models. Testing home-ag distance residuals, the Moran's index was statistically significant for TCPY (index=0.07, p=0.01) and 2,4-D (index=0.11, <0.0001) and not statistically significant for PNP (index=-0.005, p=0.93), MDA (index=-0.0002, p=0.94), OXY2 (index=-0.001, p=0.96), TCC (index=0.0001, p=0.97), nor 3-PBA (index=-0.04, p=0.16). Similarly, testing residuals from models for the home-SA_{50m} G EE models, the Moran's I was statistically significant for TCPY (index=0.07, p=0.01) and 2,4-D (index=0.11, p=0.0001), but was not statistically significant for PNP (index=-0.002, p=0.98), MDA (index=-0.005, p=0.92), OXY2 (-0.001, p=0.96), TCC (index=0.0001, p=0.97), nor 3-PBA (index=-0.002, p=0.15).

Optimized hotspot analysis was conducted for all the pesticide metabolites (Figure 2.2.). For the organophosphate metabolites, we observed hotspots for PNP and TCPY within Tupigachi (Figure 2.2.b and Figure 2.2.c). MDA had a hotspot in La Esperanza, while OXY2 had a hotspot in Malchinguí. 3-PBA had a hotspot in Malchinguí, while 2,4-D had a hotspot in Tocachi. No cold or hotspots were identified for TCC, thus were not shown.

Using GWR, the association between home-ag distance and 2,4-D concentration was negative across Pedro Moncayo, but the pseudo t-values were within -1.96 and 1.96 (Figure 2.3.). While a 1km^2 increase in agricultural surface area within a 50m buffer had significantly positive associations with 2,4-D concentrations for all observations in Pedro Moncayo (Figure 2.3.). The coefficients were strongest in south Malchinguí ($106.8 \leq \beta \leq 111.6$, pseudo t-value>1.96), which weakened as you move East. Statistically significant positive associations between 3-PBA concentration and distance was observed in the southern portion of Malchinguí ($5.91 \leq \beta \leq 7.25$, pseudo t-value>1.96, Figure 2.4.). Spatial variability of associations were found for MDA (Supplemental Figure 2.1.), PNP (Supplemental Figure 2.2), TCPY (Supplemental Figure 2.3.), and OXY2 (Supplemental Figure 2.4.), but had pseudo t-values within -1.96 and 1.96.

Discussion

This study found associations between home-ag distance and agricultural surface area with select organophosphate, pyrethroid, and herbicide metabolites, with some effect modification by sex. For males, living farther from agriculture was linked to lower levels of 2,4-D, while a higher density of agriculture within 50m of the home in the full cohort was most strongly associated with higher metabolite levels in Malchinguí, decreasing towards the West.

An increase in agricultural surface area was associated with higher odds of detectable MDA levels, particularly in males. In women, greater agricultural surface area was associated with lower TCPY concentrations. Greater agricultural area was also negatively associated with PNP levels, with the association weakening over larger buffer zones. Conversely, home-ag distance was positively linked with 3-PBA concentrations, with the strongest association in southern Malchinguí. These results suggest that open-air agriculture, such as corn, potatoes, and grains, may be a source of exposure to 2,4-D and MDA, but not PNP, TCPY or 3-PBA. Individuals with higher pesticide exposure have been associated with lower neurobehavioral performance [70], higher blood pressure[78,91], and negative health consequences [110,111]. Identifying characterizing pesticide drift from agriculture, and understanding pesticide classifications used in agricultural production, can help inform public health campaigns aimed at lowering pesticide exposure in agricultural communities.

2,4-D exposure seemed to stem from agricultural sources based on our findings and aligns with suspected use patterns that herbicides are not used in floriculture but would be used in other agricultural production. In the southern region of Malchinguí we saw the strongest association between our proximity constructs with 2,4-D concentration. This region of Malchinguí houses the largest industrial open-air agricultural plot in all of Pedro Moncayo, which may be an indicator of higher 2,4-D application amounts compared to other smallholder farming occurring in the region. Herbicides like 2,4-D are plant growth regulators that are commonly used for broadleaf weed control in grass crops or are used as a desiccant [112]. Application of 2,4-D has been shown to cause injury to certain crop yields, such as tomatoes [113], but also has been reported to cause damage to flowers [114,115]. Given the potential damage to flower yields and quality, it would be expected that 2,4-D is not used in rose production in Pedro

Moncayo, which concurs with our findings as living farther from open-air agriculture lowered 2,4-D concentrations. Alternatively, herbicide use for other agricultural crops is much more likely, especially for corn which was found to be highly prevalent in this region (see Chapter 1). A rise of herbicide use was observed in the United States with the introduction of genetically modified (GM) crops, in particular GM corn and grain crops that are resistant to herbicides. GM crops, however, are forbidden in Ecuador [116]. Instead, defoliation and desiccation are often a requirement of efficient corn harvest [112], thus application of 2,4-D to corn crops may be occurring. It is also possible that it is being used as a desiccant in dry edible beans, as herbicides have been reported to be used for these purposes in other countries [117].

The strong negative association between increasing agriculture surface area and PNP concentration suggests that exposure to parathion or methyl-parathion, the parent insecticides of PNP, is not coming from agriculture, but instead is suspected to stem from floricultural greenhouses. In a previous study using the summer 2016 ESPINA assessment, PNP was negatively associated with increasing home distance to the nearest floricultural field within 200m [11]. This indicated that the farther an individual lived from a floricultural greenhouse, the lower their PNP concentration would be, suggesting that parathion exposure is coming from floricultural greenhouses, not agriculture. Despite pesticide metabolite concentrations measurement occurring 8 years apart (2016 versus 2022) and shifts in the cohort's age group from 14 years in 206 to 20 years in 2022, findings for PNP are still complementary suggesting continued patterns of parathion use in floriculture but not or minimally in open-air agriculture in the 6-year period between 2016 and 2022. Para-nitrophenol and parathion have been documented to maintain quality, color, fragrance, and natural petal enlargement of fresh, unhardened cut velvet time roses [118,119].

The parent chemicals of MDA (malathion), TCPY (chlorpyrifos) and 3-PBA (Cyhalothrin, Cypermethrin, Deltamethrin, Fenpropathrin, Permethrin, Tralomethrin), are used on open-air agricultural crops and on floricultural crops, so the associations observed might be indicative of agricultural or floricultural use soon before or at the time of the assessment. MDA had low detectability within this cohort suggesting lower use for this time period, yet living closer to open-air agriculture did increase the odds of having detectable levels. Malathion, an organophosphate and parent chemical of MDA, could be used in agriculture to a lesser extent than observed for 2,4-D in Pedro Moncayo. Malathion is an organophosphorus insecticide, and since its initial use in the 1950s, it has been reported to be used on crops like alfalfa, cotton, rice, sorghum, and wheat [120], in addition to ornamental flower production [121]. Similar use patterns have been observed for chlorpyrifos [122,123], Cyhalothrin, Cypermethrin, Deltamethrin, Fenpropathrin, Permethrin, and Tralomethrin [124]. Thus, the suspected agricultural use of Malathion, and floricultural use of 3-PBA and TCPY are not due to chemical properties that prioritizes use in a certain classification of crop, but instead might be due to temporal patterns of use in this region during the time period studied.

Compared to other studies, associations in our study only found in smaller distances or buffer regions (<200m), with the exception of PNP. We found associations of 2,4-D concentrations with home-ag distance, and agricultural surface area within 50m. The mean home-ag distance was 19.49m, demonstrating that most participants lived close to open-air agriculture. PNP was primarily only negatively associated with agricultural surface area. Unlike 2,4-D, PNP exposure is likely coming from floricultural sources, thus greater density of agriculture would potentially be indicative of lower density of floriculture. It is also possible that sufficient parathion drift from floriculture is not happening within the close distance to agriculture (0-15m). In 2016, participants generally lived farther away from floriculture compared to agriculture, as the mean distance from participants' homes to the nearest flower plantation was 446m (SD=334) [77]. The presence of floriculture within a 50m buffer around the home would have higher likelihood of having some floricultural presence, versus using the distance to agriculture variable. Unlike PNP, we only found a positive association between home-ag distance with 3-PBA concentration. Looking at the GWR results, the association was strongest in the southern portion of Malchinguí. Malchinguí had lowest prevalence of floriculture, compared to the other parishes [11]. However, it is possible that 3-PBA parent pyrethroid chemicals are being used in floricultural greenhouses present in Southern Malchinguí, or there is another type of agriculture present in this region. Mapping floriculture and agriculture by crop type could further clarify the source of the pesticides used.

The associations we observed in smaller distances and buffer regions varied from other studies that have observed greater dispersion distances of pesticide drift in agricultural communities and may be because pesticide spraying in this region are commonly done with backpack sprayers versus aerial applications. In the California Sun Valley, chlorpyrifos use within 1 to 4 km was associated with 1 to 2 times higher dust concentration, while for diazinon application within a 2 km buffer led to 3 to 7 times high concentrations of household dust concentrations [125]. The difference in distances associated with pesticide drift may be due to farmers in the Andean region of Ecuador using backpack sprayers, compared to aerial pesticide spraying that has been observed in inland and southern regions of Ecuador[126], and other countries like the United States and China. A cross-sectional study performed in five Ecuadorian farming communities in inland North Quevedo and southern Buenavista, found that 54.9% of participants reported observing aerial pesticide spraying at least once a week, while 29% reported it occurring daily or multiple times a week on banana plantations [126]. To our knowledge, bananas are not grown in the Pedro Moncayo region of Ecuador. In addition, backpack pesticide sprayers have been reported as the predominant method for applying pesticides in Andean agricultural communities [18,104,127], commonly due to the hilly terrain[127]. Height of pesticide spraying has been found to influence the amount of drift, where areal sprayers, whether from manned or unmanned aerial spraying systems, had evidence of greater drift compared to backpack sprayers [128,129].

Findings from this study observed effect modification by sex observed between our home proximity measures with 2,4-D and MDA concentrations may be due to differential protection behaviors or differences in physical activity between males and females. Surprisingly, despite the effect modification we observed by sex, there were no statistically significant differences in pesticide metabolite concentrations for any of the metabolites by sex. Likewise, there were no statistically significant differences in characteristics by sex, such as cohabitation with an agricultural or floricultural worker, working in agriculture or floriculture, or pesticide use at home or occupationally. As participants had similar patterns of exposure, this may indicate that the pesticide exposure pathways vary by sex. In a study of occupational Chinese farmers, there were sex differences in knowledge of appropriate pesticide use, awareness of associated health risks that came with exposure, proper disposal techniques of pesticide contains, and protective measures taken when comparing men to females [130]. This has been echoed in multiple cohorts which observed that men are less likely to take protective measures or behaviors when using pesticides [130]. It is possible that men engage in less protective measures which leads them to be more susceptible to pesticide drift from agricultural sources.

When assessing extent of pesticide drift in agricultural communities, pesticide residues tend to be 5 to 10 times lower indoors than outdoors [81]. If men and women have differential patterns of time spent indoors, then this might be why we observed effect modification by sex given that distance to agriculture is a measure of pesticide drift. There was slightly higher educational attainment in women (86.91% High school graduate or above) versus men (82.26% High school graduate or above), which may be indicative of more time indoors. Data from the Southern American Physical Activity and Sedentary Behavior Network captured demographic data and physical activity patterns in six Latin American countries, including Ecuador (n=19,851). In their study, they found that women, compared to men, and individuals with higher educational attainment overall reported being less active. Assuming that higher activity would be positive correlated with time outdoors, compared to females, men in ESPINA may have higher activity levels, leading to greater time outdoors. This could help explain why we saw positive association for associations between agricultural surface area and 2,4-D concentrations in men, higher odds of having detectable levels of MDA per SD increase in agricultural surface area in men, but negative associations between surface area and TCPY concentration in females. Further exploration of effect modification on sex on the association between distance to agriculture and pesticide exposure is needed to confirm this hypothesis.

Strengths of this study include validation of geospatial constructs of pesticide exposure using urinary pesticide metabolites, in a large cohort of participants living in agricultural settings which were assessed within a single agricultural period (July – September 2022). This approach enhances our ability to accurately characterize pesticide exposure by moving beyond reliance on surveys or pesticide residue analysis. Unlike pesticide metabolite concentrations, geospatial constructs of pesticide exposure is a measurement that is more readily accessible for low-resource communities. It also allows for the estimation of long-term pesticide exposure without repeated measurements. Our study has multiple limitations. First, we were unable to account for weather patterns in our model, which could influence directionality of pesticide drift dispersion. Proximity measures, like home agricultural surface areas or distance to the nearest agricultural field, do not account for individuals' movement patterns to locations that are indoors or outdoors [81], or that have greater or lesser density of surrounding agriculture [78,80]. Incorporating participant movement patterns would improve classification of amount and frequency of pesticide exposure from pesticide drift. The agricultural map that we used for this study has 72% accuracy (see Chapter 1), but despite this, still had complementary findings compared to analyses done using 2016 ESPINA data, and strong associations with organophosphates and herbicides. Likewise, creating maps that differentiate between crop types (e.g., sweet peas, corn, wheat) or map floriculture would improve our ability to determine sources of pesticide exposure at this time point. We were also restricted in testing associations for measured pesticide metabolites, but it is possible that additional pesticides, like neonicotinoids, are being used in this region. This study also does not have access to data regarding when pesticides were applied to crops near participants' homes.

Conclusion

This study examined the relationship between urinary pesticide metabolites with two agricultural proximity constructs, home distance to the nearest agricultural field and agricultural surface area within buffers around the home. Associations were found between these measures with with urinary biomarkers of organophosphates, pyrethroids, and herbicides, with some differences by sex. For men, living farther from agriculture correlated with lower 2,4-D levels, while higher agricultural density within 50m was associated with higher concentrations, particularly in Malchinguí. An increase in agricultural surface area also raised the odds of detectable MDA levels, especially in males. PNP levels were lower with higher agricultural surface area present around the home. Additionally, home-ag distance positively correlated with

3-PBA levels, and the estimates were strongest in southern Malchinguí. The findings suggest that 2,4-D and MDA exposures are likely from open-air agricultural sources, while PNP, TCPY, and 3-PBA exposure likely comes from floriculture. These associations underscore the complexity of pesticide exposure dynamics influenced by agricultural practices, location, and gender-specific factors. Understanding the patterns of pesticide use and extent of drift in agricultural communities is crucial to create public health interventions aimed at reducing exposure, as complete eradication of pesticide is unlikely. Future studies should incorporate participant movement patterns and create maps of unique crop types to better characterize the pattern of pesticide drift.

Acknowledgements

Chapter 2, in part, is currently being prepared for submission for publication of the material. Briana N.C. Chronister; Ariana Huezo; Daniel Sousa; Harvey Checkoway; Jose Suarez-Torres; Franklin de la Cruz; Raeanne C. Moore; Jenny Quintana; Humberto Parada Jr.; Tommi Gaines; Jose R. Suarez-Lopez. *Home distance to agriculture and organophosphate, pyrethroid, and herbicide urinary metabolite concentration in Ecuadorian adolescents and young adults*. The dissertation author was the primary investigator and author of this paper.

Table 2.1. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

		Agricultural Surface Area within 50m Buffer		
Variables	**Overall**	**Lower Median $0m^2$ - $862m^2$**	**Upper Median $864m^2$ - $7019m^2$**	**p-diff**
n	500	250	250	
Age, years	20.28 (1.83)	20.15 (1.83)	20.41 (1.83)	0.10
BMI	23.59 (21.44, 25.67)	23.34 (20.91, 26.19)	23.76 (22.09, 25.28)	0.51
Sex				
Female, n (%)	252 (50.40%)	125 (50.40%)	126 (50.60%)	
Male, n (%)	248 (49.60%)	123 (49.60%)	123 (49.40%)	
Race[a]				<0.0001
Indigenous, n (%)	90 (18.00%)	26 (10.40%)	64 (25.60%)	
Mestizo, White, or Other, n (%)	410 (82.00%)	224 (89.60%)	186 (74.40%)	
Monthly Household Salary, USD				0.91
Less than $500, n (%)	259 (51.80%)	129 (51.60%)	130 (52.00%)	
$500-$999, n (%)	114 (22.80%)	58 (23.20%)	56 (22.40%)	
$1000+, n (%)	34 (6.80%)	18 (7.20%)	16 (6.40%)	
Prefer Not to Answer, n (%)	93 (18.60%)	45 (18.00%)	48 (19.20%)	
Education				0.48
Some High School and Below, n (%)	77 (15.40%)	36 (14.40%)	41 (16.40%)	
High School Graduate, n (%)	231 (46.20%)	115 (46.00%)	116 (46.40%)	
Some College-to-College Graduate, n (%)	192 (38.40%)	99 (39.60%)	93 (37.20%)	

Table 2.1. continued. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

		Agricultural Surface Area within 50m Buffer		
Variables	**Overall**	**Lower Median $0m^2$ - $862m^2$**	**Upper Median $864m^2$ - $7019m^2$**	**p-diff**
Lives with an Agricultural or Floricultural Worker				0.11
No, n (%)	134 (26.80%)	75 (30.00%)	59 (23.60%)	
Yes, n (%)	366 (73.20%)	175 (70.00%)	191 (76.40%)	
Works in Agricultural or Floricultural Worker				0.004
No, n (%)	358 (71.60%)	194 (77.60%)	164 (65.60%)	
Yes, n (%)	142 (28.40%)	56 (22.40%)	86 (34.40%)	
How often do you use pesticides in your home or property?				0.071
Always, n (%)	5 (1.00%)	1 (0.40%)	4 (1.60%)	
Often, n (%)	20 (4.00%)	5 (2.00%)	15 (6.00%)	
Sometimes, n (%)	30 (6.00%)	12 (4.80%)	18 (7.20%)	
Rarely, n (%)	160 (32.00%)	85 (34.00%)	75 (30.00%)	
Never, n (%)	188 (37.60%)	95 (38.00%)	93 (37.20%)	
I do not know/Prefer not to answer, n (%)	97 (19.40%)	52 (20.80%)	45 (18.00%)	
Uses Pesticides at Work				0.70
No, n (%)	333 (66.60%)	174 (69.60%)	159 (63.60%)	
Yes, n (%)	108 (21.60%)	49 (19.60%)	59 (23.60%)	
I do not know, n(%)	59 (11.80%)	27 (10.80%)	32 (12.80%)	
MDA (organophosphate)				0.76
Above LOD, n (%)	46 (9.20%)	22 (8.80%)	24 (9.60%)	
Below LOD, n (%)	454 (90.80%)	228 (91.20%)	226 (90.40%)	
MDA, ug/L	0.35 (0.35, 0.35)	0.35 (0.35, 0.35)	0.35 (0.35, 0.35)	0.58
MDA, SG	0.36 (0.29, 0.48)	0.36 (0.29, 0.50)	0.37 (0.31, 0.48)	0.6

Table 2.1. continued. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

Variables	Overall	Agricultural Surface Area within 50m Buffer		p-diff
		Lower Median $0m^2$ - $862m^2$	Upper Median $864m^2$ - $7019m^2$	
PNP (organophosphate)				
Above LOD, n (%)	500 (100.00%)	250 (100.00%)	250 (100.00%)	0.49
PNP, ug/L	0.63 (0.41, 0.97)	0.67 (0.42, 0.99)	0.60 (0.41, 0.93)	0.56
PNP, SG	0.66 (0.48, 0.91)	0.69 (0.51, 0.87)	0.65 (0.46, 0.92)	0.59
TCPy (organophosphate)				
Above LOD, n (%)	500 (100.00%)	250 (100.00%)	250 (100.00%)	0.95
TCPy, ug/L	3.40 (2.10, 5.75)	3.50 (2.00, 5.50)	3.25 (2.20, 5.90)	0.76
TCPy, SG	3.39 (2.26, 5.56)	3.34 (2.23, 5.36)	3.45 (2.29, 5.72)	0.92
OXY2 (organophosphate)				0.41
Above LOD, n (%)	145 (29.00%)	72 (28.80%)	73 (29.20%)	
Below LOD, n (%)	355 (71.00%)	178 (71.20%)	177 (70.80%)	
OXY2, ug/L	0.07 (0.07, 0.13)	0.07 (0.07, 0.14)	0.07 (0.07, 0.12)	0.37
OXY2, SG	0.08 (0.06, 0.15)	0.09 (0.06, 0.16)	0.08 (0.07, 0.15)	0.36
3-PBA (pyrethroid)				0.01
Above LOD, n (%)	492 (98.40%)	245 (98.00%)	247 (98.80%)	
Below LOD, n (%)	7 (1.40%)	4 (1.60%)	3 (1.20%)	
Interfering Substance, n (%)	1 (0.20%)	1 (0.40%)	0 (0.00%)	
3PBA, ug/L	0.50 (0.31, 0.86)	0.55 (0.33, 0.90)	0.43 (0.27, 0.74)	0.01
3PBA, SG	0.52 (0.32, 0.81)	0.54 (0.35, 0.85)	0.49 (0.30, 0.76)	0.24
TCC (pyrethroid)				0.27
Above LOD, n (%)	213 (42.60%)	113 (45.20%)	100 (40.00%)	
Below LOD, n (%)	287 (57.40%)	137 (54.80%)	150 (60.00%)	
TCC, ug/L	0.42 (0.42, 0.93)	0.42 (0.42, 1.00)	0.42 (0.42, 0.85)	0.57
TCC, SG	0.62 (0.43, 1.00)	0.65 (0.43, 1.01)	0.58 (0.43, 1.00)	

Table 2.1. continued. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

		Agricultural Surface Area within 50m Buffer		
Variables	**Overall**	**Lower Median $0m^2$ - $862m^2$**	**Upper Median $864m^2$ - $7019m^2$**	**p-diff**
2,4D (herbicide)				
Above LOD, n (%)	404 (80.80%)	202 (80.80%)	202 (80.80%)	
Below LOD, n (%)	96 (19.20%)	48 (19.20%)	48 (19.20%)	
2,4D, ug/L	0.27 (0.17, 0.41)	0.27 (0.16, 0.39)	0.27 (0.17, 0.43)	0.31
2,4D, SG	0.26 (0.18, 0.42)	0.26 (0.18, 0.40)	0.26 (0.18, 0.45)	0.17
Home-field distance, m	19.49 (6.28, 27.80)	28.89 (16.44, 39.86)	10.09 (2.72, 15.45)	<0.0001
50m Buffer km^2	0.001 (0.0001, 0.002)	0.0003 (0.0001, 0.001)	0.002 (0.001, 0.003)	<0.0001
100m Buffer km^2	0.005 (0.003, 0.008)	0.003 (0.002, 0.005)	0.008 (0.006, 0.011)	<0.0001
150m Buffer km^2	0.014 (0.009, 0.019)	0.011 (0.007, 0.014)	0.017 (0.013, 0.024)	<0.0001
200m Buffer km^2	0.025 (0.018, 0.034)	0.021 (0.013, 0.027)	0.031 (0.023, 0.040)	<0.0001
250m Buffer km^2	0.040 (0.028, 0.053)	0.033 (0.022, 0.044)	0.048 (0.037, 0.062)	<0.0001
300m Buffer km^2	0.058 (0.043, 0.076)	0.050 (0.034, 0.063)	0.070 (0.052, 0.089)	<0.0001
350m Buffer km^2	0.079 (0.057, 0.104)	0.066 (0.051, 0.087)	0.095 (0.072, 0.121)	<0.0001
400m Buffer km^2	0.102 (0.076, 0.138)	0.085 (0.066, 0.114)	0.124 (0.093, 0.157)	<0.0001
450m Buffer km^2	0.127 (0.095, 0.177)	0.107 (0.086, 0.140)	0.155 (0.118, 0.194)	<0.0001
500m Buffer km^2	0.154 (0.116, 0.216)	0.134 (0.105, 0.175)	0.188 (0.142, 0.243)	<0.0001

MDA=malathion dicarboxylic acid, PNP=para-nitrophenol, OXY2=2-isopropyl-4-methyl-6-hydroxypyrimidine, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, TCPY=3,5,6-Trichloro-2-pyridinol, 2,4-D=2,4-Dichlorophenoxyacetic acid, 3-PBA=3-phenoxybenzoic acid, m=meters, km=kilometers,
Values are means (SD) or medians (Q25, Q75) for continuous variables; ns and percentages for categorical variables.
[a] Two individuals self-identified as White and 1 individual self-identified as Other.
Home-field distance= distance to the nearest agricultural field

Table 2.2. Associations between a 1% increase in home distance to the nearest agricultural field or 1% increase in agricultural surface area (50m to 500m buffers), and urinary pesticide metabolite concentration.

	β% (95% CI) increase in urinary metabolite concentration per 1% increase in home distance or agricultural surface area.		
	OXY2	**3-PBA**	**TCC**
Distance (km)	-0.57 (-3.26, 2.19)	4.38 (0.28, 8.65)**	0.56 (-3.14, 4.39)
Surface Area of Agriculture Within Different Buffer Sizes (km²)			
50m	-0.38 (-36.85, 57.14)	-23.64 (-54.63, 28.53)	-23.87 (-48.73, 13.07)
100m	-3.07 (-12.97, 7.96)	-3.92 (-17.68, 12.14)	-6.31 (-14.1, 2.2)
150m	0.001 (-0.14, 0.14)	-0.06 (-0.16, 0.04)	-0.05 (-0.14, 0.04)
200m	0.01 (-0.12, 0.14)	-0.06 (-0.17, 0.06)	-0.06 (-0.16, 0.04)
250m	-0.01 (-0.15, 0.12)	-0.06 (-0.18, 0.06)	-0.05 (-0.16, 0.06)
300m	0.01 (-0.14, 0.15)	-0.05 (-0.17, 0.08)	-0.05 (-0.17, 0.07)
350m	0.02 (-0.13, 0.17)	-0.04 (-0.17, 0.09)	-0.03 (-0.16, 0.09)
400m	0.01 (-0.14, 0.16)	-0.04 (-0.17, 0.1)	-0.04 (-0.17, 0.09)
450m	0.02 (-0.14, 0.17)	-0.03 (-0.17, 0.11)	-0.05 (-0.18, 0.09)
500m	0.03 (-0.13, 0.18)	0.001 (-0.14, 0.14)	-0.05 (-0.18, 0.08)

MDA=malathion dicarboxylic acid, PNP=para-nitrophenol, OXY2-2-isopropyl-4-methyl-6-hydroxypyrimidine, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, m=meters, km=kilometers, GEE=generalized estimating equations. **$p<0.05$, *$p<0.10$

GEE Model adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

All pesticide metabolites were imputed using a constant (LODS/sqrt(2), adjusted for specific gravity, and then were natural log transformed. The LOD was 0.1 for 3-PBA and OXY2, and 0.6 for TCC. MDA was not included, as it only had detectable concentration in 9% of observations.

Table 2.3. Associations between a 1% increase in home distance to the nearest agricultural field or 1% increase in agricultural surface area (50m to 500m buffers), and urinary PNP or 2,4-D concentration overall and stratified by sex.

	β% (95% CI) increase in urinary metabolite concentration per 1% increase in home distance or agricultural surface area.					
	PNP			**2,4-D**		
Exposure	**Overall**	**Male**	**Female**	**Overall**	**Male**	**Female**
Home-field Distance	0.19 (-2.51, 2.96)	0.02 (-3.94, 4.14)	0.10 (-3.29, 3.62)	-2.85 (-6.87, 1.35)	-8.21 (-13.27, -2.86)**	2.93 (-2.82, 9.02)
Surface Area of Agriculture Within Different Buffer Sizes (km²)						
50m	-30.97 (-53.01, 1.41)*	-48.22 (-69.14, -13.11)**	-7.43 (-47.48, 63.14)	103.7 (1.35, 309.38)**	288.86 (44.46, 946.78)**	1.03 (-60.51, 158.48)
100m	-14.29 (-24.18, -3.1)**	-16.11 (-29.34, -0.4)**	-12.25 (-26.49, 4.75)	5.15 (-15.23, 30.42)	25.38 (-9.34, 73.39)	-13.27 (-31.41, 9.67)
150m	-0.08 (-0.15, -0.01)**	-0.12 (-0.22, -0.02)**	-0.04 (-0.14, 0.06)	0.01 (-0.09, 0.12)	0.08 (-0.07, 0.24)	-0.05 (-0.17, 0.08)
200m	-0.10 (-0.18, -0.02)**	-0.14 (-0.26, -0.03)**	-0.04 (-0.16, 0.07)	0.03 (-0.10, 0.16)	0.08 (-0.10, 0.27)	-0.02 (-0.19, 0.14)
250m	-0.09 (-0.18, -0.001)**	-0.13 (-0.25, -0.01)**	-0.03 (-0.16, 0.09)	0.05 (-0.09, 0.20)	0.12 (-0.07, 0.31)	-0.01 (-0.20, 0.18)
300m	-0.09 (-0.18, 0.001)*	-0.13 (-0.26, -0.001)**	-0.05 (-0.17, 0.08)	0.08 (-0.07, 0.23)	0.13 (-0.07, 0.34)	0.03 (-0.17, 0.24)
350m	-0.10 (-0.20,-0.001)**	-0.14 (-0.29, -0.001)**	-0.06 (-0.19, 0.07)	0.07 (-0.09, 0.23)	0.13 (-0.10, 0.36)	0.02 (-0.19, 0.22)
400m	-0.10 (-0.21, -0.01)**	-0.14 (-0.29, 0.02)*	-0.08 (-0.21, 0.05)	0.07 (-0.10, 0.24)	0.15 (-0.10, 0.40)	-0.01 (-0.22, 0.19)
450m	-0.11 (-0.22, -0.01)**	-0.14 (-0.31, 0.02)*	-0.09 (-0.22, 0.05)	0.08 (-0.09, 0.25)	0.17 (-0.09, 0.44)	-0.01 (-0.21, 0.19)
500m	-0.10 (-0.21, 0.01)*	-0.15 (-0.32, 0.03)	-0.07 (-0.21, 0.06)	0.08 (-0.09, 0.25)	0.17 (-0.10, 0.45)	-0.01 (-0.21, 0.19)

PNP=para-nitrophenol, 2,4-D=2,4-Dichlorophenoxyacetic acid, m=meters, km=kilometers, GEE=generalized estimating equations, km=kilometer.
**p<0.05, *p<0.10

GEE model adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

All pesticide metabolites were imputed using a constant (LODS/sqrt(2), adjusted for specific gravity, and then were natural log transformed. The LOD was 0.1 for PNP, and 0.15 for 2,4-D.

Table 2.4. Associations between a 1% increase in home distance to the nearest agricultural field or 1% increase in agricultural surface area (50m to 500m buffers), and urinary TCPY metabolite concentration overall and stratified by sex.

	β% (95% CI) increase in urinary TCPY metabolite concentration per 1% increase in home distance or agricultural surface area.		
	Overall	**Males**	**Females**
Distance (km)	-1.22 (-3.77, 1.40)	-2.77 (-6.14, 0.72)	0.59 (-4.54, 6.00)
Surface Area of Agriculture Within Different Buffer Sizes (km2)			
50m	-4.15 (-34.89, 41.09)	26.1 (-18.23, 94.46)	-28.62 (-66.77, 53.3)
100m	-3.52 (-12.05, 5.84)	4.09 (-5.77, 14.98)	-17.17 (-32.22, 1.21)*
150m	-0.05 (-0.14, 0.03)	0.03 (-0.09, 0.15)	-0.13 (-0.25, -0.01)**
200m	-0.06 (-0.17, 0.04)	-0.02 (-0.15, 0.12)	-0.11 (-0.26, 0.03)
250m	-0.05 (-0.16, 0.06)	-0.03 (-0.17, 0.12)	-0.09 (-0.26, 0.09)
300m	-0.05 (-0.17, 0.07)	-0.05 (-0.22, 0.11)	-0.06 (-0.25, 0.14)
350m	-0.06 (-0.20, 0.07)	-0.08 (-0.27, 0.10)	-0.07 (-0.27, 0.14)
400m	-0.06 (-0.20, 0.08)	-0.08 (-0.27, 0.11)	-0.07 (-0.29, 0.14)
450m	-0.05 (-0.19, 0.09)	-0.07 (-0.26, 0.13)	-0.06 (-0.28, 0.15)
500m	-0.03 (-0.17, 0.11)	-0.05 (-0.24, 0.15)	-0.04 (-0.26, 0.18)

TCPy=3,5,6-Trichloro-2-pyridinol, m=meters, km=kilometers, GEE=generalized estimating equations

**p<0.05, *p<0.10

GEE model adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

All pesticide metabolites were imputed using a constant (LODS/sqrt(2), adjusted for specific gravity, and then were natural log transformed. The level of detection was 00.1 μg/L for TCPY.

Table 2.5. Odds (OR 95% CI) of having PNP or 2,4-D concentrations in the upper median of the cohort, compared to those in the lower median, for a standard deviation increase in home distance to the nearest agricultural field, or in agricultural surface area (50m to 500m buffers).

	PNP[a]			2,4-D[a]		
Exposure	**Overall**	**Male**	**Female**	**Overall**	**Male**	**Female**
Home-field Distance	1.06 (0.88, 1.28)	1.07 (0.82, 1.4)	1.05 (0.8, 1.38)	0.96 (0.8, 1.16)	0.77 (0.59, 1.02)*	1.2 (0.91, 1.59)
Surface Area of Agriculture Within Different Buffer Sizes						
50m	0.82 (0.67, 0.99)**	0.68 (0.51, 0.91)**	0.95 (0.72, 1.25)	1.09 (0.9, 1.32)	1.39 (1.04, 1.85)**	0.85 (0.64, 1.14)
100m	0.77 (0.63, 0.94)**	0.73 (0.55, 0.97)**	0.82 (0.62, 1.09)	0.91 (0.75, 1.11)	1.08 (0.81, 1.42)	0.76 (0.56, 1.03)*
150m	0.77 (0.63, 0.94)**	0.76 (0.57, 1.01)*	0.78 (0.58, 1.04)*	0.95 (0.78, 1.15)	1.12 (0.85, 1.49)	0.8 (0.59, 1.08)
200m	0.75 (0.62, 0.92)**	0.72 (0.54, 0.96)**	0.78 (0.58, 1.06)	0.97 (0.8, 1.18)	1.15 (0.87, 1.52)	0.81 (0.59, 1.09)
250m	0.77 (0.63, 0.95)**	0.74 (0.55, 0.98)**	0.8 (0.6, 1.08)	0.97 (0.8, 1.18)	1.14 (0.86, 1.51)	0.82 (0.6, 1.11)
300m	0.78 (0.64, 0.95)**	0.72 (0.54, 0.96)**	0.84 (0.62, 1.13)	1 (0.82, 1.22)	1.12 (0.84, 1.48)	0.89 (0.66, 1.2)
350m	0.77 (0.63, 0.94)**	0.68 (0.5, 0.91)**	0.85 (0.63, 1.15)	0.98 (0.8, 1.2)	1.07 (0.8, 1.42)	0.89 (0.65, 1.21)
400m	0.76 (0.62, 0.94)**	0.67 (0.49, 0.9)**	0.84 (0.62, 1.14)	0.97 (0.79, 1.19)	1.06 (0.8, 1.42)	0.87 (0.63, 1.19)
450m	0.74 (0.6, 0.91)**	0.65 (0.47, 0.88)**	0.82 (0.6, 1.12)	0.98 (0.8, 1.21)	1.05 (0.78, 1.4)	0.91 (0.66, 1.25)
500m	0.73 (0.6, 0.91)**	0.63 (0.46, 0.86)**	0.83 (0.61, 1.13)	0.98 (0.8, 1.21)	1.03 (0.77, 1.38)	0.93 (0.68, 1.27)

Home-field distance= Distance from the participant's home to the border of the nearest agricultural field, PNP=para-nitrophenol, 2,4-D=2,4-Dichlorophenoxyacetic acid, m=meters, km=kilometers. **p<0.05, *p<0.10

[a] Variables were categorized to individuals who had concentrations above and below (reference) the median.

Models adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

A standard deviation of the distance variable are 16.86m/0.02km for home-field distance, 0.001 km^2 for a 50m buffer, 0.006 km^2 for a 100m buffer, 0.015 km^2 for a 150m buffer, 0.027 km^2 for a 200m buffer, 0.043 km^2 for a 250m buffer, 0.062 km^2 for a 300m buffer, 0.084 km^2 for a 350m buffer, 0.110 km^2 for a 400m buffer, 0.139 km^2 for a 450m buffer, 0.172 km^2 for a 500m buffer.

Table 2.6. Odds of having MDA concentrations above the LOD, compared to those below the LOD, for a standard deviation increase in home distance, or in agricultural surface area (50m-500m buffers).

	MDA[a]		
Exposure	**Overall**	**Male**	**Female**
Distance	0.93 (0.68, 1.27)	0.59 (0.34, 1.02)*	1.23 (0.80, 1.90)
50m	1.33 (1.00, 1.75)**	1.48 (0.91, 2.38)	1.22 (0.84, 1.76)
100m	1.35 (1.01, 1.81)**	1.85 (1.13, 3.03)**	1.15 (0.77, 1.72)
150m	1.19 (0.88, 1.63)	1.63 (0.99, 2.67)*	1.01 (0.65, 1.57)
200m	1.07 (0.78, 1.48)	1.43 (0.87, 2.35)	0.89 (0.55, 1.44)
250m	1.10 (0.79, 1.51)	1.55 (0.95, 2.54)*	0.83 (0.51, 1.36)
300m	1.12 (0.81, 1.55)	1.64 (1.01, 2.67)**	0.80 (0.49, 1.32)
350m	1.10 (0.79, 1.53)	1.64 (1.02, 2.65)**	0.75 (0.45, 1.24)
400m	1.11 (0.79, 1.54)	1.64 (1.03, 2.62)**	0.74 (0.44, 1.24)
450m	1.16 (0.83, 1.61)	1.65 (1.04, 2.62)**	0.82 (0.49, 1.35)
500m	1.19 (0.85, 1.64)	1.66 (1.04, 2.63)**	0.87 (0.53, 1.42)

MDA=malathion dicarboxylic acid, LOD=level of detection, m=meters, km=kilometers. **$p<0.05$, *$p<0.10$

Models adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

[a] Urinary pesticide metabolite concentrations were categorized as below (reference) or above the LOD.

A standard deviation of the distance variable are 16.86m/0.02km for home-ag distance, 0.001 km^2 for a 50m buffer, 0.006 km^2 for a 100m buffer, 0.015 km^2 for a 150m buffer, 0.027 km^2 for a 200m buffer, 0.043 km^2 for a 250m buffer, 0.062 km^2 for a 300m buffer, 0.084 km^2 for a 350m buffer, 0.110 km^2 for a 400m buffer, 0.139 km^2 for a 450m buffer, 0.172 km^2 for a 500m buffer.

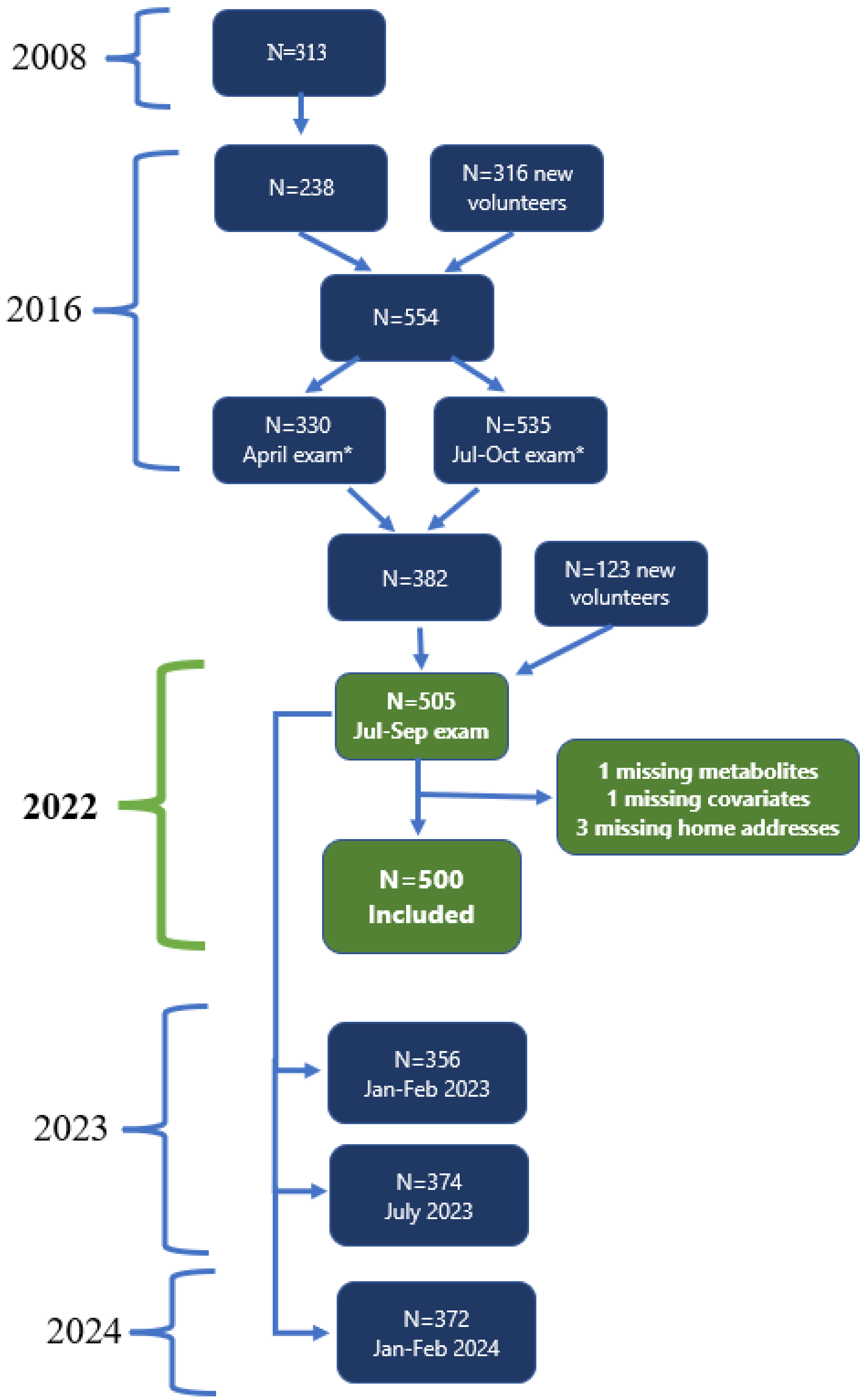


Figure 2.1. Participant Flow Chart of in person ESPINA assessments from 2008 to February 2024.

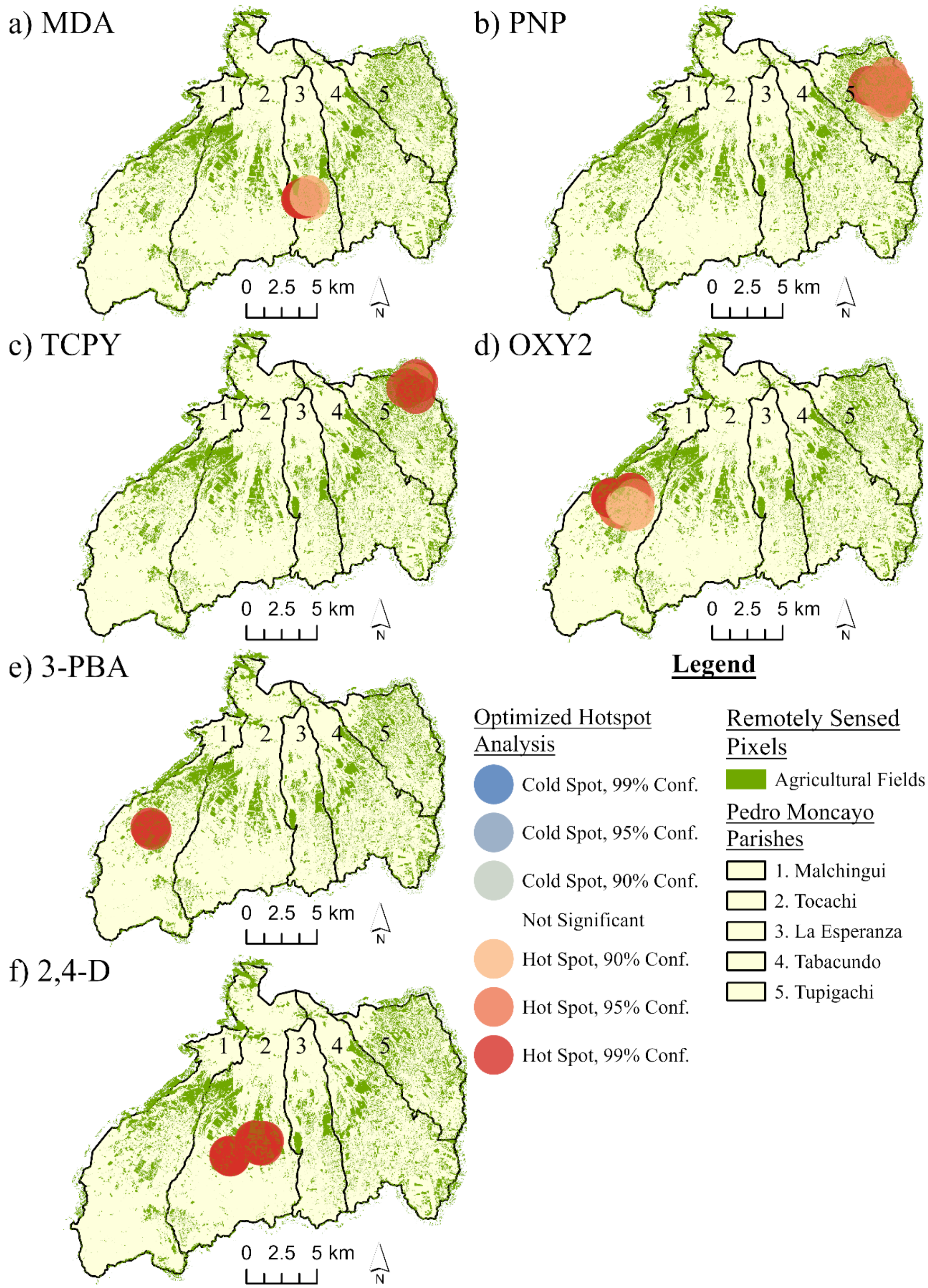


Figure 2.2. Optimized hotspot analysis of pesticide metabolite concentrations in Pedro Moncayo. No cold or hot spots were identified for TCC, thus was not shown.

Figure 2.3. Geospatially weighted regression assessed whether a 1km increase in home distance or a 1km increase in agricultural surface area within 50m is associated with urinary 2,4-D concentration in Pedro Moncayo. Models were adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always). 1=Malchingui, 2= Tocachi, 3=La Esperanza, 4=Tabacundo, 5=Tupigachi

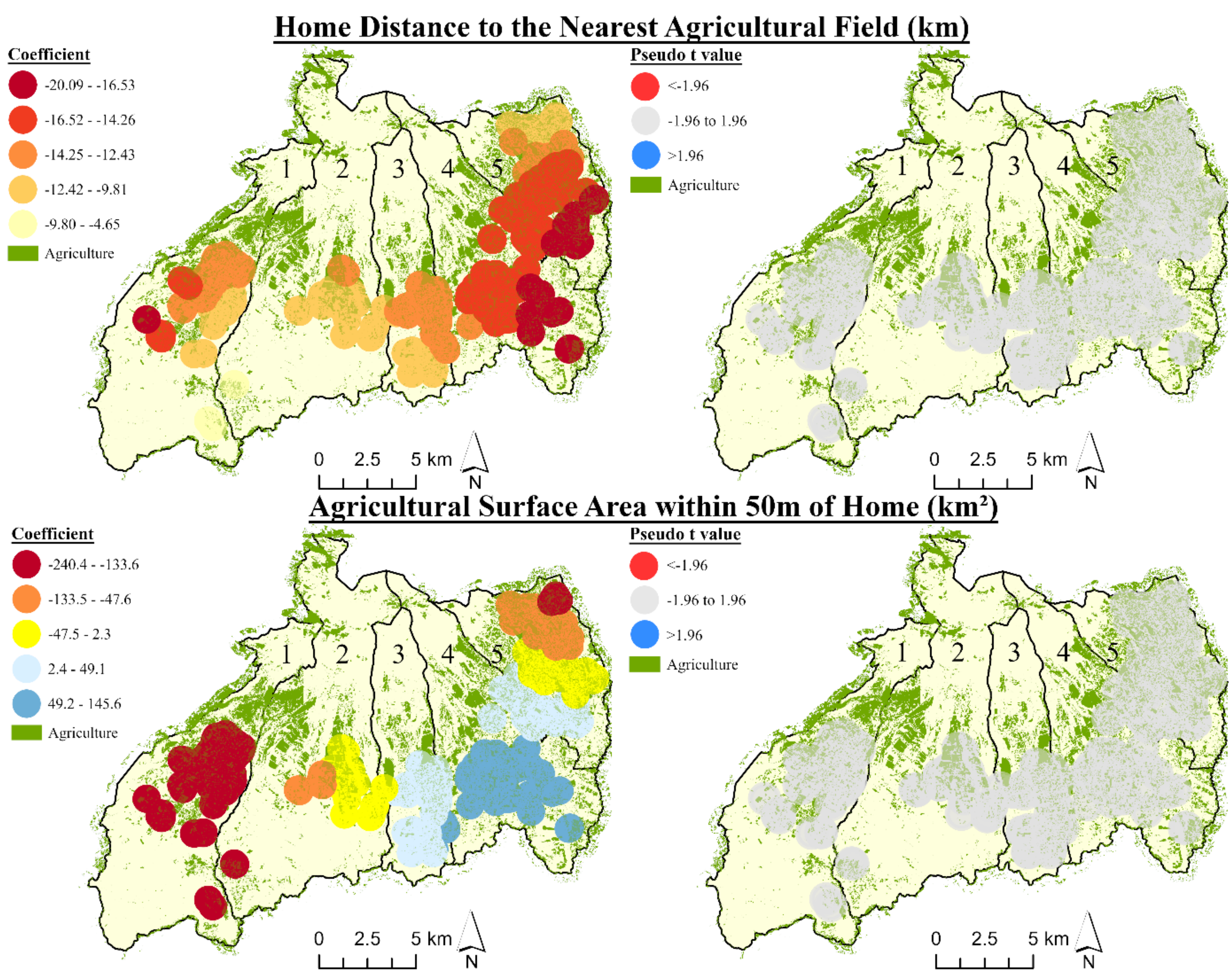
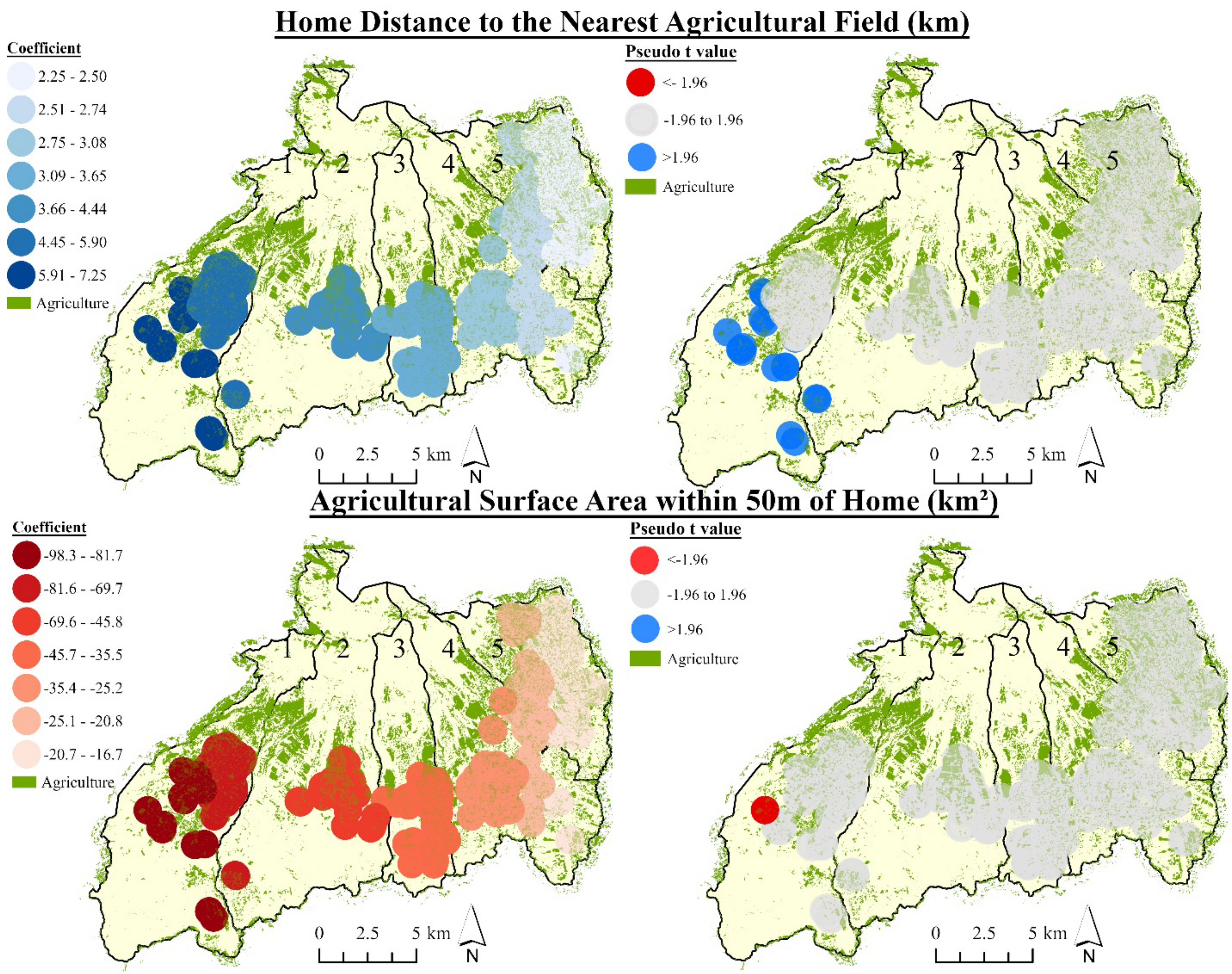

Home Distance to the Nearest Agricultural Field (km)
Coefficient
-20.09 - -16.53
-16.52 - -14.26
-14.25 - -12.43
-12.42 - -9.81
-9.80 - -4.65
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture
1
2
3
4
5
0 2.5 5 km
N
Agricultural Surface Area within 50m of Home (km²)
Coefficient
-240.4 - -133.6
-133.5 - -47.6
-47.5 - 2.3
2.4 - 49.1
49.2 - 145.6
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture

Figure 2.4. Geospatially weighted regression assessed whether a 1km increase in home distance or a 1km increase in agricultural surface area within 50m is associated with urinary 3-PBA concentration in Pedro Moncayo. Models were adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always). 1=Malchingui, 2= Tocachi, 3=La Esperanza, 4=Tabacundo, 5=Tupigachi


Home Distance to the Nearest Agricultural Field (km)
Coefficient
2.25 - 2.50
2.51 - 2.74
2.75 - 3.08
3.09 - 3.65
3.66 - 4.44
4.45 - 5.90
5.91 - 7.25
Agriculture
Pseudo t value
<- 1.96
-1.96 to 1.96
>1.96
Agriculture
1
2
3
4
5
0 2.5 5 km
N
Agricultural Surface Area within 50m of Home (km²)
Coefficient
-98.3 - -81.7
-81.6 - -69.7
-69.6 - -45.8
-45.7 - -35.5
-35.4 - -25.2
-25.1 - -20.8
-20.7 - -16.7
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture

Supplemental Table 2.1. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by sex.

		Sex		
Variables	**Overall**	**Females**	**Males**	**p-diff**
n	500	252	248	
Age, years	20.28 (1.83)	20.34 (1.79)	20.22 (1.88)	0.44
BMI	23.59 (21.44, 25.67)	24.28 (22.10, 26.65)	23.04 (20.84, 24.70)	<0.0001
Sex				
Female, n (%)	252 (50.40%)	-	-	
Male, n (%)	248 (49.60%)	-	-	
Race[a]				0.70
Indigenous, n (%)	90 (18.00%)	47 (18.65%)	43 (17.34%)	
Mestizo, White, or Other, n (%)	410 (82.00%)	205 (81.35%)	205 (82.66%)	
Monthly Household Salary, USD				0.91
Less than $500, n (%)	259 (51.80%)	136 (53.97%)	123 (49.60%)	
$500-$999, n (%)	114 (22.80%)	50 (19.84%)	64 (25.81%)	
$1000+, n (%)	34 (6.80%)	11 (4.37%)	23 (9.27%)	
Prefer Not to Answer, n (%)	93 (18.60%)	55 (21.83%)	38 (15.32%)	
Education				0.07
Some High School and Below, n (%)	77 (15.40%)	33 (13.10%)	44 (17.74%)	
High School Graduate, n (%)	231 (46.20%)	114 (45.24%)	117 (47.18%)	
Some College-to-College Graduate, n (%)	192 (38.40%)	105 (41.67%)	87 (35.08%)	

Supplemental Table 2.1. continued. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

		Sex		
Variables	**Overall**	**Females**	**Males**	**Overall**
Lives with an Agricultural or Floricultural Worker				0.37
No	134 (26.80%)	72 (28.57%)	62 (25.00%)	
Yes	366 (73.20%)	180 (71.43%)	186 (75.00%)	
Works in Agricultural or Floricultural Worker				0.15
No	358 (71.60%)	188 (74.60%)	170 (68.55%)	
Yes	142 (28.40%)	64 (25.40%)	78 (31.45%)	
How often do you use pesticides in your home or property?				0.17
Always	5 (1.00%)	3 (1.19%)	2 (0.81%)	
Often	20 (4.00%)	6 (2.38%)	14 (5.65%)	
Sometimes	30 (6.00%)	15 (5.95%)	15 (6.05%)	
Rarely	160 (32.00%)	80 (31.75%)	80 (32.26%)	
Never	188 (37.60%)	92 (36.51%)	96 (38.71%)	
I do not know/Prefer not to answer	97 (19.40%)	56 (22.22%)	41 (16.53%)	
Uses Pesticides at Work				0.23
No	333 (66.60%)	173 (68.65%)	160 (64.52%)	
Yes	108 (21.60%)	48 (19.05%)	60 (24.19%)	
I do not know	59 (11.80%)	31 (12.30%)	28 (11.29%)	
MDA				0.24
Above LOD	46 (9.20%)	27 (10.71%)	19 (7.66%)	
Below LOD	454 (90.80%)	225 (89.29%)	229 (92.34%)	
MDA, ug/L	0.35 (0.35, 0.35)	0.35 (0.35, 0.35)	0.35 (0.35, 0.35)	0.49
MDA, SG corrected	0.36 (0.29, 0.48)	0.36 (0.29, 0.49)	0.37 (0.31, 0.48)	0.42

Supplemental Table 2.1. continued. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

Variables	Overall	Sex: Females	Sex: Males	Overall
PNP				
Above LOD	500 (100.00%)	252 (100.00%)	248 (100.00%)	
PNP, ug/L	0.63 (0.41, 0.97)	0.64 (0.43, 0.98)	0.63 (0.40, 0.96)	0.42
PNP, SG corrected	0.66 (0.48, 0.91)	0.66 (0.51, 0.92)	0.66 (0.46, 0.90)	0.21
TCPy				
Above LOD	500 (100.00%)	252 (100.00%)	248 (100.00%)	
TCPy, ug/L	3.40 (2.10, 5.75)	3.50 (2.15, 5.55)	3.20 (2.00, 5.90)	0.93
TCPy, SG corrected	3.39 (2.26, 5.56)	3.49 (2.33, 5.45)	3.34 (2.19, 5.69)	0.83
OXY2				0.11
Above LOD	145 (29.00%)	65 (25.79%)	80 (32.26%)	
Below LOD	355 (71.00%)	187 (74.21%)	168 (67.74%)	
OXY2, ug/L	0.07 (0.07, 0.13)	0.07 (0.07, 0.11)	0.07 (0.07, 0.15)	0.41
OXY2, SG corrected	0.08 (0.06, 0.15)	0.08 (0.06, 0.15)	0.09 (0.07, 0.17)	0.28
3PBA				0.37
Above LOD	492 (98.40%)	247 (98.02%)	245 (98.79%)	
Below LOD	7 (1.40%)	4 (1.59%)	3 (1.21%)	
Interfering Substance	1 (0.20%)	1 (0.40%)	0 (0.00%)	
3PBA, ug/L	0.50 (0.31, 0.86)	0.50 (0.30, 0.90)	0.50 (0.31, 0.80)	0.79
3PBA, SG corrected	0.52 (0.32, 0.81)	0.52 (0.32, 0.78)	0.52 (0.33, 0.83)	0.74
TCC				0.04
Above LOD	213 (42.60%)	119 (47.22%)	94 (37.90%)	
Below LOD	287 (57.40%)	133 (52.78%)	154 (62.10%)	

PNP=para-nitrophenol, TCPY=3,5,6-Trichloro-2-pyridinol, OXY2-2-isopropyl-4-methyl-6-hydroxypyrimidine, 3-PBA=3-phenoxybenzoic acid, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, SG=specific gravity, µg=microgram, L=liters, m=meters, km=kilometers, LOD=level of detection.
Values are means (SD) or medians (Q25, Q75) for continuous variables; ns and percentages for categorical variables.

Supplementary Table 2.1. continued. Participant Characteristics of participants from the ESPINA Cohort, overall and stratified by agricultural surface area within 50m buffers median splits.

		Sex		
Variables	**Overall**	**Females**	**Males**	**Overall**
TCC, ug/L	0.42 (0.42, 0.93)	0.42 (0.42, 1.00)	0.42 (0.42, 0.85)	0.40
TCC, SG corrected	0.62 (0.43, 1.00)	0.63 (0.43, 1.05)	0.58 (0.43, 0.95)	0.54
2,4D				0.13
Above LOD	404 (80.80%)	197 (78.17%)	207 (83.47%)	
Below LOD	96 (19.20%)	55 (21.83%)	41 (16.53%)	
2,4D, ug/L	0.27 (0.17, 0.41)	0.27 (0.16, 0.40)	0.27 (0.18, 0.42)	0.77
2,4D, SG corrected	0.26 (0.18, 0.42)	0.25 (0.17, 0.39)	0.27 (0.20, 0.45)	0.44
Distance to Agriculture, m	19.74 (7.08, 27.89)	19.75 (7.18, 27.68)	19.72 (6.48, 28.41)	0.91
50m Buffer km^2	0.001 (0.000, 0.002)	0.001 (0.000, 0.002)	0.001 (0.000, 0.002)	0.23
100m Buffer km^2	0.005 (0.003, 0.008)	0.005 (0.003, 0.008)	0.006 (0.003, 0.009)	0.08
150m Buffer km^2	0.014 (0.009, 0.019)	0.014 (0.010, 0.017)	0.014 (0.009, 0.021)	0.034
200m Buffer km^2	0.025 (0.018, 0.034)	0.025 (0.018, 0.032)	0.025 (0.017, 0.038)	0.081
250m Buffer km^2	0.040 (0.028, 0.053)	0.040 (0.030, 0.052)	0.040 (0.026, 0.057)	0.17
300m Buffer km^2	0.058 (0.043, 0.076)	0.058 (0.044, 0.073)	0.058 (0.040, 0.080)	0.28
350m Buffer km^2	0.079 (0.057, 0.104)	0.079 (0.058, 0.101)	0.079 (0.055, 0.106)	0.43
400m Buffer km^2	0.102 (0.076, 0.138)	0.103 (0.077, 0.137)	0.101 (0.073, 0.140)	0.49
450m Buffer km^2	0.127 (0.095, 0.177)	0.129 (0.095, 0.175)	0.124 (0.095, 0.179)	0.46
500m Buffer km^2	0.154 (0.116, 0.216)	0.157 (0.116, 0.216)	0.153 (0.116, 0.217)	0.46

TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, 2,4-D=2,4-Dichlorophenoxyacetic acid, SG=specific gravity, µg=microgram, L=liters, m=meters, km=kilometers, LOD=level of detection.

Values are means (SD) or medians (Q25, Q75) for continuous variables; ns and percentages for categorical variables.

[a] Two individuals self-identified as White and 1 individual self-identified as Other.

Supplemental Table 2.2. Associations between a 1% increase in home distance to the nearest agricultural field or 1% increase in agricultural surface area (50m to 500m buffers), and urinary pesticide metabolite concentration using model 1.

β% (95% CI) increase in urinary pesticide metabolite concentration per 1% increase in home distance or agricultural surface area.

	PNP	TCPY	OXY2	3-PBA	TCC	2,4-D
Distance	0.42 (-2.26, 3.16)	-1.43 (-3.99, 1.2)	-0.2 (-4.62, 4.43)	4.62 (0.48, 8.94)**	0.5 (-1.8, 2.85)	-2.49 (-6.51, 1.71)
Surface Area of Agriculture Within Different Buffer Sizes						
50m	-29.85 (-51.67, 1.84)*	4.59 (-28.81, 53.67)	-1.10 (-47.49, 86.25)	-25.71 (-56.27, 26.2)	-20.72 (-41.82, 8.03)	119.02 (8.82, 340.8)**
100m	-14.5 (-24.05, -3.75)**	-1.2 (-9.69, 8.09)	-6.45 (-22.54, 12.99)	-3.36 (-17.4, 13.07)	-6.8 (-14.8, 1.95)	7.18 (-13.34, 32.56)
150m	-0.09 (-0.16, -0.02)**	-0.04 (-0.12, 0.05)	-0.04 (-0.19, 0.1)	-0.05 (-0.15, 0.05)	-0.05 (-0.14, 0.04)	0.02 (-0.09, 0.13)
200m	-0.11 (-0.19, -0.03)**	-0.04 (-0.14, 0.05)	-0.04 (-0.18, 0.1)	-0.05 (-0.16, 0.07)	-0.06 (-0.16, 0.03)	0.04 (-0.09, 0.17)
250m	-0.1 (-0.18, -0.01)**	-0.03 (-0.14, 0.08)	-0.05 (-0.19, 0.09)	-0.05 (-0.17, 0.07)	-0.05 (-0.16, 0.06)	0.08 (-0.07, 0.22)
300m	-0.1 (-0.19, 0)**	-0.02 (-0.14, 0.1)	-0.03 (-0.17, 0.12)	-0.04 (-0.17, 0.08)	-0.06 (-0.17, 0.06)	0.10 (-0.06, 0.25)
350m	-0.11 (-0.21, -0.01)**	-0.04 (-0.17, 0.09)	-0.02 (-0.17, 0.13)	-0.04 (-0.17, 0.09)	-0.05 (-0.17, 0.07)	0.09 (-0.08, 0.25)
400m	-0.11 (-0.22, -0.01)**	-0.04 (-0.17, 0.1)	-0.03 (-0.18, 0.12)	-0.04 (-0.18, 0.09)	-0.06 (-0.19, 0.07)	0.08 (-0.09, 0.25)

MDA=malathion dicarboxylic acid, PNP=para-nitrophenol, TCPy=3,5,6-Trichloro-2-pyridinol, OXY2-2-isopropyl-4-methyl-6-hydroxypyrimidine, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, 2,4-D=2,4-Dichlorophenoxyacetic acid, m=meters, km=kilometers. **p<0.05, *p<0.10

Model 1 adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College-to-College Graduate). All pesticide metabolites were imputed using a constant (LODS/sqrt(2), adjusted for specific gravity, and then were natural log transformed. The level of detection was 0.5 µg/L for MDA, 0.1 µg/L for PNP, TCPy and OXY2, and 0.6 µg/L for TCC.

Supplemental Table 2.3. Gender interactions between home distance to the nearest agricultural field and sex.

	β (95% CI) for the sex interaction term with distance to the nearest agricultural field (sex|distance)			
Outcome	**Model 1**	**P-value**	**Model 2**	**P-value**
MDA	-4.41 (-8.87, 0.05)	0.05	-4.17 (-8.56, 0.22)	0.06
PNP	-4.35 (-13.60, 4.90)	0.36	0.24 (-0.11, 0.59)	0.18
TCPY	-24.71 (-61.76, 12.33)	0.19	-21.26 (-59.41, 16.88)	0.27
OXY2	-3.19 (-8.11, 1.72)	0.20	-2.55 (-7.05, 1.96)	0.27
TCC	0.66 (-9.50, 10.81)	0.90	0.60 (-10.51, 11.72)	0.92
3-PBA	-0.19 (-9.00, 8.61)	0.97	0.42 (-8.55, 9.38)	0.93
2,4-D	0.18 (-0.09, 0.44)	0.19	-7.92 (-15.27, -0.56)	0.03

2,4-D=2,4-Dichlorophenoxyacetic acid, 3-PBA=3-phenoxybenzoic acid, km=kilometers, m=meters, MDA=malathion dicarboxylic acid, OXY=2-isopropyl-4-methyl-6-hydroxypyrimidine, PNP=para-nitrophenol, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, TCPY=3,5,6-Trichloro-2-pyridinol

**p<0.05, *p<0.10

Model 1 adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate).

Model 2 adjusts for Model 1 and living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

All pesticide metabolites were imputed using a constant (LODS/sqrt(2), adjusted for specific gravity, and then were natural log transformed. The level of detection was 0.5 µg/L for MDA, 0.1 µg/L for PNP, TCPy and OXY2, and 0.6 µg/L for TCC.

Supplemental Table 2.4.Gender interactions between the agricultural surface area within a 50m and 100m buffer region.

	β (95% CI) for the sex interaction term with distance to the nearest agricultural field (sex*distance)							
	Surface area within 50m				**Surface Area within 100m**			
	Model 1	**P-value**	**Model 2**	**P-value**	**Model 1**	**P-value**	**Model 2**	**P-value**
MDA	43.4 (-55.4, 142.2)	0.86	48.6 (-50.9, 148.1)	0.34	11.4 (-10.0, 32.8)	1.04	14.9 (-4.8, 34.5)	0.14
PNP	-53.6 (-115.6, 8.5)	0.09	-49.9 (-111.9, 12.2)	0.12	-20.0 (-46.9, 6.8)	0.14	-18.8 (-47.5, 10.0)	0.20
TCPY	530.4 (3.4, 1,057.4)	0.05	483.1 (-52.2, 1,019.1)	0.08	172.3 (38.8, 305.8)	0.01	184.9 (45.8, 324.1)	0.01
OXY2	37.1 (-34.2, 108.3)	0.31	25.8 (-39.3, 90.8)	0.44	21.1 (-7.4, 49.6)	0.15	19.5 (-9.1, 48.1)	0.18
TCC	38.5 (-67.3, 144.3)	0.48	34.6 (-76.5, 145.6)	0.54	-21.3 (-44.6, 2.0)	0.07	4.0 (-28.9, 36.9)	0.81
3-PBA	54.5 (-60.5, 169.5)	0.35	53.7 (-61.7, 169.0)	0.36	19.39 (-13.8, 52.6)	0.25	18.9 (-15.8, 53.6)	0.29
2,4-D	35.5 (-168.5, 239.4)	0.73	70.6 (-136.4, 277.7)	0.50	27.5 (-37.1, 92.0)	0.40	35.9 (-30.7, 102.5)	0.29

2,4-D=2,4-Dichlorophenoxyacetic acid, 3-PBA=3-phenoxybenzoic acid, km=kilometers, m=meters, MDA=malathion dicarboxylic acid, OXY=2-isopropyl-4-methyl-6-hydroxypyrimidine, PNP=para-nitrophenol, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, TCPY=3,5,6-Trichloro-2-pyridinol

**$p<0.05$, *$p<0.10$

Model 1 adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate).

Model 2 adjusts for model 1 and living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

All pesticide metabolites were imputed using a constant (LODS/sqrt(2), adjusted for specific gravity, and then were natural log transformed. The level of detection was 0.5 µg/L for MDA, 0.1 µg/L for PNP, TCPy and OXY2, and 0.6 µg/L for TCC.

Supplemental Table 2.5. The odds of having detectable levels of OXY2 and TCC metabolites or having 3-PBA concentrations in the upper median for a standard deviation increase our agriculture proximity constructs (50m to 500m buffer).

	OXY2[b]	3-PBA[a]	TCC[b]
Distance	0.98 (0.8, 1.2)	1.17 (0.96, 1.42)	1.09 (0.91, 1.32)
Surface Area of Agriculture Within Different Buffer Sizes (km^2)			
50m	1.01 (0.83, 1.24)	0.97 (0.8, 1.17)	0.87 (0.72, 1.06)
100m	0.96 (0.78, 1.19)	1.02 (0.84, 1.25)	0.94 (0.77, 1.14)
150m	0.93 (0.75, 1.15)	1 (0.82, 1.22)	0.95 (0.78, 1.15)
200m	0.9 (0.73, 1.12)	1 (0.82, 1.22)	0.95 (0.78, 1.15)
250m	0.87 (0.7, 1.07)	0.99 (0.81, 1.21)	0.98 (0.8, 1.19)
300m	0.89 (0.72, 1.1)	1.02 (0.84, 1.25)	1.02 (0.84, 1.25)
350m	0.88 (0.7, 1.09)	1.06 (0.87, 1.3)	1.04 (0.85, 1.26)
400m	0.86 (0.69, 1.08)	1.09 (0.89, 1.33)	1.02 (0.83, 1.24)
450m	0.86 (0.69, 1.08)	1.08 (0.87, 1.32)	1.02 (0.83, 1.25)
500m	0.88 (0.7, 1.11)	1.07 (0.87, 1.32)	1.03 (0.84, 1.27)

OXY2-2-isopropyl-4-methyl-6-hydroxypyrimidine, 3-PBA=3-Phenoxybenzoic acid, TCC=trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, m=meters, km=kilometers. **p<0.05, *p<0.10

Models adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

[a] Odds of having urinary metabolite concentrations in the upper median, compared to those in the lower median, for a SD increase in home-ag distance or home-ag SA.
[b] Urinary pesticide metabolite concentrations were categorized as being below (ref) or above the LOD. Odds of having detectable levels of urinary metabolite concentrations, compared to those below the level of detection, for a SD increase in home-ag distance or home-ag SA.

A standard deviation of the distance variable are 16.86m/0.02km for home-ag distance, 0.001 km^2 for a 50m buffer, 0.006 km^2 for a 100m buffer, 0.015 km^2 for a 150m buffer, 0.027 km^2 for a 200m buffer, 0.043 km^2 for a 250m buffer, 0.062 km^2 for a 300m buffer, 0.084 km^2 for a 350m buffer, 0.110 km^2 for a 400m buffer, 0.139 km^2 for a 450m buffer, 0.172 km^2 for a 500m buffer.

Supplemental Table 2.6. The odds of having TCPY concentrations in the upper median for a SD increase in home distance to the nearest agricultural field, or a SD increase in agricultural surface area (50m to 500m buffer), overall and stratified by sex.

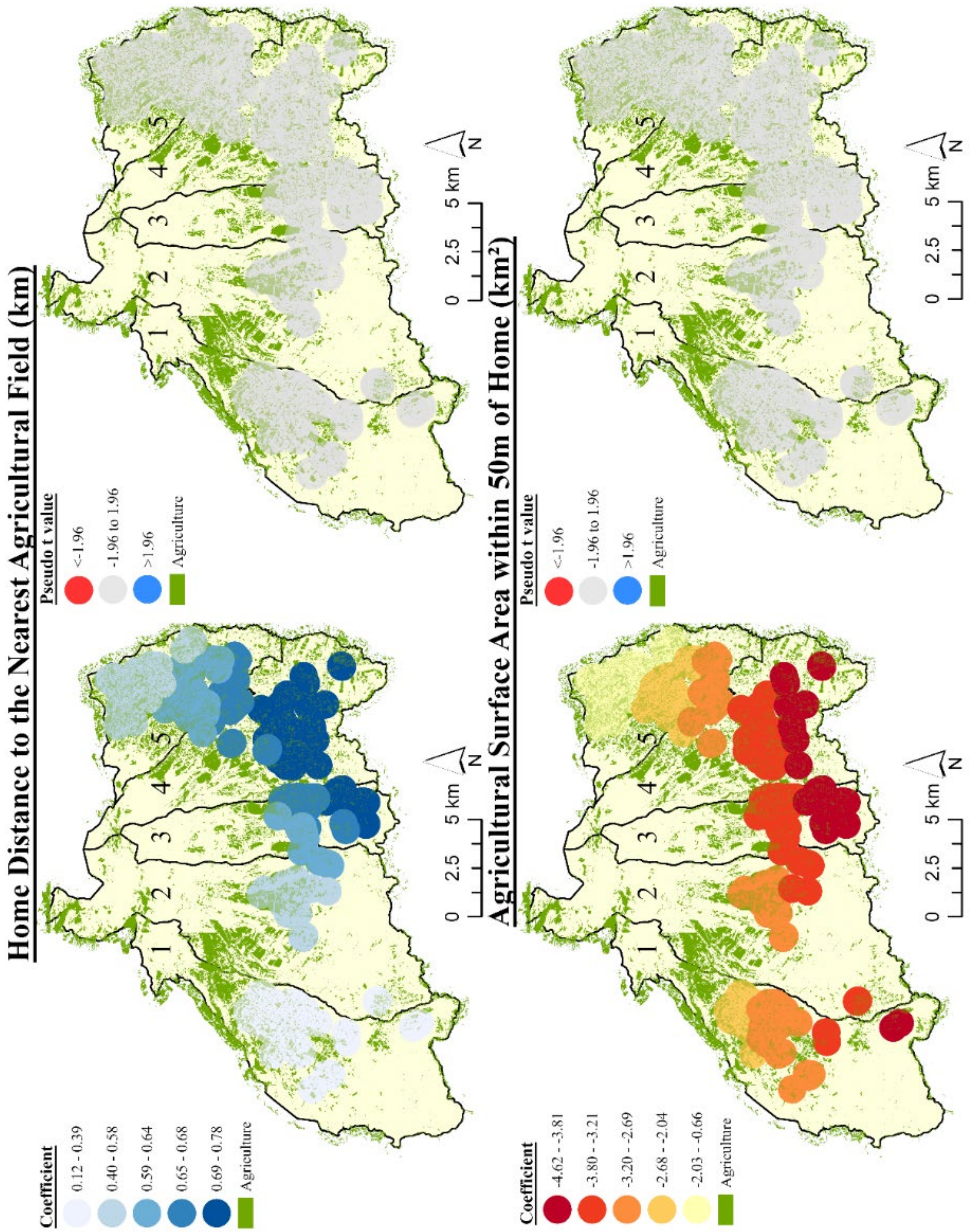
		TCPY	
Exposure	**Overall**	**Male**	**Female**
Home-ag Distance	1.01 (0.83, 1.21)	0.9 (0.68, 1.19)	1.14 (0.87, 1.51)
Surface Area of Agriculture Within Different Buffer Sizes			
50m	1 (0.83, 1.22)	1.11 (0.83, 1.47)	0.93 (0.7, 1.23)
100m	0.99 (0.81, 1.2)	1.16 (0.87, 1.54)	0.86 (0.64, 1.14)
150m	0.97 (0.79, 1.17)	1.1 (0.83, 1.47)	0.83 (0.62, 1.12)
200m	0.99 (0.81, 1.2)	1.04 (0.79, 1.38)	0.91 (0.68, 1.22)
250m	1.02 (0.84, 1.25)	1.07 (0.8, 1.42)	0.96 (0.72, 1.28)
300m	1.05 (0.86, 1.28)	1.08 (0.81, 1.43)	1.01 (0.75, 1.35)
350m	1.06 (0.87, 1.29)	1.08 (0.81, 1.45)	1 (0.74, 1.34)
400m	1.07 (0.87, 1.31)	1.09 (0.81, 1.46)	1 (0.74, 1.36)
450m	1.06 (0.86, 1.3)	1.08 (0.8, 1.44)	1 (0.74, 1.36)
500m	1.07 (0.87, 1.31)	1.07 (0.8, 1.44)	1.02 (0.75, 1.39)

Models adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

Odds of having urinary metabolite concentrations in the upper median, compared to those in the lower median, for a SD increase in home-ag distance or home-ag SA.

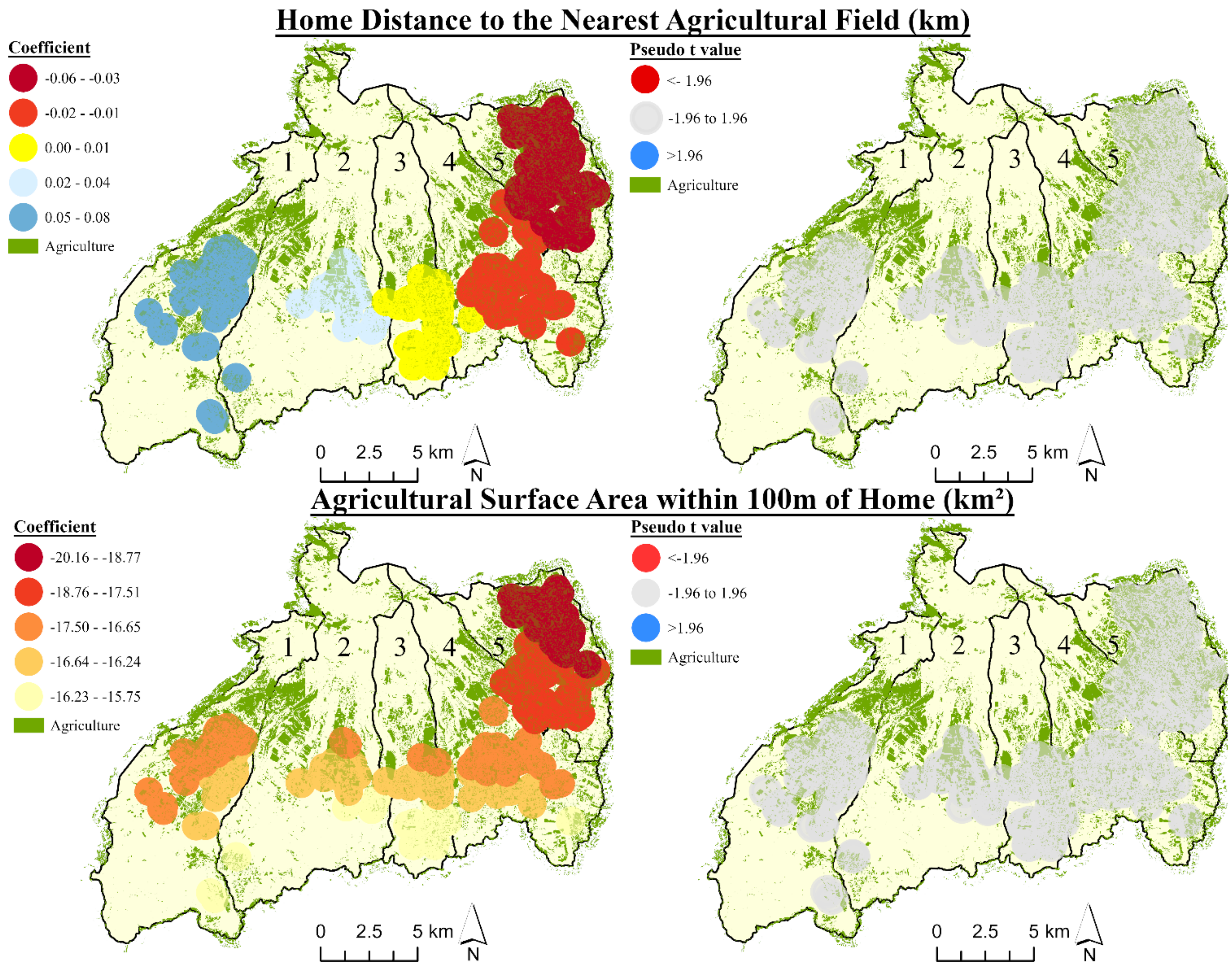
A standard deviation of the distance variable are 16.86m/0.02km for home-ag distance, 0.001 km^2 for a 50m buffer, 0.006 km^2 for a 100m buffer, 0.015 km^2 for a 150m buffer, 0.027 km^2 for a 200m buffer, 0.043 km^2 for a 250m buffer, 0.062 km^2 for a 300m buffer, 0.084 km^2 for a 350m buffer, 0.110 km^2 for a 400m buffer, 0.139 km^2 for a 450m buffer, 0.172 km^2 for a 500m buffer.

Supplemental Figure 2.1. Geospatially weighted regression assessed whether a 1km increase in home distance or a 1km increase in agricultural surface area within 50m is associated with urinary MDA concentration in Pedro Moncayo. Models were adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).



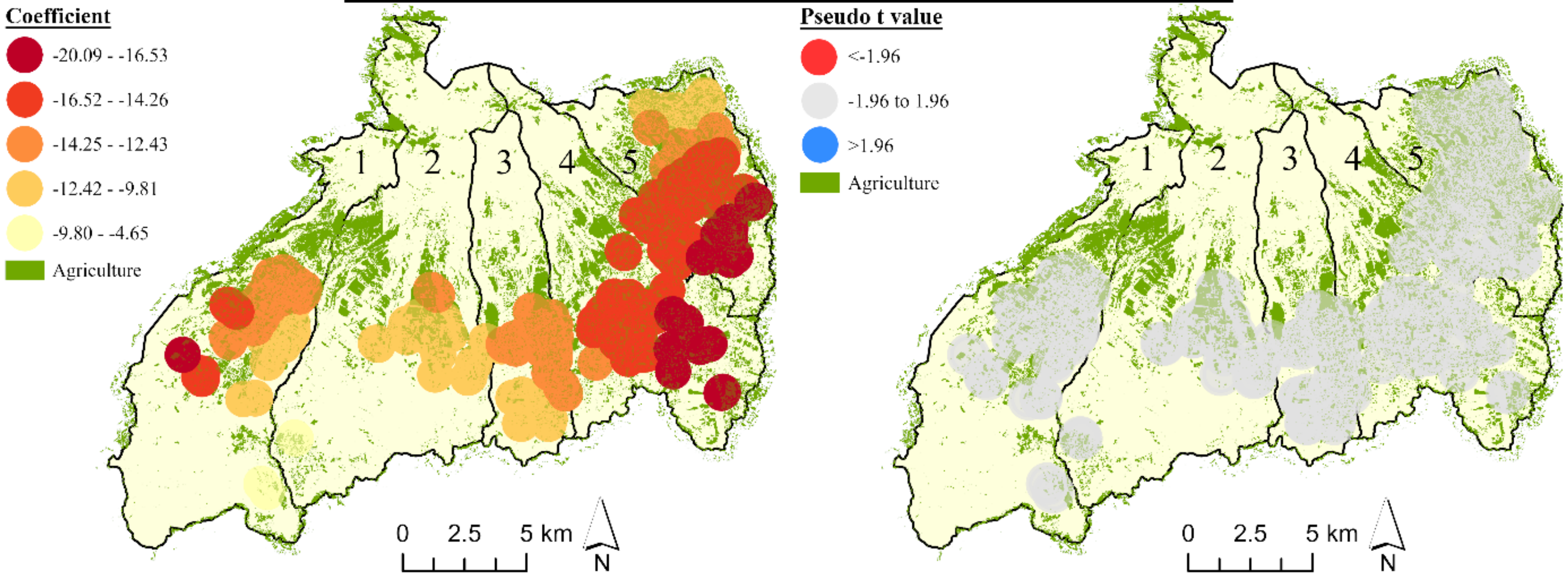
Home Distance to the Nearest Agricultural Field (km)
Coefficient
0.12 - 0.39
0.40 - 0.58
0.59 - 0.64
0.65 - 0.68
0.69 - 0.78
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture
1
2
3
4
5
0
2.5
5 km
N
Agricultural Surface Area within 50m of Home (km²)
Coefficient
-4.62 - -3.81
-3.80 - -3.21
-3.20 - -2.69
-2.68 - -2.04
-2.03 - -0.66
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture

Supplemental Figure 2.2. Geospatially weighted regression assessed whether a 1km increase in home distance or a 1km increase in agricultural surface area within 50m is associated with urinary PNP concentration in Pedro Moncayo. Models were adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

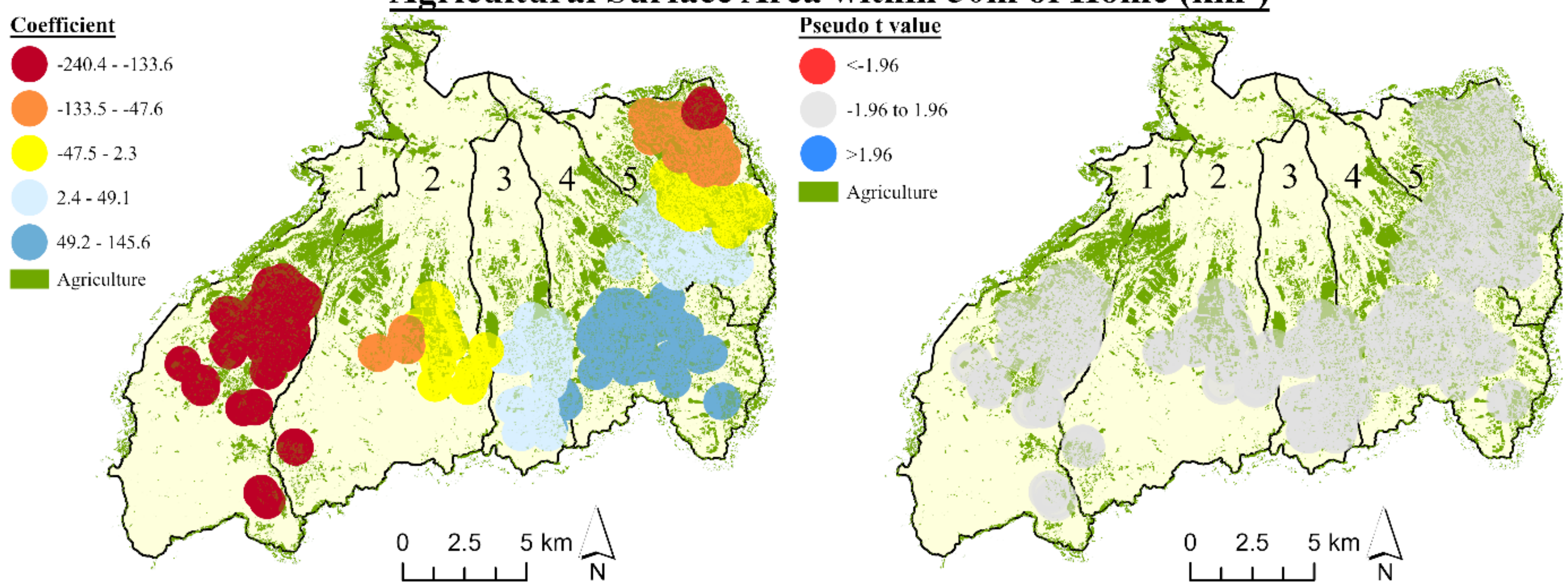

Home Distance to the Nearest Agricultural Field (km)
Coefficient
-0.06 - -0.03
-0.02 - -0.01
0.00 - 0.01
0.02 - 0.04
0.05 - 0.08
Agriculture
Pseudo t value
<- 1.96
-1.96 to 1.96
>1.96
Agriculture
1 2 3 4 5
0 2.5 5 km
N
Agricultural Surface Area within 100m of Home (km²)
Coefficient
-20.16 - -18.77
-18.76 - -17.51
-17.50 - -16.65
-16.64 - -16.24
-16.23 - -15.75
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture

Supplemental Figure 2.3. Geospatially weighted regression assessed whether a 1km increase in home distance or a 1km increase in agricultural surface area within 50m is associated with urinary TCPY concentration in Pedro Moncayo. Models were adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).

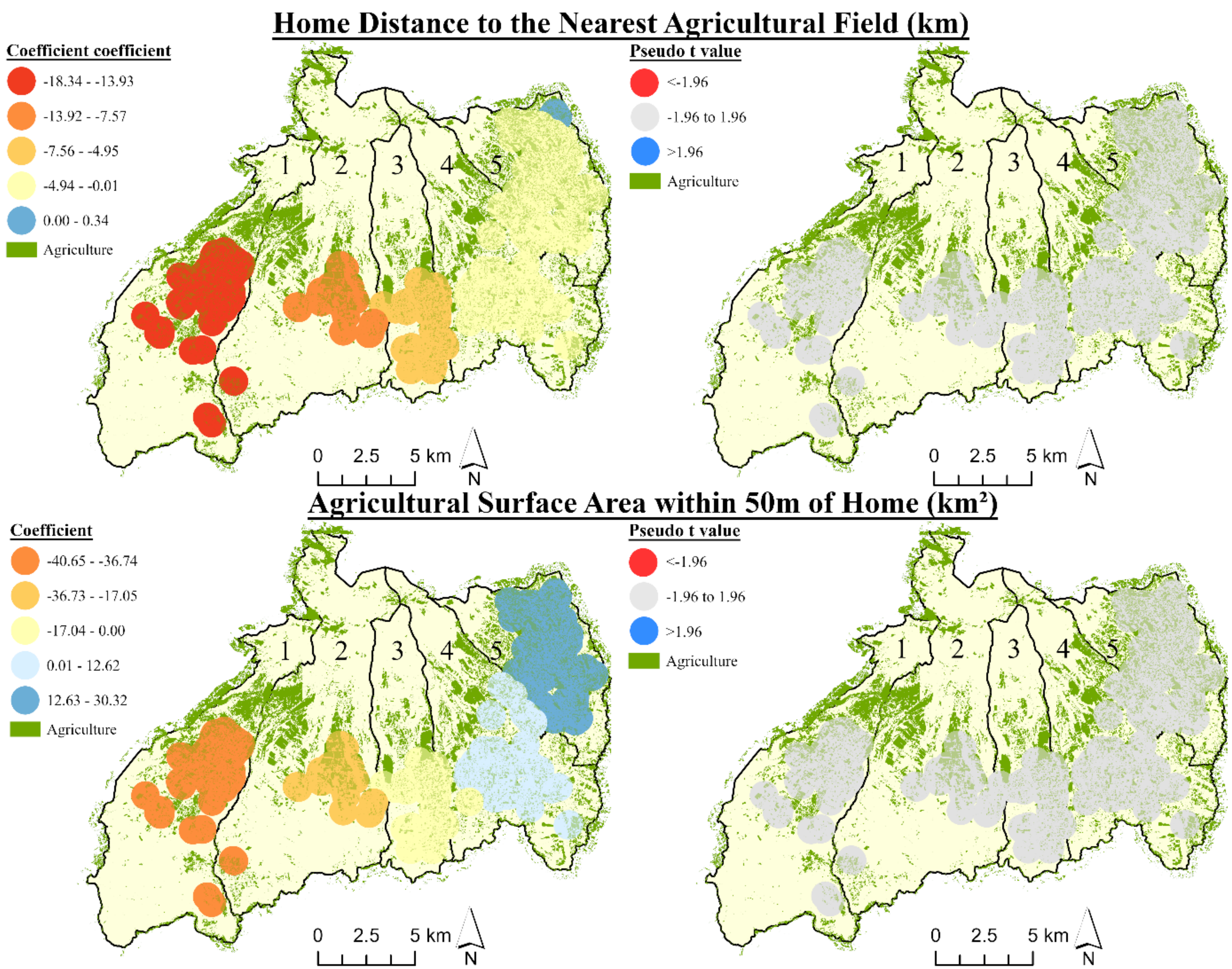
Home Distance to the Nearest Agricultural Field (km)



Agricultural Surface Area within 50m of Home (km²)



Supplemental Figure 2.4. Geospatially weighted regression assessed whether a 1km increase in home distance or a 1km increase in agricultural surface area within 50m is associated with urinary OXY2 concentration in Pedro Moncayo. Models were adjusted for age, BMI, gender (ref=Female, Male), race (ref=Indigenous, White Mestizo or Other), living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=No, Yes), monthly household income, Education (ref=Less than High School Graduate, High School, Some College to College Graduate), frequency of home pesticide use (ref="I don't know if it is used", Never, Rarely, Sometimes, Often, Always).


Home Distance to the Nearest Agricultural Field (km)
Coefficient coefficient
-18.34 - -13.93
-13.92 - -7.57
-7.56 - -4.95
-4.94 - -0.01
0.00 - 0.34
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture
1
2
3
4
5
0 2.5 5 km
N
Agricultural Surface Area within 50m of Home (km²)
Coefficient
-40.65 - -36.74
-36.73 - -17.05
-17.04 - 0.00
0.01 - 12.62
12.63 - 30.32
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture

Chapter 3 Home Proximity to Agriculture is Associated with Greater Depression and Anxiety Symptoms in Adolescents and Young Adults Living in an Ecuadorian Agricultural Community

Abstract

Introduction: Depression and Anxiety is a top 5 contributor of Disability Adjusted Life Years in Ecuadorians. Elevated depression and anxiety prevalence has been observed in occupational populations with direct pesticide exposure, like farmers. Individuals living in agricultural communities are potentially at risk of having depression and anxiety symptoms.

Methods: 484 adolescents and adults living in the agricultural canton of Pedro Moncayo, Ecuador, were assessed in 2022. Anxiety and depression symptoms were measured using the Generalized Anxiety Disorder-7 (GAD-7) and Beck's Depression Inventory-II (BDI-2), respectively. Participant home distance to the nearest agricultural plot (home-ag distance) and surface area of agriculture (home-ag SA) for 50m, 100m, and 200m buffers around the home were estimated. Generalized estimating equations (GEE) assessed whether home-ag distance and home-ag SA was associated with GAD-7 and BDI-II score. Odds ratios of "Mild" or "Moderate or Severe" depression or anxiety symptoms versus minimal symptoms were calculated using logistic regression. Optimized Getis-Ord Gi* identified symptom hot and cold spots. Geospatially weighted regression (GWR) was conducted. GEE, logistic regression, and GWR models were adjusted for demographic, socioeconomic, and alternative pesticide exposure pathways.

Results: A 10% increase in home-ag distance was associated with lower anxiety (-3.04% [95% CI: -4.93%, -1.15%]) and depression (-6.26% [95%CI: -10.69%, -1.83%]) symptoms Associations between home-ag SA anxiety or depression symptoms were not identified. Living

16.93m farther from an agricultural plot lowered the odds of having both Mild (OR=0.75 [0.6, 0.93]) and Moderate or Severe (OR=0.69 [0.5, 0.93]) anxiety symptoms, and lowered the odds of having Moderate or Severe depression symptoms (OR=0.67 [0.45, 0.98]). GWR shows that the association between home-ag distance with depression symptoms was strongest in Malchinguí and weakened as you moved West. While for anxiety symptoms, it was strongest in Tupigachi and weakened as you moved East.

Conclusions: Living near open-air agricultural crops was associated with greater depression and anxiety symptoms in adolescents, after controlling for socio-demographic factors. This suggests that pesticide drift from agricultural activities may negatively impact depression and anxiety symptoms, which is consistent with previous findings within our cohort. Mitigating pesticide exposures for people living near agricultural crops is warranted.

Introduction

Depression and Anxiety are a top 5 contributors of Disability Adjusted Life Years in Ecuadorians [131,132], and an estimated 21.1% of the attributable depression burden and 16.8% of the attributable anxiety burden in Ecuadorians are due to preventable risks, like environmental exposures [133]. Individuals with depression or anxiety are at higher risk of psychosocial outcomes, like increased suicidality [134–136], social functioning problems, and poor health [135–137]. In the last 50 years, thousands of new, non-natural chemicals have been developed and used in agricultural industries globally, especially in Latin America and developing countries [138–141]. This green revolution places agricultural communities at increased risk of chronic exposure through drift from sprayed fields, residues in homes, and soil, water, or food contamination [5,123,138,142]. Pesticide exposure may increase depression and anxiety risk of farmers and adults living in agricultural communities.

Oral administration of pyrethroids (cypermethrin [143] and deltamethrin [143]), herbicides (24,-D [144,145], glyphosate [146]), and organophosphates (malathion[147] and chlorpyrifos [148]) in rats and mice have led to changes in anxiety and depression like behaviors. Epidemiological evidence suggests that pesticide-related toxicity can lead to mood disorders, such as depression and anxiety [149,150]. Occupational populations that have chronic exposure to chemicals, such as farmers, have been shown to have elevated depression and anxiety prevalence when compared to non-occupational populations, which has been exacerbate in individuals with a history of pesticide poisonings [150–154]. In a cohort of farm workers from Baja California, Mexico, increased AChE inhibition was found to be associated with generalized anxiety, and combined depression-anxiety symptoms [155]. In adolescents living in Pedro Moncayo, lower AChE activity was associated with higher depression symptoms, which was stronger in females and in younger participants [156]. When assessed at two time points, inhibition of AChE activity kwas associated with greater depression symptoms, with stronger effects in girls as well[13]. Farmers living in France who used herbicides had a 1.93 (95%CI: 0.95, 3.91) increased hazard of having depression symptoms [153].

The relationship between pesticide exposure and mental health outcomes have been observed to a lesser extent in para-occupational (individuals living with workers that have direct pesticide exposure) and non-occupational populations who experience indirect exposure. For para-occupational populations, female spouses of licensed pesticide applicators had greater odds of experiencing depression [157]. Similar associations have been observed in non-occupational populations. Compared to agricultural communities with lower pesticide expenditure, residents of agricultural communities with higher rates of pesticide expenditure were at a greater risk for hospitalization due to mood disorders [158]. Higher ambient pyrethroid exposure in agricultural communities, estimated using PUR data, increased the odds of depression in elderly [159]. Prenatal pyrethroid exposure was linked to depression in children [160]. In clinical case studies, organophosphate poisonings have increased depressive symptoms [161–163].

A limitation that arises when assessing the effects of pesticide exposure on mental health outcomes is that quantification of pesticide metabolites can only measure short-term exposure due to fast metabolism. Pesticide exposure biological measurements, like urinary pesticide metabolites, describes short term exposure as they are metabolized quickly (~≤96 hours) [124,164–166]. Leveraging metabolite measurement to assess long term exposure would require multiple measurements over time which is often prohibitive due to its high cost. Geospatial proxies for pesticide exposure, like home distance to agriculture and surface area of agriculture around the home, are measures that have commonly been applied to assess health risks associated with pesticide exposure by pesticide drift [10]. As Pedro Moncayo has ideal growing conditions year-round, agricultural activity and pesticide applications may occur continuously throughout the year. Using a geospatial proxies for pesticide exposure has the capability of capturing more long-term pesticide exposure than urinary pesticide metabolites. Thus, home distance and surface area of agriculture can potentially capture effects of long-term pesticide exposure on depression and anxiety symptoms within this cohort.

Distance to agriculture has been used as a proxy pesticide drift measure to estimate pesticide exposure. Distance to agriculture has been found to be negatively associated with residues found in household dust [142,167] and air contamination concentrations [81], demonstrating its potential to estimate pesticide drift and assess exposure risk. There has been evidence that individuals that live farther from agriculture are more likely to have less pesticide exposure compared to those who live closer (see Chapter 2). In the ESPINA cohort, it was identified that residential proximity (individuals living closer) to floriculture was associated with altered neurobehavior among children living closes to crops, demonstrating mental health alterations have varied by distance to a pesticide spray source [77]. Our study aims to use distance to agriculture as a proxy measurement for pesticide exposure by pesticide drift and assess whether it is associated with anxiety or depression symptoms in Ecuadorian young adults.

Methods

Study Population

Similar to Chapter 2, this analysis included data from the 2022 ESPINA summer assessments, as the agricultural map created in Chapter 1 was for 2022. The participant flowchart can be found in Figure 3.1. As a summary, ESPINA began in 2008, when 313 children (4-9 years) living in Pedro Moncayo were recruited either through the 2004 Survey of Access and Demand of Health Services (SADHS) (73%) or through community announcements (27%) [94]. Between 2008 and February 2024, there have been six in-person follow-up assessments, in the spring (April) and summer (July-Oct) of 2016 [13], the summer of 2022 (July-Sep), the winter (Jan-Feb) and summer (July) of 2023, and winter of 2024 (Jan-Feb) (Figure 2.1.). Participants completed thorough surveys for the summer 2016, summer 2022, and winter 2024 assessments. Urinary pesticide metabolite concentrations were measured for the summer 2016 and summer 2022 assessments. Of the 505 participants who completed the 2022 assessment, 94 individuals had completed all proceeding assessments (2008, spring 2016, and summer 2016), 348 individuals completed the winter 2023 assessment, 365 individuals completed the summer 2023 assessment, and 362 completed the Winter 2024 assessment. A

All study visits for the Summer 2022 assessment occurred in local schools, primarily on the weekend. During the study visit participants completed a self-administered Qualtrics survey using a study phone or tablet that captured information on demographics, housing, pesticide use behaviors, and socioeconomic information, such as income, education level, and occupation.

Anxiety and Depression symptom measurement

Depression symptoms were assessed using the Spanish version of the Beck Depression Inventory-II (BDI-II)[168]. This is a self-report assessment that contains 21 items which measures depressive symptoms over the past two weeks. Each question has a scale response from 0 ("Not at All") to 3 ("Extreme form"). To score the BDI-II all items are added, and total scores can range from 0 to 63. Depression symptom severity can be grouped into four categories: Minimal (0 to 13), Mild (14-19), Moderate (20-28), and Severe (29-63). This test has demonstrated good psychometric properties in worldwide [169] and Ecuadorian populations [170]. The English and Spanish versions of the BDI-II have shown good internal consistency and test-retest reliability in young adults [171].

Anxiety symptoms were assessed using the Spanish version of the Generalized Anxiety Disorder Scale (GAD-7), which is a 7-item self-reported assessment tool that measures anxiety symptoms over the past 7 days. Items are rated from 0 (“Not at All”) to 3 (“Nearly Every Day”). When scoring this test, responses are totaled and have a range of 0 to 21 [172]. The total scores can be categorized into severity groups of Minimal (0-4), Mild (5-9), Moderate (10-14) and Severe (14-21) anxiety symptomology [172]. The Spanish version of the GAD-7 has demonstrated good validity [173].

The GAD-7 and BDI-II were completed by the participants in a private room with a trained psychologist or study staff.

Agricultural proximity construct creation

ESPINA participants reported their home addresses, which were geolocated manually by ESPINA staff. Agricultural fields were identified using methods reported in Chapter 1. In summary, spectral mixture analysis was conducted on Sentinel-2 T17NQA and T17NRA images from January 1, 2021, to October 31, 2022. A time-series of vegetation fraction images was created, and clustering of distinct agricultural temporal end members (tEMs) was identified in the Uniform Manifold Approximation and Projection (UMAP) feature space manually. The tEMs were used to unmix the processed Sentinel-2 images, and an agricultural map was created that had 72.57% accuracy and 75.31% precision. Country-level, state-level, and county-level borders were provided by the World Bank [101]. All layers were reprojected to have the WGS 1984 UTM Zone 17S projection.

Two agricultural proximity constructs were created. The distance from the participants’ home to the border of the nearest agricultural field (home-ag distance), and agricultural surface area for different radii (buffer sizes) around the participants home (home-ag SA). The buffer regions ranged from 50m (home-ag $SA_{50m)}$ to 500m (home-ag SA_{500m}), by every 50 m. Similar studies have used buffer regions ranging from 0 to 8,000 meters [10]. Smaller buffers were assessed first, as the primary pesticide application method used in this region use hand-sprayers which have shorter pesticide drift than aerial sprayers [82]. However, no associations were discovered, so larger buffer sizes were not assessed.

Imputation of covariates

Missing values of our covariates were imputed to help maximize the sample size of the analysis, primarily using values participants reported during the winter 2023 or 2016 ESPINA assessments. For behaviors of pesticide use at home, 11 observations were imputed with values reported in 2023 while 6 were imputed using quantities reported in 2016. Pesticide use at work was imputed using 2023 ESPINA, where five individuals reported no use, five individuals reported use, and four individuals reported "I don't know/prefer not to answer." Eight more observations were imputed as "I don't know/prefer not to answer." For occupation in agriculture or floriculture, eight individuals were reported based on their occupation reported in 2023, and three individuals were imputed based on their parent's occupation reported in 2013 (n=1 Agricultural worker, n=2 Not an agricultural or floricultural worker). Using data from the 2023 assessment we imputed salary for 3 individuals, and recoded two individuals as "Prefer not to Answer." After imputation of the covariates, the sample size was limited to individuals who had geospatial location of their homes, had a measure for GAD-7 or the BDI-II, and did not have missing covariates; 484 out of 505 (95.8%) individuals examined in 2022 were included in this analysis.

Statistical Analysis

Descriptive analyses were conducted for participant characteristics for the overall cohort and stratified by a median split of agricultural surface area within a 50m buffer around the participant's home. This was done by calculating the means and standard deviation (SD) for normally distributed continuous data, median and interquartile ranges (IQR) for non-normally distributed variables and counts and column percentages for count data. The p-trend was calculated by identifying differences in covariate values across the 50m surface area median split using unadjusted linear regression (p-trend). Means of the urinary metabolites were calculated for their observed values, concentrations after imputation with a constant, and for specific gravity adjusted concentrations. A Pearson correlation was run to assess whether GAD-7 and BDI-II score were correlated.

Participant characteristics were mapped to look at their spatial distributions. The point layer containing home location was rasterized using 1.5 km squares to retain participant anonymity. For continuous variables, the values were averaged for all the points that were located within that 1.5 km square. For dichotomous variables, the proportion of the characteristic across all points within the square where represented. For example, for sex we represented the proportion of each 1.5 square that reported being male. The most frequently reported value for each 1.5m was mapped for categorical variables that had more than 2 categories, like monthly household income.

Generalized estimating equations (GEE) identified the associations between our two exposures, home distance to nearest agricultural field (home-ag distance) and agricultural surface area around participants homes for a 50m (home-ag SA_{50m}), 100m (home-ag SA_{100m}), and 200m (home-ag SA_{200m}) buffer, and our outcomes, BDI-II and GAD-7 scores. Both distance and surface area exposure proxies will be used as they are related yet capture different aspects of exposure. Home-ag distance, agricultural surface area, GAD-7, and BDI-II were not normally distributed, thus were natural log transformed. Beta estimates were then back-transformed to determine the percent difference (β%) in GAD-7 or BDI-II scores for a 10% increase in home-ag distance or home-ag SA by taking 1.10 to the power of the coefficient, subtracting 1, and multiplying by 100.

Two models were included for our GEE models, and confounders were identified *a priori*. Model 1 included anthropometric, demographic, and socioeconomic variables. This included age, BMI, gender (reference [ref]=Female, Male), race (ref=Indigenous, White Mestizo or Other), monthly household income (Less than $500, $500-$999, $1000+, ref=Prefer Not to Answer), and Education (ref=Less than High School Graduate, High School, Some College-to-College Graduate). It is possible that other secondary pesticide exposure pathways would confound our association between pesticide drift and urinary pesticide metabolite concentrations. Therefore, our Model 2 adjusted for Model 1 covariates, and additional adjustment for confounders that captured para-occupational [94,174,175], occupational [90], and home use pesticide exposure pathways [176]. These covariates included living with an agricultural or floricultural worker (ref=No, yes), working in agriculture or floriculture (ref=No, Yes), uses pesticides at work (ref=I do not know/Prefer not to answer, No, Yes), frequency of home pesticide use (ref=I do not know/Prefer not to Answer, Never, Rarely, Sometimes, Often, Always). We introduced an interaction term between home-ag distance and home-ag SA with (e.g., GAD-7 score=distance + sex + distance*sex + covariates). If the interaction was statistically significant ($p<0.05$), we stratified the GEE models by sex.

The model residuals from all GEE models were output and the Global Moran's index (I) test were conducted to understand whether there was spatial autocorrelation. A statistically significant Global Moran's I indicate that there is spatial clustering of errors, a potential indicator for model misspecification [106]. If clustering of residuals was identified, optimized Getis-Ord Gi* statistic identified hot and cold spots within a 90% confidence interval; golden search was used to identify an ideal Euclidean distance band [107,108]. Unlike the standard hotspot analysis tool, the optimized version applies the False Discovery Rate (FDR) correction method to account for multiple testing and spatial dependence, thereby reducing the potential for Type I errors. To de-identify individual's home, all non-significant Gi* statistic points were masked, and hotspot and cold spot diameters were increased to have a diameter of 1350m.

To determine whether there is spatial variation between the home-ag distance and agricultural surface area with depression and anxiety symptoms, GWR was conducted. The GWR model calculates a separate regression equation for each home, allowing the association to vary across the county [109]. The GWR models used golden search neighborhood selection method to identify the optimal distance band [109]. Models will assess for the association between a 1km increase in home-ag distance with depression and anxiety symptoms, adjusting for model 2 covariates. The GWR distance beta (β) coefficient and pseudo t-values were mapped, and each point was given an 1350m diameter for de-identification purposes.

Logistic regression models calculated the odds of having "Mild" and "Moderate or Severe" (reference [ref]= "Minimal") symptoms of depression and anxiety for a standard deviation increase in home distance (km) and surface area (km^2), adjusting for Model 1 and 2 covariates.

Statistical analysis was done using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and geospatial analysis was done using ArcGIS Pro 3.0.0 (ESRI Inc.).

Results

A total of 484 individuals were included in the analysis, of which 51.24% were females, 17.98% were Indigenous, and the average age was 20.29 years (range: 16-25 years) (Table 3.1.). Most of the participants (46%) were high school graduates and 52% had a household monthly income of less than $500. Most (73%) participants lived with an agricultural worker but 72% did not work in agriculture (including floriculture) and 67% did not use pesticides at work. The average BDI-II and GAD-7 score was 10.32 (SD=9.59; range=0-46) and 4.85 (SD=4.20; range=0-19) respectively. For BDI-II, 68.18% of the cohort had minimal symptoms, 15.08% had mild symptoms, 10.74% had moderate symptoms, while 5.99% of the cohort had severe depression symptoms. For GAD-7, 55.58% of the cohort had minimal anxiety symptoms, 31.82% had mild symptoms, 8.68% had Moderate symptoms, while 3.93% reported severe anxiety symptoms. GAD-7 and BDI-II scores were correlated ($r=0.68$, $p<0.0001$). Stratifying by a median split of home-ag SA_{50m}, individuals in the upper median were less likely to be Indigenous or but more likely to work in agriculture or floriculture.

Participant characteristics were mapped (Figure 3.2.). Most Indigenous participants lived in Tabacundo or Tupigachi (Figure 3.2.d). There was a cluster of individuals who were 20.7 to 22.6 years old living near the border of Tocachi and La Esperanza (Figure 3.2.b), and a cluster of individuals with some college to college graduates education levels in Malchinguí and La Esperanza (Figure 3.2.f). The other characteristics had fairly even distributions throughout Pedro Moncayo.

Results from the GEE models can be found in Table 3.2. For a 10% increase in home distance to the nearest agricultural field, there was a -2.94% (-4.77%, -1.10%) lower GAD-7 score and a -6.26% (-10.6%, -1.92%) lower BDI-II score using Model 1. When we controlled for additional pesticide exposure pathways (Model 2), the association strengthened for GAD-7 (-3.04% [-4.93%, -1.15%]) but stayed the same for BDI-II (-6.26% [-10.69%, -1.83%]). We did not find evidence of interaction by sex on any association.

The Global Moran's index tested for spatial autocorrelation of residuals from the GEE model 2 for the association between home-ag distance with BDI-II and GAD-7 score. The index for BDI-II (index=0.11, p<0.0001) and GAD-7 (index=0.07, p=0.006) were statistically significant, so hotspot analysis and GWR models were run. GWR assessed whether the linear associations between home-ag distance varied spatially (Figure 3.3.). For the BDI-II, a 1 km increase in home-ag distance was negatively associated with depressive symptomatology for all the parishes. However, the strongest negative associations were observed in southern Malchinguí ($-95.1 \leq \beta \leq -102.9$), which weakened as it North then further East. The association had a pseudo t-value below 1.96 for all parishes, except for points in Tupigachi. One the other hand, the strongest negative associations for GAD-7 were observed in Tupigachi, and weakened as it moves West. The range of the estimates was much lower for the GAD-7 ($-29.99 \leq \beta \leq -34.07$) that for BDI-II ($-47.25 \leq \beta \leq -102.87$). Hot and cold spots of depression symptoms were identified in Pedro Moncayo (Figure 3.4.). Optimized hotspot analysis identified a cold spot for depression symptoms in Tocachi and in the southern region of Tabacundo, and a hotspot in La Esperanza. No hot or cold spots were identified for anxiety symptoms, thus were not shown.

The logistic regression model identified the odds of having Mild and Moderate or Severe symptoms, compared to having minimal symptoms, for a standard deviation increase in home-ag distance (SD=16.93m), home-ag SA_{50m} (SD=0.001km^2), home-ag SA_{100m} (SD=0.004km^2) , or home-ag SA_{200m} (SD=0.014km^2) (Table 3.3.). Within a 50m buffer around the home, individuals who live with 0.001km^2 more agricultural surface area had a 30% higher risk of having mild anxiety symptoms (OR=1.3 [1.04, 1.63]). Living 16.93m farther from an agricultural field was protective against having Mild (OR=0.75 [0.6, 0.93]) and Moderate or Severe (OR=0.69 [0.5, 0.93]) anxiety symptoms. It also lowered the risk of having Moderate or Severe depression symptoms by 33% (OR=0.67 [0.45, 0.98]).

Discussion

This study analyzed the associations between two agricultural proximity constructs, home distance to the nearest agricultural field and agricultural surface areas within various buffers around the home, with depression and anxiety symptoms. The analysis identified that living farther from agriculture was associated with lower depression and anxiety symptoms, in models that both did and did not account for alternative pesticide exposure pathways. Spatial variation of these associations were identified in Pedro Moncayo, where the strongest association for BDI-II was identified in Malchinguí. The strongest associations for the GAD-7 were in Tupigachi, however the distribution was more uniform compared to the BDI-II. GAD-7 and BDI-II had cold spots for symptoms in Tocachi, while hotspots were found in La Esperanza for the BDI-II and Tupigachi for the GAD-7. Living farther from agriculture also decreased the risk of having Moderate or Severe depression and anxiety symptoms. These findings suggest that off-target drift of pesticides from agriculture in this region may be affecting the mental health of adults living in this agricultural community. Our results highlights the potential risk of having worse mental health outcomes that agricultural communities face and is one of the few studies that have looked at various constructs of residential proximity to agriculture and their association with depression and anxiety symptoms.

Other studies have found varying associations between proximity to agriculture with depression and anxiety symptoms, that both agree and disagree with our findings. There is limited evidence that directly looks at the associations between home-ag distance or home-ag SA with mental health outcomes, but some have used similar constructs. A study in Brazil compared hospitalization rates for mood disorders in agricultural communities with varying levels of pesticide expenditures [158]. Compared to residents of an agricultural community with lower pesticide expenditure, residents of agricultural communities with higher pesticide expenditure had higher risk for hospitalizations due to mood disorders [158]. This would be suggestive that agricultural areas with greater pesticide application rates would have a higher risk of mood disorders. In contrast to our findings, two studies reported either null or inverse associations. In a study of 57 adults in Bangladesh (μ_{age}=42.32 years), residential proximity to farming lands was not associated with depression symptoms, measured using the epidemiological studies depression scale (CES-D) [177]. The sample size was fairly small, so it is possible it was under powered to observe this association. In a sample of 147,549 Japanese individuals 65 or older, farmers who lived in regions with less agricultural density had higher prevalence of depression [178]. The authors attributed this difference to the lack of social support in regions where there is less agriculture [178], versus due to differential exposure to pesticides.

Geospatial patterns in associations between home-ag distance and depression symptoms may be due to differential pesticide application rates in the region. We observed a hotspot for BDI-II scores in La Esperanza in a region where there were older participants (Figure 3.2.b), mostly Some College-to-College graduates (Figure 3.2.f) who and under 25% of individuals worked in agriculture (Figure 3.2.g) or used pesticides at home (Figure 3.2.h). Outside of pesticide drift, these age, education, occupation, and personal pesticide use could have influenced the hotspot. But after adjusting for our covariates in the GWR, the strongest associations between home distance and lower BDI-II scores were observed in Malchinguí, not La Esperanza. This pattern of association was similar to what we observed for 2,4-D in Chapter 2, as the same Malchinguí region had the strongest positive association between increasing agricultural surface area and 2,4-D concentration ($103.3 \leq \beta \leq 111.6$), especially in the Middle to Southern region of this Parish. The Middle region of Malchinguí houses one of the largest industrial agricultural plots in Pedro Moncayo and can be seen in Figure 1.4.b, and it is possible that higher rates of 2,4-D application are occurring in these farms compared to others in the region. Compared to smallholder farming, industrial farming has a larger scale of operations, greater access to resources, and are more likely to use farming practices that do not use traditional or organic methods. Unfortunately, Ecuador lacks PUR policies, so more information is needed to confirm whether differential pesticide application rates for smallholder versus industrial agriculture occur in this region. No hotspots were observed for anxiety symptoms, despite seeing negative associations with home-ag distance across Pedro Moncayo. Variations in estimates were small (0-4.17), with the greatest estimates observed in Tupigachi. Tupigachi has the highest density of agriculture observed across the five parishes (30.1%; See Figure 1.8.), which may be why there are stronger associations observed in this parish.

Lower depression and anxiety symptoms with increasing home-ag distances may be due to a reduction in exposure to 2,4-D and malathion pesticides, and plausibly to reductions in other pesticide biomarkers that are used in agricultural crops but were not measured by our study. The results of Chapter 2 found that 2,4-D and MDA concentrations potentially stemmed from agricultural sources, as there were negative associations between home-ag distance or agricultural surface area with concentrations of these metabolites. The parent chemicals for these biomarkers are the herbicide 2,4-D, and the organophosphates malathion (MDA). Our findings align with other epidemiological studies that have identified a link between self-reported organophosphate exposure and symptoms of depression[102,153,158,162,179–181] , and with anxiety [180] to a lesser extent. Links between OP exposure and mood changes are frequently observed in individuals who have experienced high-dose exposure, like for cases of pesticide poisoning [161,162]. Among adolescents in ESPINA, participants that had lower concurrent AChE activity or greater inhibition of AChE activity between two examinations a few months apart, had higher depression symptoms [13,156]. Organophosphates are known to inhibit cholinesterase in the blood and brain[182,183], which can lead to the overstimulation of cholinergic nicotinic and muscarinic receptors in the nervous system [184]. Evidence has supported that adrenergic-cholinergic balance may influence depression[185], suggesting that changes in the central cholinergic system may contribute to increased depression symptoms[13].

Links between 2,4-D exposure and depression are more limited, and there are no studies in adolescents. Pesticide applicators who reported having used herbicides, like 2,4-D, had a higher risk of having a depression diagnosis in the Agricultural Health Study [186]. While amongst farmers between the ages of 37 and 78, individuals who reported ever using herbicides had 93% higher risk of having depression, classified as having ever been treated or hospitalized for depression [153]. Unlike these studies, a majority of this cohort did not report having occupational exposure to pesticides. While adjusting for alternative para-occupational, occupational, or home use pesticide exposure pathways, negative association between home-ag distance and GAD-7 score strengthened. Thus, pesticide exposure stemming from drift may be sufficient to observe mental health alterations. 2,4-D is a chlorophenoxy herbicide, typically used to control broad-leaved weeds or is used as a desiccant for corn [187]. Influences of 2,4-D exposure on mental health may be due to its toxicity. Exposure to this chemical has multiple mechanisms of toxicity, such as cell membrane damage, uncoupling of oxidative phosphorylation, and reduced metabolism of acetylcoenzye A[188]. 2,4-D exposure has been linked to worse neurobehavioral performance in ESPINA participants. Urinary 2,4-D concentration was also found to be negatively associated with five neurobehavioral domains, but was statistically significant for attention and inhibition, klanguage, and Memory and Learning [70].

The proportion of those experiencing anxiety and depression symptoms was lower in our cohort compared to other studies in the region. In a sample of 167 Ecuadorians (17-78 years) living in the Zamora-Chinchipe province of Ecuador, it was found that 28% of individuals had moderate depression while 32% of individuals had severe depression symptoms based on the BDI-II [189]. While another population of women farmers in Ecuador living in the Coastal and Highlands region reported 27.2% to 34.5% of their cohort had Moderate or Severe anxiety symptoms measured using the GAD-7 [190]. This study reported that 74% to 79% of women had at least one child, and women who did have children experienced higher anxiety symptoms. Only 5% of the ESPINA cohort reported having at least 1 child in 2022, thus might be why we did not see comparable anxiety symptoms. Our cohort is also younger compared to those studies, this may be why we observed lower rates of anxiety and depression symptoms. Findings in the literature may explain the difference by age, as there has been an observed U-shaped curve with depression across the lifespan, where symptomology is higher in adolescents and young adults, lowest in midlife, and higher later in life [191].

This study presents some strengths and limitations. A strength of this study is our ability to use agricultural proximity measures that have had some validation for the specific metabolites that they may represent. Given the lack of pesticide use reporting data in Ecuador, we are unable to weight our home-ag distance and agricultural surface area measures with reported pesticide use for these fields. By understanding the associations between these distance variables and urinary pesticide metabolites in this cohort, it improves potential hypothesis as to what pesticides may influence depression and anxiety symptoms. LGBTQ status has been associated with increased anxiety and depression symptoms [192], especially amongst minority populations [193]. However, we were unable to examine the relationships between affective symptoms and sexual orientation as sexual orientation data was not captured during the summer 2022 assessment. A limitation of this analysis is that the remotely sensed agricultural map had an accuracy of 72%, therefore, our home distance and surface areas measure are not perfect representations of agriculture in this region. Due to this, there is some noise in the exposure construct which may indicate that the associations would be stronger with greater accuracy of our agriculture map. However, the strong associations observed with home distance with depression and anxiety symptoms signals that the measure does capture agricultural adequately. Likewise, analyses in Paper 2 demonstrated the pesticides that are potentially being used on agriculture in this region included 2,4-D [193]. The BDI-II and GAD-7 may serve as indicators for severity of depression and anxiety; however, they are only captured at one time point and capture symptoms within a 2-week period. Repeated assessments of affective symptoms using tools like ecological momentary assessment would improve the characterization of pesticide exposure and affective symptoms. Replicating this study using clinical diagnoses would improve our understanding of the relationship between distance to agriculture with depression and anxiety.

Conclusion

The study analyzed the associations between home proximity to agriculture and mental health symptoms, finding that living farther from agricultural fields was linked to lower depression and anxiety symptoms. Spatial variations in these associations were observed, with specific areas, like Malchinguí and La Esperanza, demonstrating stronger associations. The findings suggest that pesticide drift from agricultural activities may negatively impact mental health, with hotspots for depression and anxiety symptoms identified in certain regions. This aligns with other studies indicating that higher pesticide use in agricultural areas is associated with increased mood disorders, although some research has found no or inverse relationships.

These results underscore the potential mental health risks of living near agricultural fields, particularly due to pesticide exposure.

Acknowledgements

Chapter 3, in part, is currently being prepared for submission for publication of the material. Briana N.C. Chronister; Jose Suarez-Torres; Danilo Martinez; Sheila Gahagan; Daniel Sousa; Humberto Parada Jr.; Jenny Quintana; Tommi Gaines; Raeanne C. Moore; Jose R. Suarez-Lopez. *Home proximity to agriculture is associated with greater depression and anxiety symptoms in adolescents and young adults living in an Ecuadorian agricultural community.* The dissertation author was the primary investigator and author of this paper.

Table 3.1. Participant demographics overall and stratified by a median split of agricultural surface area within 50m buffer.

Variables	Overall	Agricultural Surface Area within 50m Buffer		p-diff
		Lower Median $0m^2$ - $862m^2$	Upper Median $864m^2$ - $7019m^2$	
n	484	242	242	
Age, years	20.29 (1.84)	20.18 (1.85)	20.40 (1.83)	0.19
Sex				
Female, n (%)	248 (51.24%)	124 (51.24%)	124 (51.24%)	
Male, n (%)	236 (48.76%)	118 (48.76%)	118 (48.76%)	
Race[a]				<0.0001
Indigenous, n (%)	87 (17.98%)	24 (9.92%)	63 (26.03%)	
Mestizo, White, or Other, n (%)	397 (82.02%)	218 (90.08%)	179 (73.97%)	
Monthly Household Salary, USD				0.73
Less than $500, n (%)	252 (52.07%)	127 (52.48%)	125 (51.65%)	
$500-$999, n (%)	106 (21.90%)	53 (21.90%)	53 (21.90%)	
$1000+, n (%)	33 (6.82%)	18 (7.44%)	15 (6.20%)	
Prefer Not to Answer, n (%)	93 (19.21%)	44 (18.18%)	49 (20.25%)	
Education				0.60
Some High School and Below, n (%)	74 (15.29%)	36 (14.88%)	38 (15.70%)	
High School Graduate, n (%)	220 (45.45%)	108 (44.63%)	112 (46.28%)	
Some College-to-College Graduate, n (%)	190 (39.26%)	98 (40.50%)	92 (38.02%)	
Lives with an Agricultural or Floricultural Worker				0.12
No, n (%)	129 (26.65%)	72 (29.75%)	57 (23.55%)	
Yes, n (%)	355 (73.35%)	170 (70.25%)	185 (76.45%)	

%=percent, m=meters, km=kilometers, p-diff=p-difference, USD=United States Dollar
Values are means (SD) or medians (Q25, Q75) for continuous variables; ns and percentages for categorical variables.
[a] Two individuals self-identified as White and 1 individual self-identified as Other.

Table 3.1. continued. Participant demographics overall and stratified by a median split of agricultural surface area within 50m buffer.

		Agricultural Surface Area within 50m Buffer		
Variables	**Overall**	**Lower Median $0m^2$ - $862m^2$**	**Upper Median $864m^2$ - $7019m^2$**	**p-diff**
n	484	242	242	
Works in Agricultural or Floricultural Worker				0.01
No, n (%)	350 (72.31%)	189 (78.10%)	161 (66.53%)	
Yes, n (%)	134 (27.69%)	53 (21.90%)	81 (33.47%)	
How often do you use pesticides in your home or property?				0.09
Always, n (%)	5 (1.03%)	1 (0.41%)	4 (1.65%)	
Often, n (%)	20 (4.13%)	5 (2.07%)	15 (6.20%)	
Sometimes, n (%)	28 (5.79%)	12 (4.96%)	16 (6.61%)	
Rarely, n (%)	155 (32.02%)	82 (33.88%)	73 (30.17%)	
Never, n (%)	181 (37.40%)	91 (37.60%)	90 (37.19%)	
I do not know/Prefer not to answer, n (%)	95 (19.63%)	51 (21.07%)	44 (18.18%)	
Uses Pesticides at Work				0.08
Yes, n (%)	104 (21.49%)	48 (19.83%)	56 (23.14%)	
No, n (%)	325 (67.15%)	169 (69.83%)	156 (64.46%)	
I do not know, n (%)	55 (11.36%)	25 (10.33%)	30 (12.40%)	
BDI-II Depression Symptom Severity				0.95
Minimal (0 to 13), n (%)	330 (68.18%)	164 (67.77%)	166 (68.60%)	
Mild (14 to 19), n (%)	73 (15.08%)	39 (16.12%)	34 (14.05%)	
Moderate (20 to 28), n (%)	52 (10.74%)	26 (10.74%)	26 (10.74%)	
Severe (29 to 63), n (%)	29 (5.99%)	13 (5.37%)	16 (6.61%)	
BDI-II Raw Score, mean (SD)	10.32 (9.59)	9.99 (9.26)	10.66 (9.91)	0.44

%=percent, BDI-II=Becks Depression Inventory-II, m=meters, km=kilometers, p-diff=p-difference
Values are means (SD) or medians (Q25, Q75) for continuous variables; ns and percentages for categorical variables.

Table 3.1. continued. Participant demographics overall and stratified by a median split of agricultural surface area within 50m buffer.

		Agricultural Surface Area within 50m Buffer		
Variables	**Overall**	**Lower Median $0m^2$ - $862m^2$**	**Upper Median $864m^2$ - $7019m^2$**	**p-diff**
n	484	242	242	
GAD-7 Anxiety Symptom Severity				0.34
Minimal (0 to 4), n (%)	269 (55.58%)	143 (59.09%)	126 (52.07%)	
Mild (5 to 9), n (%)	154 (31.82%)	69 (28.51%)	85 (35.12%)	
Moderate (10 to 14), n (%)	42 (8.68%)	20 (8.26%)	22 (9.09%)	
Severe (15 to 21), n (%)	19 (3.93%)	10 (4.13%)	9 (3.72%)	
GAD-7 Total Score, mean (SD)	4.85 (4.20)	4.71 (4.20)	4.98 (4.20)	0.50
Distance to Agriculture, m	16.39 (7.08, 27.89)	29.13 (16.68, 39.96)	10.35 (2.50, 15.84)	<0.0001
50m Buffer km^2	0.001 (0.000, 0.002)	0.000 (0.000, 0.001)	0.002 (0.001, 0.003)	<0.0001
100m Buffer km^2	0.005 (0.003, 0.008)	0.003 (0.002, 0.005)	0.008 (0.006, 0.011)	<0.0001
150m Buffer km^2	0.014 (0.009, 0.019)	0.011 (0.007, 0.014)	0.017 (0.013, 0.023)	<0.0001
200m Buffer km^2	0.025 (0.017, 0.033)	0.021 (0.013, 0.027)	0.031 (0.023, 0.040)	<0.0001

%=percent, GAD-7= Generalized Anxiety Disorder-7, m=meters, km=kilometers, p-diff=p-difference
Values are means (SD) or medians (Q25, Q75) for continuous variables; ns and percentages for categorical variables.

Table 3.2. The percent difference in GAD-7 or BDI-II score for a 10% increase in distance to the nearest agricultural field, or 10% increase in agricultural surface area within home buffer regions (50m -200m).

	GAD-7		BDI-II	
Exposure	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Residential distance to the nearest agricultural field (km)	-2.94 (-4.77, -1.10)**	-3.04 (-4.93, -1.15)**	-6.26 (-10.6, -1.92)**	-6.26 (-10.69, -1.83)**
Surface Area of Agriculture Within Different Buffer Sizes (km^2)				
50m	26.18 (-3.99, 56.35)*	25.38 (-5.34, 56.11)	56.22 (-17.23, 129.68)	52.79 (-21.68, 127.27)
100m	2.59 (-6.69, 11.86)	1.26 (-8.14, 10.66)	17.16 (-5.82, 40.14)	12.99 (-9.99, 35.96)
200m	0.02 (-0.04, 0.08)	0.01 (-0.05, 0.07)	0.08 (-0.05, 0.2)	0.05 (-0.08, 0.17)

BDI-II=Beck's Depression Inventory II, GAD-7=General Anxiety Disorder, km=kilometers, m=meters.
**$p<0.05$, *$p<0.10$
Model 1 adjusted for age, gender (Female [ref], Male), race (Indigenous [ref], White Mestizo or Other), monthly household income (Less than $500, $500-$999, $1000+, Prefer Not to Answer [ref]), and Education (Less than High School Graduate [ref], High School, Some College to College Graduate).

Model 2 adjusts for model 1 and living with an agricultural or floricultural worker (No [ref], yes), working in agriculture or floriculture (No [ref], Yes), uses pesticides at work (I do not know/Prefer not to answer [ref], No, Yes), frequency of home pesticide use (I do not know/Prefer not to Answer [ref], Never, Rarely, Sometimes, Often, Always).

Table 3.3. The odds of having Mild or Moderate or Severe (vs. Minimal) symptoms for a standard deviation increase in home distance to the nearest agricultural field or agricultural surface area within a 50m, 100m, and 200m buffer.

	GAD-7			BDI-II		
	Minimal	**Mild**	**Moderate or Severe**	**Minimal**	**Mild**	**Moderate or Severe**
Residential distance to the nearest agricultural field (km)	reference	0.75 (0.6, 0.93)**	0.69 (0.5, 0.93)**	reference	1.04 (0.79, 1.36)	0.67 (0.45, 0.98)**
Surface Area of Agriculture Within Different Buffer Sizes (km^2)						
50m	reference	1.3 (1.04, 1.63)**	1.27 (0.93, 1.72)	reference	0.97 (0.73, 1.29)	1.12 (0.77, 1.62)
100m	reference	1.02 (0.82, 1.28)	1.09 (0.79, 1.49)	reference	0.91 (0.69, 1.21)	0.98 (0.67, 1.44)
200m	reference	0.96 (0.76, 1.2)	1.02 (0.73, 1.44)	reference	1.03 (0.76, 1.4)	0.99 (0.65, 1.51)

BDI-II=Beck's Depression Inventory-II, GAD-7=General Anxiety Disorder-7, m=meters, km=kilometers.
**$p<0.05$, *$p<0.10$

Model adjusted for age, gender (Female [ref], Male), race (Indigenous [ref], White Mestizo or Other), monthly household income (Less than $500, $500-$999, $1000+, Prefer Not to Answer [ref]), and Education (Less than High School Graduate [ref], High School, Some College to College Graduate), living with an agricultural or floricultural worker (No [ref], yes), working in agriculture or floriculture (No [ref], Yes), uses pesticides at work (I do not know/Prefer not to answer [ref], No, Yes), frequency of home pesticide use (I do not know/Prefer not to Answer [ref], Never, Rarely, Sometimes, Often, Always).

A standard deviation of the proximity variables are 16.93m/0.02km for home-ag distance, 0.001 km^2 for a 50m buffer, 0.004 km^2 for a 100m buffer, and 0.014 km^2 for a 200m buffer.

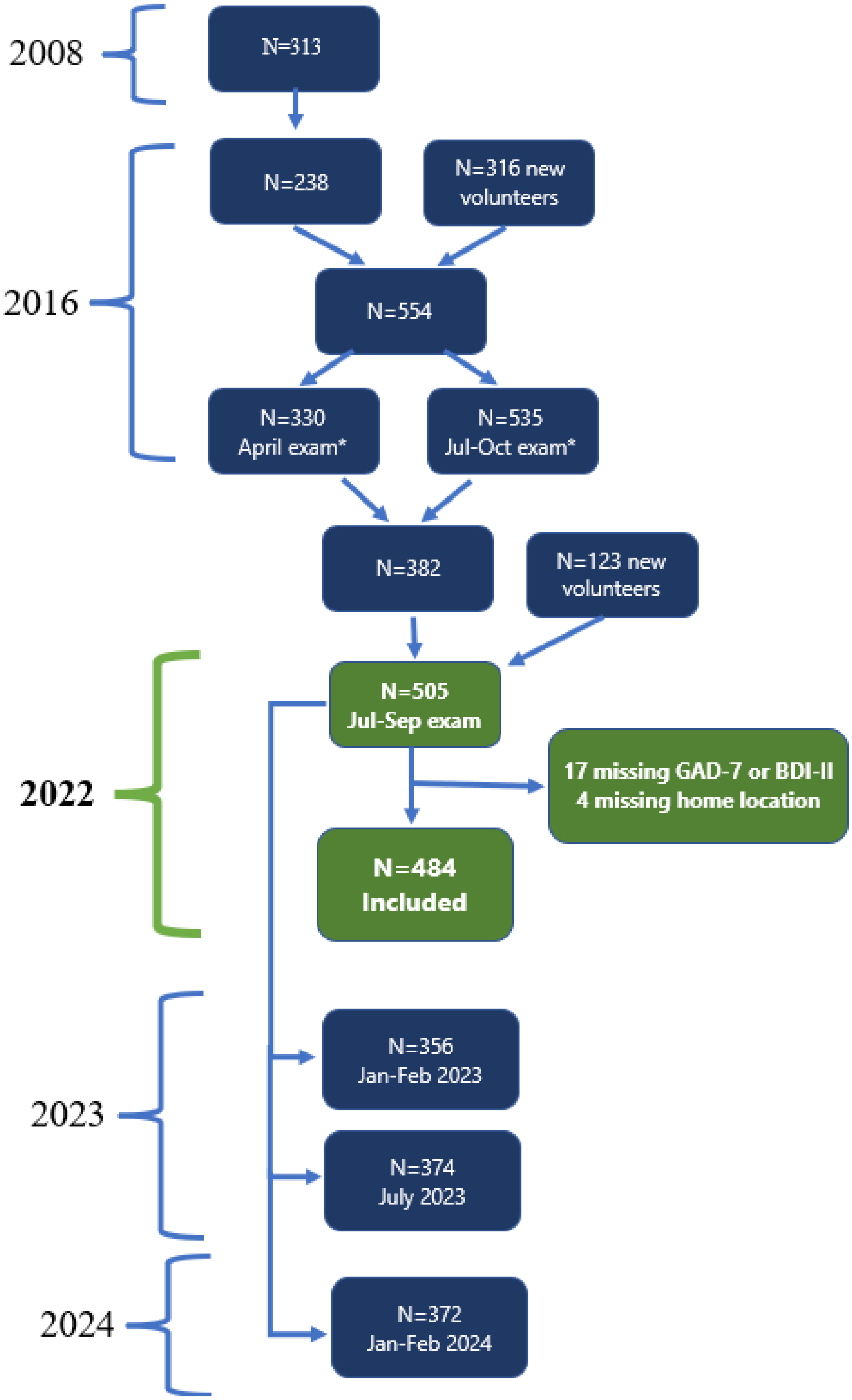


Figure 3.1. Participant flowchart in person ESPINA assessments from 2008 to February 2024.

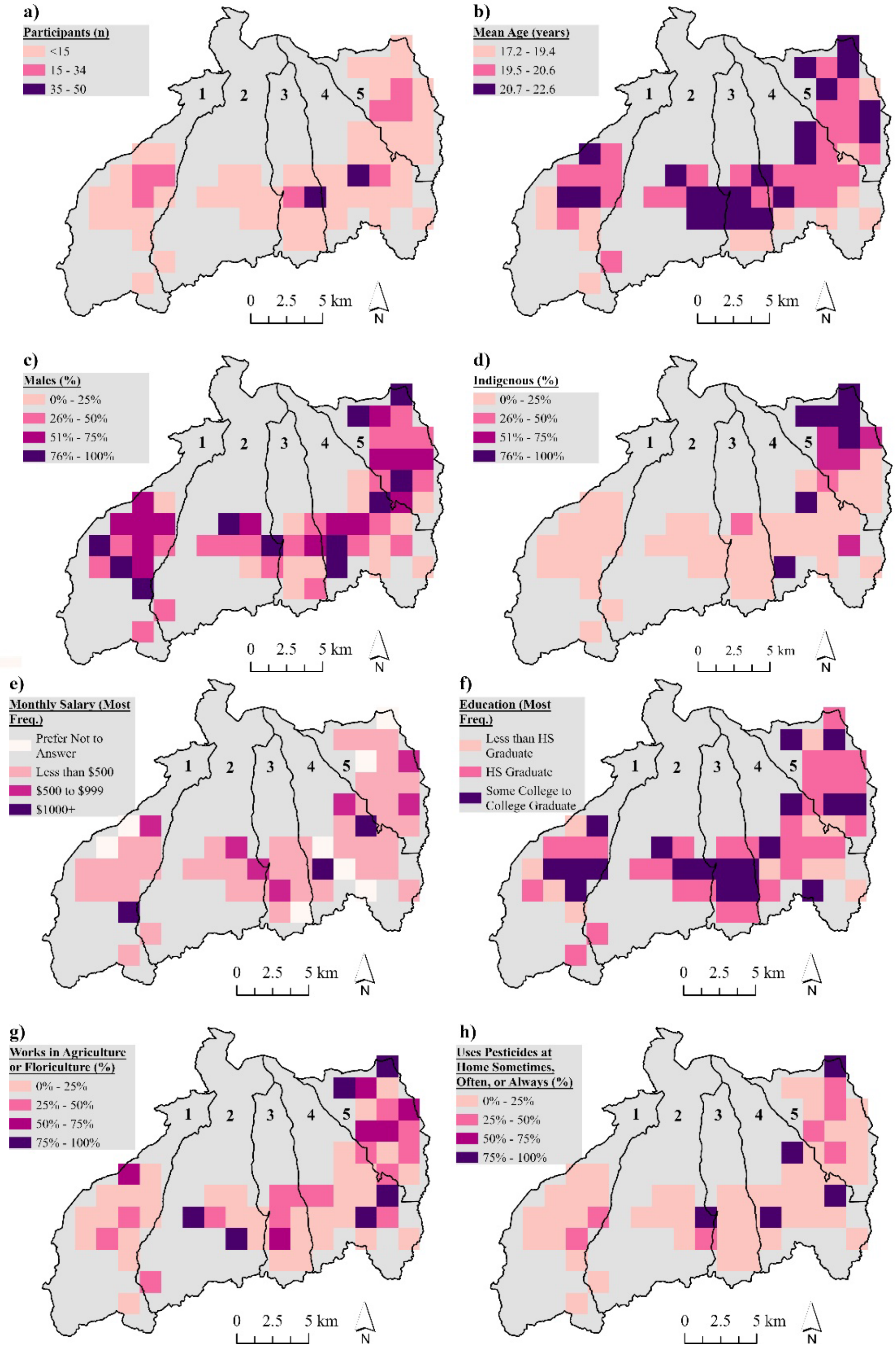


Figure 3.2. Participant characteristics distributions across Pedro Moncayo. 1=Malchinguí, 2=Tocachi, 3=La Esperanza, 4=Tocachi, 5=Tupigachi.

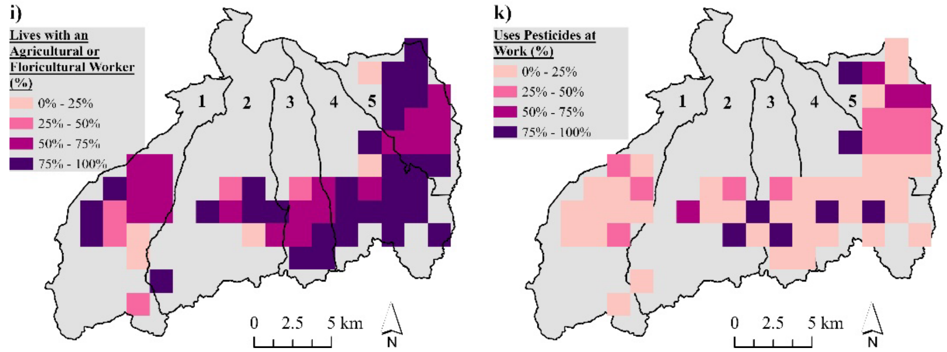
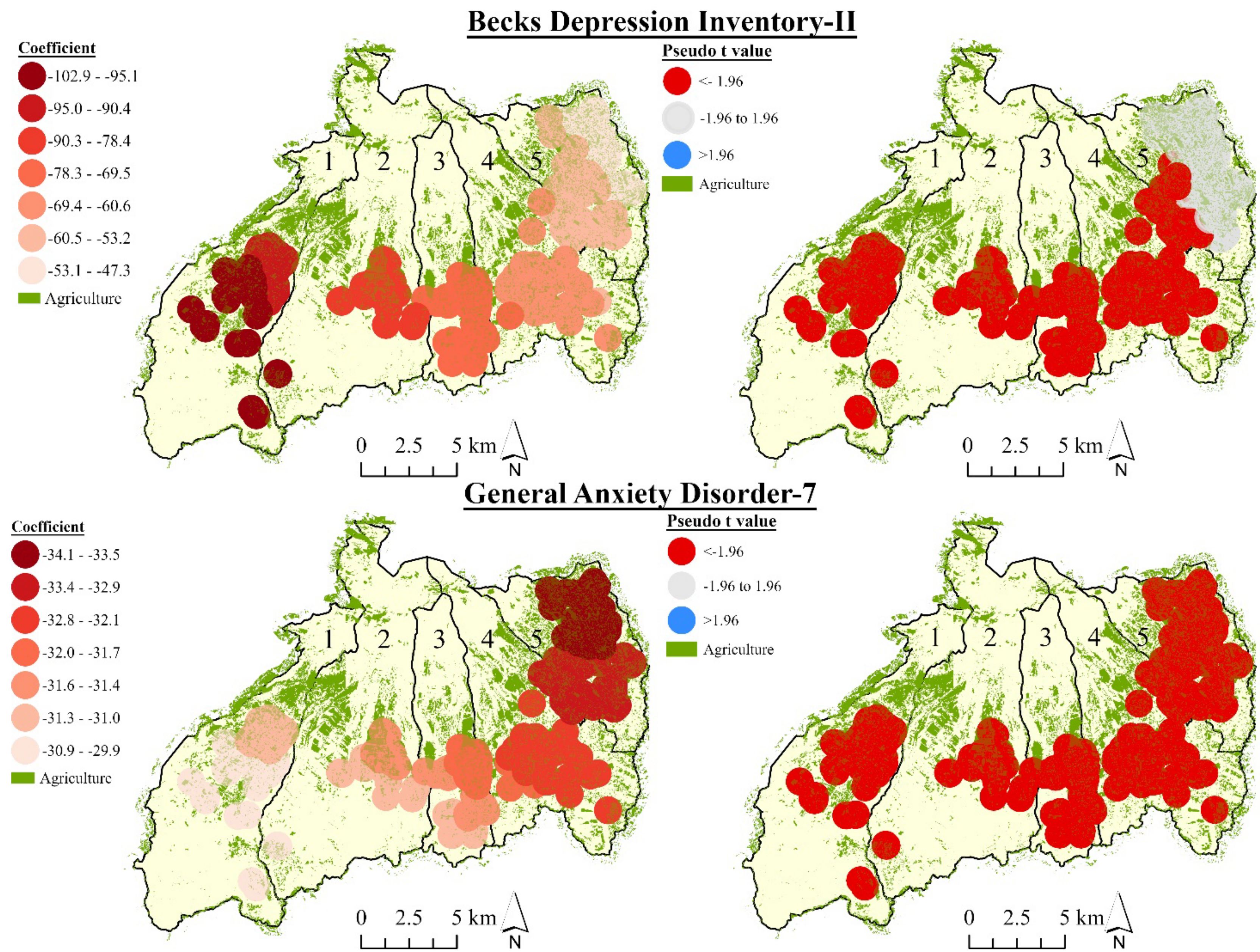


Figure 3.2. continued. Participant characteristics distributions across Pedro Moncayo. 1=Malchinguí, 2=Tocachi, 3=La Esperanza, 4=Tocachi, 5=Tupigachi.

Figure 3.3. Geospatially weighted regression looking at the association between a 1 km increase in home distance to the nearest agricultural field, and depression or anxiety symptoms. Models were adjusted for age, gender, race, monthly household income, and Education, living with an agricultural or floricultural worker, working in agriculture or floriculture, uses pesticides at work, frequency of home pesticide use. 1=Malchinguí, 2=Tocachi, 3=La Esperanza, 4=Tocachi, 5=Tupigachi.


Becks Depression Inventory-II
Coefficient
-102.9 - -95.1
-95.0 - -90.4
-90.3 - -78.4
-78.3 - -69.5
-69.4 - -60.6
-60.5 - -53.2
-53.1 - -47.3
Agriculture
Pseudo t value
<- 1.96
-1.96 to 1.96
>1.96
Agriculture
1
2
3
4
5
0 2.5 5 km
N
General Anxiety Disorder-7
Coefficient
-34.1 - -33.5
-33.4 - -32.9
-32.8 - -32.1
-32.0 - -31.7
-31.6 - -31.4
-31.3 - -31.0
-30.9 - -29.9
Agriculture
Pseudo t value
<-1.96
-1.96 to 1.96
>1.96
Agriculture

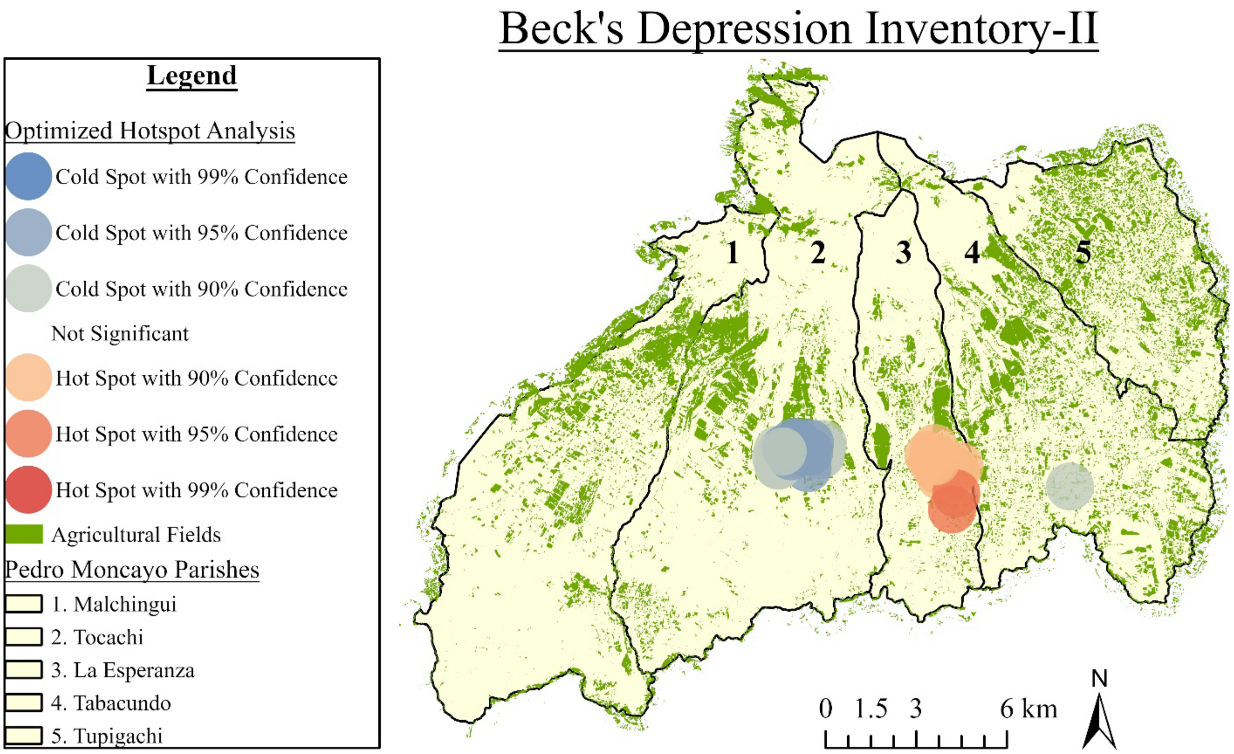


Figure 3.4. Optimized hotspot analysis of depression symptoms in Pedro Moncayo. Hotspot analysis for anxiety symptoms are not shown as only not significant points were observed. 1=Malchinguí, 2=Tocachi, 3=La Esperanza, 4=Tocachi, 5=Tupigachi.

CONCLUSION

Contemporary data on agricultural locations is lacking in Pedro Moncayo, Ecuador, complicating the estimation of pesticide drift by agricultural sources and subsequent health effects from pesticide exposure. The region's floriculture industry has surged since 1983, making Pedro Moncayo a major center for rose production, and contributing to significant pesticide use. Individuals living near agricultural areas face risks from pesticide drift. Using can be estimated from agricultural pesticide use reports. Ecuador lacks pesticide use reporting policies which further complicates accurate exposure assessment. Despite the widespread floriculture industry in this region, preliminary research in adolescents living in Pedro Moncayo found that individuals whose homes were farther from floricultural greenhouses had higher concentrations of pesticide metabolites like TCPY. This means that other agricultural production, like corn or grains, may also be a source of pesticide exposure in this community. The study highlights the need for better understanding and monitoring of pesticide exposure, particularly its impact on mental health in young adults, given the high prevalence of agriculture and floriculture in the region. Thus, this study had three aims. Aim 1 was to use manifold learning and the Segment Anything Model to identify small- and large-scale agriculture in an equatorial agricultural community. Aims 2 and 3 used the agricultural map from Aim 1 and ESPINA 2022 data. Aim 2 identified whether home distance to the nearest agriculture field, or agricultural field surface area near homes, are associated with urinary metabolite concentrations of organophosphate, pyrethroid, and herbicide pesticides amongst Ecuadorian adults. Lastly, Aim 3 identified whether home distance to the nearest agricultural field, or agricultural field surface area near homes, are associated with depression and anxiety symptoms amongst Ecuadorian adults.

Chapter 1 (Aim 1) examined the use of manifold learning (UMAP) and object segmentation (SAM) on Sentinel-2 V fraction time series and PlanetScope EVI2 time series to identify agriculture in Pedro Moncayo, Ecuador. PlanetScope images demonstrated better precision (76.8%) and specificity (93.2%), while Sentinel-2 images provided higher accuracy (62.0%) and sensitivity (44.3%) in Malchinguí. The combination of T17NQA and T17NRA Sentinel-2 tiles produced an agricultural map with 72.57% accuracy and 75.31% precision. UMAP effectively differentiated vegetation clusters, whereas SAM achieved moderate success in segmenting high-granularity images but struggled with lower granularity and larger areas. Despite these challenges, this study is the first to integrate manifold learning and SAM for agricultural characterization using Sentinel-2 and PlanetScope imagery. The results emphasize the need for further research and parameter optimization to improve the effectiveness of these models in remote sensing applications.

Chapter 2 (Aim 2) examined the relationship between urinary pesticide metabolite concentrations and two agricultural proximity measures: home distance to the nearest agricultural field and agricultural surface area within buffers around the home. Associations were found between these measures and metabolites of organophosphates, pyrethroids, and herbicides, with some differences by sex. For men, living farther from agriculture was associated with lower 2,4-D levels, while higher agricultural density within 50m was associated with higher concentrations, particularly in Malchinguí. An increase in agricultural surface area also raised the odds of having detectable MDA levels, especially in men. PNP levels were lower with higher agricultural surface area around the home, suggesting exposure might originate from floricultural sources rather than agriculture. Additionally, home-ag distance was positively associated with 3-PBA levels, with the strongest estimates in southern Malchinguí. The findings suggest that 2,4-D and MDA exposures likely stem from agricultural sources, while PNP, TCPY, and 3-PBA exposures likely come from floriculture. These associations underscore the complexity of pesticide exposure dynamics influenced by agricultural practices, location, and gender-specific factors. Understanding the patterns of pesticide use and extent of drift in agricultural communities is crucial for creating public health interventions aimed at reducing exposure, as complete eradication of pesticides is unlikely. Future studies should incorporate participant movement patterns and create maps of unique crop types to better characterize the pattern of pesticide drift.

Chapter 3 (Aim 3) analyzed the associations between home distance to agriculture and mental health symptoms, finding that living farther from agricultural fields was linked to lower depression and anxiety symptoms. Spatial variations in these associations were observed. The negative association between living farther from agriculture with depression was strongest in Malchinguí, where there is a large industrial agriculture presence. While the strongest association for anxiety symptoms was located in Tupigachi, which had the most agricultural surface area. The spatial variation in associations demonstrates that geographical differences in pesticide drift may be occurring, that could potentially be due to differential patterns of pesticide applications rates between industrial and smallholder farming in chemicals like 2,4-D. It may also be due to differential pesticide use patterns by farmers, and by crop type. These results elucidate the potential mental health risks of living near agricultural fields, potentially due to agricultural pesticide drift.

A recurrent theme throughout these three chapters is the importance of location when it comes to pesticide exposure in agricultural communities. With the global patterns of pesticide use in agriculture, it is unlikely that pesticide use in agricultural practices will completely be eradicated in agricultural communities like Pedro Moncayo. Characterizing pesticide drift patterns can help improve public health interventions and inform recommendations that would help mitigate exposure to pesticides. This is especially true since a majority of participants did not report using pesticides in the home, nor work in agriculture or farming, but still had evidence of pesticide exposure based on urinary pesticide metabolite concentrations. Although pesticide use in the region may be pervasive, there are regions that seem to have higher pesticide application rates, like the middle of Malchinguí, or have greater density of agriculture, like Tupigachi. These findings could inform decision-making among community members when deciding on where to live, or where their leisure time is spent. Although we suspect higher applications rates in industrial agriculture, associations between home proximity to agriculture and urinary metabolite concentrations throughout the region suggest that there is potentially pesticide use in small holder farming as well. Improving education on alternative pest control methods could greatly reduce exposure of community members as a whole. Further work needs to be done to enhance agricultural mapping, characterize pesticide drift, and understand the relationship between pesticide exposure and mental health as previously described.

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