Spatial Variations in Otitis Media, Hearing Impairment, and Cognitive Development among a Southeast Asian Population

Dissertation

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By

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Abstract

Background: Otitis media (OM), a prevalent middle ear inflammation, is a leading cause of medical consultations and antibiotic prescriptions among children globally, imposing significant financial burdens on healthcare systems. Untreated acute OM can progress to chronic suppurative OM, a primary cause of pediatric hearing loss and potential cognitive delays, affecting speech acquisition. Environmental factors such as air pollution and socioeconomic conditions contribute to OM's multifactorial etiology, yet research on these associations, especially in low- and middle-income countries (LMICs), remains limited. The impact of preventive measures such as pneumococcal conjugate vaccines (PCVs), known to reduce AOM incidence and subsequent hearing loss, on cognitive development requires further investigation. This dissertation addresses these gaps through an aggregated analysis integrating spatial data, examining OM prevalence, hearing loss, and cognitive development among children in Bohol, Philippines, while identifying demographic, environmental, and socioeconomic correlates.

Methods: Utilizing data from a follow-up assessment of a randomized controlled trial (ISRCTN 62323832) evaluating an 11-valent PCV in Bohol, this dissertation integrated demographic, socioeconomic, and health data collected via parental questionnaires, ear assessments, and cognitive tests. This study redefined neighborhoods using a square grid methodology to standardize geographic units. Then I aggregated participant data at the neighborhood level and created maps to visualize the spatial distribution of each outcome. I assessed global spatial autocorrelation using Moran’s I index, supplemented by Local Indicators of Spatial Association (LISA) maps to pinpoint local clusters. The three specific aims were: (1) to identify factors associated with OM prevalence using multivariable ordinary least squares (OLS) and spatial regression models; and to assess spatial heterogeneity in associations using geographically weighted regression (GWR); (2) to examine characteristics associated with hearing loss incidence through Poisson regression and evaluate spatial non-stationarity of the associations with GWR; and (3) to assess factors associated with cognitive development and regional variations in the associations using OLS regression and GWR.

Results: Areal OM prevalence averaged 41% and exhibited significant spatial clustering (Moran’s $I=0.31$, $p<0.001$). OM prevalence was associated with household size, maternal insurance coverage, breastfeeding practices, and exposure to traffic-related air pollution. Neighborhood-level hearing loss prevalence averaged 8.5% without significant global spatial autocorrelation (Moran’s $I=0.048$, $p=0.26$), with associations found for OM prevalence, distance from hospitals, household smoking exposure, and household wealth. Cognitive development showed significant global spatial autocorrelation (Moran’s $I=0.17$, $p<0.001$), and was associated with OM prevalence, household wealth, and parental education levels. GWR identified regional variations in these associations, emphasizing the spatial heterogeneity. PCV coverage was not statistically significantly associated with any outcomes on neighborhood level.

Discussion: The dissertation explores critical health and developmental outcomes among a cohort of children in Bohol, Philippines, within the context of an LMIC. Aim 1 reveals the role of reducing respiratory pathogen exposure, enhancing breastfeeding rates, and promoting health insurance coverage in mitigating OM prevalence. Surprisingly, proximity to healthcare facilities did not significantly correlate with OM prevalence, highlighting multifaceted influences of healthcare accessibility. Aim 2 delves into pediatric hearing loss, emphasizing its associations with poor healthcare access and household smoking, with socioeconomic disparities showing the protective effect of economic advantage. Aim 3 demonstrates that higher household wealth and parental education correlate with improved cognitive outcomes. The spatial approach, integrating GWR, illuminates localized variations in each outcome, suggesting tailored public health strategies are crucial. While the cross-sectional nature of this study limits causal inference, the findings advocate for comprehensive interventions addressing health and socioeconomic disparities. These insights, although specific to the study population, provide valuable context to inform public health strategies in other LMICs. The methodologies employed offer a framework guiding similar public health interventions across diverse LMIC settings, facilitating targeted and effective approaches to enhance child health and development outcomes. This dissertation advocates for nuanced, community-specific policies and practices to mitigate health disparities, thereby contributing to the broader effort to improve global child health.

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Chapter 1. Introduction and Specific Aims

Otitis media (OM), which is middle ear inflammation, occurs as a result of influenza, sore throat, or respiratory infection, and it ranks among the primary reasons for medical consultations and antibiotic prescriptions among children worldwide (1-3). It also imposes a significant financial burden on the healthcare system (1, 4). Untreated or incompletely treated acute otitis media (AOM) is likely to develop into chronic suppurative otitis media (CSOM), which is one of the main causes of mild to moderate hearing loss among children (1, 5-8). Hearing loss may lead to delayed development of receptive and expressive communication skills (speech and language) (9). The younger the age of onset of hearing impairment, the greater the impact on speech and language development (10, 11). OM may also have a negative effect on cognitive development, specifically development of language skills (10, 12-21). Early diagnosis and effective treatment of CSOM can improve language and cognitive development (11, 22-24).

Both OM and hearing impairment are multifactorial, including both individual factors and environmental or structural causes, such as air pollution, heavy metal exposure, contaminated water, access to care, and overcrowding (3, 7, 8, 25-32). Studies in high-income countries have explored environmental factors of OM such as air pollution, but they used data from fixed site monitoring stations or an urban/rural classification to measure the exposure (25-28). These methods are too coarse to accurately describe spatial heterogeneity of air pollution exposure. To better understand the association between environmental factors and OM and its sequelae, we must first describe the spatial heterogeneity of OM and hearing impairment, and then identify the associated factors using spatial analysis methods. Knowledge of spatial heterogeneity of diseases and associated risk factors can guide intervention planning and evaluation, especially in low- and middle- income countries (LMICs) that bear most burden of the disease yet have limited resources. Spatial variations in OM, hearing loss and cognitive development have not been examined among children in LMICs.

In industrialized countries, different formulations of pneumococcal conjugated vaccines (PCVs) have been shown to prevent AOM, and hence reduce the burden of CSOM and hearing loss (6-8, 31, 33-38). Since 2007, the World Health Organization (WHO) has recommended that childhood immunizations schedules globally include PCV, and this recommendation still stands in their latest position paper published in 2019 (39-41). Vaccinations which reduce the risk of AOM, CSOM and hearing loss may therefore result in stronger cognitive development, however few studies have investigated these secondary impacts of any type of vaccination (42-48).

To date, no randomized controlled trials on PCV in LMICs have examined the long-term benefit of PCV on the prevention of ear diseases and their sequelae, including hearing loss and the potential impact on cognitive development, one of the core metrics to evaluate long-term impact of vaccines (42, 49). Preliminary analysis indicated spatial variation in OM, hearing loss, and cognitive development among a cohort of children in Bohol, Philippines. Therefore, in my dissertation, the objective was to better understand the spatial variations of OM, hearing loss, and cognitive development in that population, and to identify the key characteristics associated with any variation. The long-term secondary impact of vaccine coverage among children on these outcomes was also examined. This information can guide future interventions by identifying target areas and populations to work with and improve health equity.

I performed secondary data analysis with data from three sources. The first was a follow-up assessment during 2016-2019 of a randomized controlled trial in Bohol, Philippines in July 2000 to December 2004 that studied the effectiveness of PCV against pneumonia (50). Shapefiles of political boundaries, roads, and healthcare facilities were downloaded from Philippine Geoportal (https://www.geoportal.gov.ph) and the Bohol Provincial Planning and Development Office (https://ppdo.bohol.gov.ph/). The specific aims for my dissertation are as follows:

Aim 1: To identify the key characteristics associated with OM in Bohol, Philippines and determine if the key characteristics are consistent across the study area.

Research questions: Are demographic, environmental, and socioeconomical characteristics, including PCV coverage in the neighborhood, preschool and daycare attendance, low birth weight, parental education and employment, smoke exposure, malnutrition, breastfeeding, access to healthcare, and traffic-related air pollution, associated with the observed spatial variation in OM across the study area? Are these associations spatially consistent within the study area?

Working hypothesis:

I hypothesized that variables that vary geographically (e.g., access to healthcare, air pollution exposure and vaccine coverage in the neighborhood) were associated with local OM rate. I further hypothesized that key characteristics vary across the study area, so that certain areas would benefit more from higher vaccine coverage in the neighborhood.

<u>Aim 2</u>: To identify the key factors associated with hearing loss among a cohort of children in Bohol, Philippines and determine if the key factors are consistent across the study area.

Research questions: Are factors, including PCV coverage in the neighborhood, local prevalence of OM, household socioeconomic status, low birth weight, parental education and employment, smoke exposure, malnutrition, distance to healthcare, and traffic-related noise pollution associated with pediatric hearing loss among a cohort of children in Bohol, Philippines? Are these associations spatially consistent across the study area?

Working hypothesis:

I hypothesized that local prevalence of hearing loss was associated with geographically related factors, including vaccine coverage in the neighborhood, distance to healthcare, and traffic-related noise exposure.

<u>Aim 3</u>: To identify the key factors associated with cognitive development among a cohort of children in Bohol, Philippines, and examine whether the key factors are consistent across the study area.

Research questions: Is the observed spatial variation in cognitive development associated with factors such as PCV coverage in the neighborhood, household socioeconomic status, preschool attendance, parental education and employment level, smoke exposure, breastfeeding, pediatric hearing loss, and traffic-related noise pollution.

Working hypothesis:

I hypothesized that environmental factors related to participants' residential locations were associated with the variations in cognitive development. I further hypothesized that local hearing loss prevalence was associated with full scale IQ.

Chapter 2. Background and Significance

2.1 Epidemiology of Otitis Media

2.1.1 Overview

Otitis media (OM) is middle ear inflammation or infection of bacterial or viral origin, which may occur following a cold, influenza, or respiratory infection (1, 3, 51). Although it affects all age groups, OM most commonly occurs among young children (3, 17, 52). It is one of the most frequent diseases among young children worldwide and a leading cause of medical consultation and antibiotics prescriptions (1, 2, 53). Before the introduction of the PCV, over 80% of children experienced at least one episode of OM by the age of 3 years, 80% to 90% experienced a case of OM throughout their life, and 40% had 6 or more recurrences by their 7th birthday (3, 5, 17).

OM is a spectrum of diseases including acute otitis media (AOM), otitis media with effusion (OME), and chronic suppurative otitis media (CSOM) (34). As an umbrella term, OM stands for middle ear inflammation with no reference to pathogenesis or etiology; AOM is a rapid onset of signs and symptoms of middle ear inflammation; OME refers to fluid in the middle ear with no signs or symptoms of an ear infection; and CSOM is a spontaneous perforated tympanic membrane (TM) with persistent middle ear drainage for more than 2-6 weeks (3, 54, 55).

Estimates of annual number of cases worldwide are 709 million AOM cases, with half of those in children under the age of five years, and 31 million CSOM cases, with a quarter of them in under-five years (5). Low- and middle- income countries (LMICs) are disproportionally affected by OM. The point prevalence of AOM measured in a 3-day survey in Philippines was 9.6% in 2010 (56). Globally, the prevalence of OM-related hearing impairment was estimated at 31 per 10,000, and 21,000 people die of OM complications, mainly through brain abscess and meningitis (5, 57). AOM incidence in South Asia, sub-Saharan Africa, and Oceania is two to eight times higher compared to other the World Health Organization (WHO) areas (5). The prevalence of OM-related hearing impairment was the highest in Asia South (97.04 per 10,000), followed by Oceania (51.23 per 10,000), and West, East, and Central Sub Sahara African (30 to 35 per 10,000). In Indonesia, OM-related disabling hearing loss was found at a rate of 44.2 per 10,000, and OM contributed to 57% of all hearing loss among school children (58).

OM also imposes a huge economic burden. The annual costs of disease caused by OM is estimated at $3-5 billion for the United States, and the estimated costs per AOM episode varies from $108 to $1330 (1, 4). The true impact would be larger considering indirect, non-medical costs (1).

2.1.2 Sequelae of OM

OM can be treated with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) and/or antibiotics and the prognosis for most OM patient is excellent (3, 59, 60). Early diagnosis and effective antibiotic therapy are core components for treatment.

However, once untreated or under-treated OM continues to a late chronic phase, it could develop into well-established, intractable mucoperiosteal disease that leads to hearing loss and bring long-term sequelae (55). The sequelae of AOM include TM scarring and hearing impairment from chronic suppurative CSOM (3, 5). TM scarring can irritate nerve endings and cause tinnitus.

Chronic middle ear diseases are the main cause of mild to moderate hearing impairment among children, disproportionally burdening the developing world, where hearing impairment and deafness cause enormous educational, vocational, and social problems, and influence quality of life (Figure 2) (3, 5, 55, 61). Therefore, it is crucial to identify key characteristics associated with OM to prevent these severe outcomes and improve the quality of life for millions of affected individuals, especially in LMICs where the burden is greatest.

Globally, the prevalence of OM-associated hearing loss is estimated to be 31 per 10,000 individuals (range: 0.7-95) (5). As an important cause of preventable hearing loss, CSOM is most likely to follow incompletely treated AOM, particularly in developing countries (Figure 1) (5). According to WHO estimates in 2021, over 5% of the population worldwide have disabling hearing loss, including 34 million children (62). Approximately 80% of those with disabling hearing loss live in LMICs, mainly in Africa, the Western Pacific regions, and the Southeast Asia (62).

A disease map showing the geographical variability of OM and its sequelae can help identify regions with particularly high or low rates, which can guide future studies in defining and testing hypotheses about a disease. The spatial patterns of OM have only been examined at a global level using WHO regions (Figure 1 and Figure 2) (5). To my knowledge, no published study has described the pattern of OM and its sequelae at a subnational level in LMICs, which bear the greatest burden of OM sequelae and have the most limited public health resources.

2.1.3 Risk Factors

OM is a multifactorial disease, resulting from both host factors and environmental factors (3). On individual level, people are most susceptible during 6-24 months of age, and OM is slightly more common in males (3, 59, 63). Race/ethnicity, immunodeficiencies, genetic predisposition, family history of recurrent AOM, vitamin A deficiency, allergies, craniofacial anomaly, upper respiratory tract infections (URTIs), and cochlear implants have all been identified as factors associated with OM risk (3, 30, 59). Environmental factors associated with increased OM risk include passive smoke exposure, having older siblings, low socioeconomic status, daycare attendance, use of pacifier, and lack of breastfeeding (1, 3, 30, 59, 64-69). In LMICs, the risk of AOM developing into CSOM and its complications also increases with malnutrition, human immune-deficiency virus (HIV) infection, tuberculosis, malaria, contaminated water, poor hygiene, overcrowding, and limited access to healthcare (5, 32, 69, 70).

Limited access to healthcare is considered a major risk factor for OM and its sequelae in different settings while it is not fully studied, especially in LMICs (5, 69). In addition to whether the family can afford health care, distance from the health care facilities is an important metric for healthcare access, especially in LMICs (71). The few studies on distance to healthcare and OM and its sequalae had inconclusive results. Children in India who lived closer to a healthcare facility had higher risk of an AOM attack and more AOM hospital encounters, probably due to access rather than real difference in rates (32). Incompletely treated cases of AOM are likely to develop into CSOM, one of the main causes of mild to moderate hearing loss among children (6-8). In Nigeria, rural residence and long distance to health facilities were found to be associated with protracted non-healing ear discharge among CSOM patients, which introduce increasing risk of complications (72). In Cambodia, travel distance was the most commonly cited barrier to accessing care among patients with CSOM, but no statistical relationship was identified between distance to the hospital and markers of disease severity among surgery patients (73). These findings suggest that while proximity to healthcare can increase access and initial treatment, other factors such as quality of care and follow-up play crucial roles in preventing complications.

Air pollution has also been identified as one of the environmental risk factors related to OM (25). Brauer et al. measured overall traffic-related air pollution for the home addresses of more than 4,000 infants in Netherlands and Germany and found positive association with physician OM diagnosis within the first 2 years of age (26). Nitrous dioxide (NO_2) is one pollutant consistently to be found associated with higher OM risk (25). High NO_2 concentration was associated with higher OM visits at the emergency departments in Italy and the United States, more outpatient physician OM visits in Canada, and more parent-reported and physician-diagnosed OM in various European countries (25-28, 74). Most of the studies measured air pollution with fixed site monitoring stations which can capture temporal variations but miss the spatial variation of air pollutants across the study area (25). Some use urban/rural classification instead of data from monitoring stations, which provides even less information as variations within those urban and rural spaces are missed and thus introduces greater potential misclassification of the exposure. Meanwhile, evidence from LMICs is still limited (25).

2.2 Cognitive development of children with hearing impairment

Hearing loss, one of the sequelae of OM, is a serious concern, especially for children, since it may impact early communication, language development, cognitive and psychosocial development, academic performance, and vocational development in the long run (10, 12, 13, 20, 55). The younger the age of onset of hearing impairment, the greater the potential impact (10). The American Speech-Language-Hearing Association (ASHA) identifies four major impacts of hearing loss on children: delays in the development of receptive and expressive communication skills, language deficits resulting in learning problems and reduced academic achievement, social isolation and poor self-regard due to communication difficulties, and limitations in vocational choices (9).

OM affects children at an age of dynamic phase of speech and language development. Children with OM may experience periodic-degraded language input due to mild to moderate hearing loss caused by OM that lasts for weeks or even months (75). Such experience could result in poorer verbal skills and less attention to oral language, which may lead to fewer verbal interactions and more solitary time (2).

Moreover, as children typically learn vocabulary through listening to others and talking with others through about third grade, those with hearing loss have delays in vocabulary accumulation, especially in abstract vocabulary. After the third grade, vocabulary acquisition leans more on text exposure. Learning to read is more difficult for children with hearing loss, since reading is based on the phonological system which is less than adequate among those with hearing loss. Delay in reading skills development and little support from vocabulary for decoding or sounding out words make comprehension particularly hard for readers with hearing loss. With compromised comprehension, reading is less enjoyable and readers typically choose to read less, which in turn diminishes their vocabulary and then drives them farther away from reading. (10)

Studies on the relationship between cognitive development and hearing impairment caused by OM have been inconclusive (55). Factors that have been found to mediate the effect include early onset of OM, frequent infections under the age of 12 months, long infection period, poor or no access to medical care, pre-existing language or cognitive deficit, parenting practices, malnutrition, and environmental factors such as passive smoking, and overcrowding (10, 12-14, 16, 20, 21, 75). As the sequelae of OM mainly affect hearing, the verbal domain of cognitive development is expected to be influenced the most. Traffic-related air pollution, one of the environmental factors of OM, has also been found to be associated with substantially slower growth in all cognitive measurements, specifically working memory and inattentiveness, among primary school children in Spain (76, 77). Evidence from LMICs is limited, where children with hearing impairment may not have necessary specialized support to attain equal educational progress as other children.

2.3 Pneumococcal Conjugate Vaccine

2.3.1 Vaccine Characteristics

Streptococcus pneumoniae is the leading cause of bacterial OM (3). Pneumococcal conjugated vaccines (PCVs) are composed of the pneumococcal capsular polysaccharides purified from serotypes of *S. pneumoniae* that cause the most invasive diseases. Since the first introduction in the United States in 2000, PCVs have been found to be safe and effective at reducing *S. pneumoniae* related morbidity and mortality (39-41). Multiple formulations of PCVs have also been reported to provide protection against ear infections and hearing loss associated with meningitis infections (33-37, 78-80).

Most of the efficacy studies have reported the results with an underlying assumption that the effect of PCV is the same throughout the study area. However, this assumption does not always hold true. Vaccine efficacy was found to increase with distance from the main study hospital (81). Efficacy varies from -14% for children residing within 1.5 km of the hospital to 55% for those living more than 8.5 km away. Notably, only the group situated the farthest from the hospital demonstrated a statistically significant difference in vaccine efficacy. These findings suggest that vaccination programs targeting children in areas with limited access to healthcare services might be more cost-effective than universal programs.

Since 2007, WHO has recommended that childhood immunizations schedules globally include PCV (39-41). PCV is recommended to be administered from as early as six weeks of age (41). Countries with regulatory approval for PCV use have witnessed huge reduction in invasive pneumococcal disease and pneumonia (82). By March 2020, 146 out of the 194 WHO member states had included PCV in their national immunization program (82). High-income countries were early adopters of PCV. For example, in 2000 the Unites States approved PCV7 for children younger than 2 years and high-risk children aged 2-4 years (83). On the other hand, LMICs suffer from limited access to the vaccine and resources. Gavi, the Vaccine Alliance, had introduced PCV to 60 of the 73 Gavi-eligible counties, reaching 215 million children by the end of 2019 (84). Not being a Gavi-eligible country, Philippines procured PCV in 2013, and had half of the target population fully vaccinated by 2019 (85).

2.3.2 Secondary Impact of Vaccines

The impact of vaccination is broader than direct medical cost savings and reduction in incidence of the targeting infection and/or disease. Immunization provide protection against not only an illness but also any short-term and long-term effects of the illness on people's physical, socioemotional, cognitive, and professional development and long-term benefit in economic productivity (44, 49, 86).

A small but growing literature explores secondary impact of vaccines. For example, a longitudinal study of more than 1,800 children in India linked *Haemophilus influenzae* type b (Hib)-vaccinated children with higher height-for-age, higher scores on

English and mathematics tests, and more schooling grades attained compared to those Hib-unvaccinated at the age of 11-12 years (45). Maternal tetanus immunization was also found be associated with significant schooling gains among children in Bangladesh whose parents had no schooling (46). A study in Philippines using propensity score matching also found that children with complete childhood vaccination for measles, polio, diphtheria, pertussis and tetanus (DPT), and tuberculosis (TB) had increased test scores by about half a standard deviation than those with no vaccinations (43). Similar growth, cognition, and academic benefits have been observed among measles-vaccinated children in Ethiopia, India, Vietnam, and South Africa (44, 48). India's Universal Immunization Program was also associated with higher height-for-age and weight-for-age z-scores and more schooling grades (47, 87, 88). Although evidence on secondary impact of PCV is limited, a study using the whole population in Iceland found PCV to be associated with both lower AOM incidence and fewer AOM episodes among children under the age of 3 years (38). The topic is understudied yet important for us to understand how PCV improves child wellbeing.

2.4 Significance of the Current Study

OM, hearing loss, and cognitive development all depend on multiple factors, factors on both individual and environmental levels. The spatial variation of each of these outcomes in LMICs is understudied but important as these countries bear a disproportionally heavy burden of OM and pediatric hearing loss, and children there suffer from limited specialized support to attain equal progress in cognitive development.

To my knowledge, no published study has described the pattern of OM, pediatric hearing loss, or cognitive development on a local level in LMICs. The purpose of this study is to identify the key characteristics associated with OM, hearing loss, and cognitive development on neighborhood level in LMICs and determine if the key characteristics are consistent across the study area. The study also examines potential long-term secondary impact of vaccine coverage on the three outcomes.

Figure 1. Incidence rate estimates of chronic suppurative otitis media (CSOM) per thousand people by World Health Organization region in 2005.

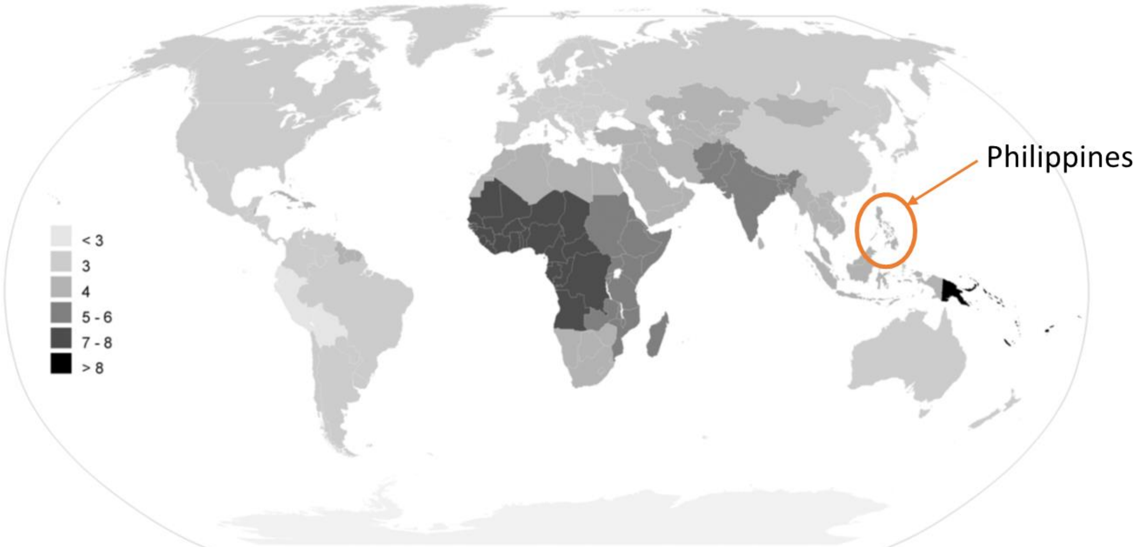
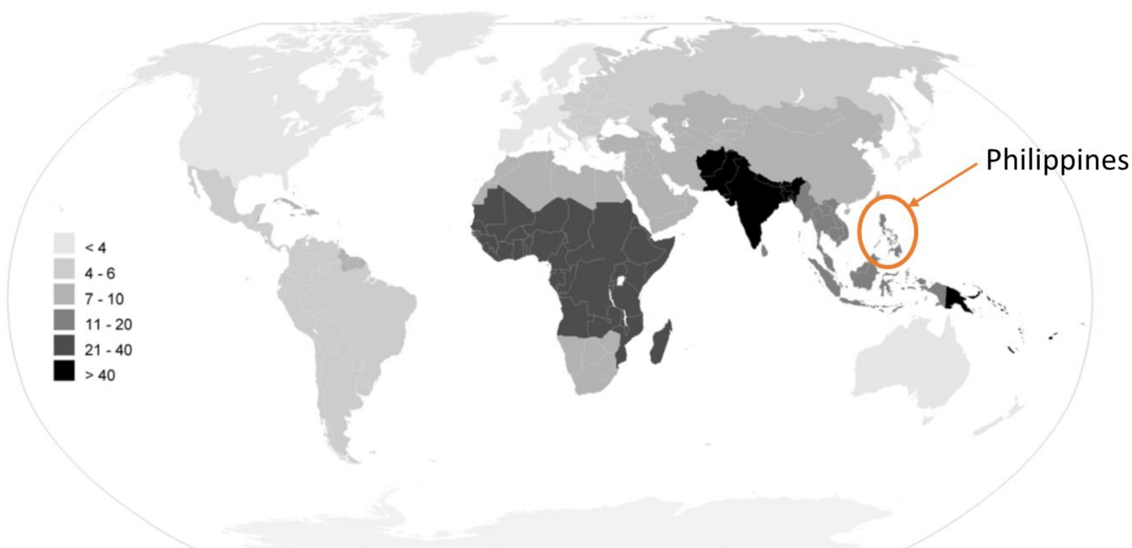


Figure 2. Otitis media-associated hearing loss (>25 dB for best ear) prevalence rate estimates per ten thousand people by World Health Organization region in 2005.



Chapter 3. Research Design and Methods

3.1 Data Source

I used secondary data from the follow-up assessment of a double-blind randomized controlled trial (RCT, International Standard Randomized Controlled Trial Number [ISRCTN] 62323832) on an 11-valent pneumococcal conjugated vaccine (PCV) in Bohol, Philippines among children under the age of 2 years (50). The parent trial included 12,191 infants born into the study area in July 2000 to December 2004, and 8,926 (73.2%) of those children enrolled in the follow-up assessment conducted between September 2016 and February 2020 (50). The province of Bohol, which is in the Central Visayas region in Philippines, consists of 1 component city and 47 municipalities. The study area consists of seven districts in Southwestern Bohol (Tagbilaran City, Dauis, Panglao, Baclayon, Cortes, Corella, and Balilihan), a predominantly rural agricultural area (397 km2) with a population of 175,000 in 2000 (Figure 3) (50, 81). According to the land use map from Provincial Planning and Development Office in Bohol, most of the study area is built-up areas, with some agro-industrial croplands in Cortes and Corella, and some forest or watershed areas coverage in Balilihan (Figure 4).

During the parent trial, researchers enrolled and vaccinated participants in 48 government primary health care centers. Sanofi Pasteur prepared and manufactured the PCV used for investigation (1 μg of *S. pneumoniae* capsular polysaccharide for types 1, 4, 5, 7F, 9V, 19F, and 23F conjugated to tetanus toxoid; and 3 μg of polysaccharide conjugated to diphtheria toxoid for types 3, 14, and 18C; and 10μg of polysaccharide for type 6B conjugated to diphtheria toxoid; Lyon, France), while saline served as placebo (50). Researchers allocated treatment and placebo vaccines using individual-level block randomization. The allocation was blinded to nurses administering the vaccine and the child participants. Sanofi Pasteur generated a list of random permutations of the letters A to F using SAS software (SAS Institute, Inc, Cary, NC), with three letters assigned to the vaccine and three to the placebo. After enrolling a child, the study allocated them to the next available letter on the list, which was concealed from the study nurse until the time of allocation. Subsequently, the study nurse administered the lettered solution and recorded the letter on the case report form. The clinical team who reviewed the study data were also blinded to the assignment (89).

The researchers closely monitored participants with thorough follow-up and tracking of migrants. For the follow-up study, field personnel visited the home address of each child enrolled in the parent trial. If the child still lived there, they were invited to participate in the follow-up study. In case of relocation, field personnel asked the neighbors for the new residential location or contact information, if possible. Field personnel made multiple attempts to reach the family, either by visiting the most recent known residential address or calling their mobile phones.

Once a participant was located, field personnel obtained verbal parental consent and verbal assent for children under 18 years of age, or verbal consent for children aged 18 years or older. After providing verbal consent, one parent or primary caregiver completed a questionnaire which included questions on demographics, socioeconomic, behavioral and health conditions. Children were then asked to visit the study office in Tagbilaran for otoscopic screening, ear cleaning, tympanometry, distortion product otoacoustic emissions, and audiologic screening (90).

I downloaded the shapefiles of political boundaries and all the roads in the study area from the website of the Bohol Provincial Planning and Development Office (https://ppdo.bohol.gov.ph/) and locations of all healthcare facilities in Bohol, Philippines from Philippine Geoportal (https://www.geoportal.gov.ph).

The study protocol was reviewed and approved by the OSU Institutional Review Board (Study ID: 2022B0182).

3.2 Variable Definitions

3.2.1 Otitis Media (OM, ear disease)

During the follow-up study, researchers classified ear disease into four categories with an algorithm integrating findings from an otoscopic examination (e.g., ear pain, otorrhea), tympanometric measurements (e.g., ear canal volume), and assessment of video otoscopy recordings by Ear, Nose, and Throat (ENT) specialists (91). The four categories were normal (no evidence of ear disease), mild ear disease (acute OM [AOM], OM with effusion [OME], myringosclerosis, or healed perforation of the tympanic membrane [TM]), moderate ear disease (dry perforation of the TM or adhesive OM), or severe ear disease (chronic suppurative OM [CSOM]). In the current study, participants were grouped into two categories: no ear disease and having ear disease. All forms of ear diseases from mild to severe were categorized as having ear disease.

3.2.2 Hearing Loss

As part of the follow-up assessment, child participants received audiology screening using noise-attenuating earphones in a quiet environment to identify potential hearing loss. All children who met any of the following criteria were referred for a formal audiology evaluation at the Bohol Hearing Center (BHC):

a. Possible or portable hearing loss according to the audiology screening;

b. History of ear discharge, ear drum perforation, or hearing problem;

c. An abnormal tympanogram during the ear disease screening; or

d. A failed distortion product otoacoustic emissions (DPOAEs) test during the ear disease screening.

Hearing loss levels were then assessed using three distinct audiometry tests, contingent upon whether the child was referred for a formal audiology evaluation at the BHC and if they attended the referral (91). The formal audiology testing at the BHC was considered the gold standard and was conducted on 783 participants. The HearScreen test during ear examination collected hearing data from 8,176 participants, and HearTest device used during ear examination collected hearing data from 642 participants. Some participants had hearing data from more than one source. Based on the data from 379 children who had hearing data from all three sources, a concordance analysis found that the HearScreen results had a greater concordance with the BHC results. Thus, the hearing data used for this analysis included 783 BHC hearing test results, 7,404 HearScreen results, and 26 HearTest results, adding up to a total of 8,213. Pure tone average (PTA) was calculated for each ear by averaging the decibel (dB) levels heard at frequencies of 1000, 2000, and 4000 Hz for air conductance (AC). The severity of hearing loss was classified as outlined in previous studies. Briefly, hearing levels were categorized into five groups: no hearing loss, mild hearing loss (16-30 dB PTA), moderate hearing loss (31-60 dB PTA), severe hearing loss (61-80 dB PTA), or profound hearing loss (> 80 dB PTA). For the analysis, I created a dichotomous variable for whether participants had hearing loss in at least one ear.

3.2.3 Cognitive Development

All children underwent cognitive assessment during follow-up using the Wechsler Intelligence Scale for Children® Fifth Edition (WISC-V) to evaluate their strengths and weaknesses in cognitive functioning. The WISC-V designed for children aged 6 to 16 years and 11 months, assesses intellectual abilities across five cognitive domains (23). Widely recognized as the gold standard for measuring Intelligence Quotient (IQ) in children, it is extensively used by school and clinical psychologists (92-94). Our study extended the use of the WISC-V to include participants up to 19 years old, independent of the standard age norms, as we applied our own norms using z-scores. This approach allowed us to focus on differences using raw scores rather than adherence to specific age ranges. This extension was justified by the continuous trajectory of cognitive development through late adolescence, and supported by previous research indicating the

WISC-V's applicability in older adolescents (95). The current study used full-scale IQ (FSIQ) from the WISC-V as a measurement of cognitive development, which is an overall measurement of child's intellectual functioning. From the raw scores, age-group-specific z-score was constructed and standardized separately for 4-month age groups as: ((FSIQ score – mean(FSIQ score)) / Standard Deviation(FSIQ score)). Results on cognitive development were presented in standard deviation units.

3.2.4 Primary Independent Variables

3.2.4.1 Vaccine Coverage in the Neighborhood

The parent trial aimed to enroll all infants born into the study area after its commencement till the enrollment of the planned number of study participants (50). Out of 15,593 infants born in the study area, 2,406 were not eligible for the trial due to reasons such as foreseen migration (n=2,292). Additionally, 993 children were eligible but did not enroll due to death before 6 weeks of age (n=154), being non-users of health centers (n=249), medical reasons (n=57), and refusal (n=533). Among the 12,194 enrolled children, 12,191 received the allocated intervention, accounting for 90% of the eligible children and 78% of all infants born into this area from 2000 to 2004.

This analysis aimed to investigate the association between PCV coverage in the neighborhood and areal prevalence of OM and its sequalae. OM is most prevalent among young children, particularly those aged 1-4 years, with the highest incidence occurring during the first year of life (3). Therefore, it is crucial to focus on the relevant population within this age group to assess the vaccine's impact accurately.

In this analysis, I defined vaccine coverage (VC) in each neighborhood as $VC_i = \frac{NV_i}{N_i}$, where VC_i represented VC in neighborhood i, NV_i was the number of children who received all three doses of PCV in the neighborhood, and N_i represented the total number of children enrolled in the trial in neighborhood i, regardless of their vaccination status (PCV or placebo) (81, 96). Using the number of children enrolled in the parent study as the denominator ensures that the coverage rate is reflective of the population that was directly exposed to and benefited from the vaccination.

3.2.4.2 Distance to Healthcare

To measure distance to healthcare for the neighborhood, I calculated the Euclidean distance in kilometers (km) from the residential location of each participant to the closest hospital. For each neighborhood, I calculated the mean distance of the participants to the close hospital to represent distance to healthcare for that neighborhood.

3.2.4.3 Traffic-related air Pollution

I used the Provincial Planning and Development Office (PPDO) of Bohol's categorization of roads into six groups: national road, provincial road, municipal road, barangay (village) road, private road, and trial (97). I quantified traffic-related air pollution using the total length of national road and provincial roads within the neighborhood (Figure 5). National and provincial roads are the major roads in the area. According to the sources disclosed in the shapefile that I downloaded from the Bohol PPDO website, shapefiles of all national and provincial roads were reported from local agencies, while information on other types of roads may come from Google Earth or Bing Maps. Therefore, I chose to include national and provincial roads only.

3.2.4.4 Traffic-related Noise Pollution

The major source of traffic-related noise pollution of concern was Tagbilaran Airport. The airport was situated in the city center of Tagbilaran and closely surrounded by residential zones (Figure 6). It served the area since its opening in 1960s until it was closed and replaced by the Bohol-Panglao International Airport in November 2018 (98). It reached its capacity and was congested in the 2000s and 2010s. After its closure, multiple purposes have been proposed, and during the past few years, it has been serving as a venue for local market, seasonal festivals, and political campaign rallies (99, 100). To measure noise pollution from the airport, I calculated the Euclidean distance in km from Tagbilaran Airport to residential location of each participant and then calculated the mean of the individual measures of distance.

3.2.5 Other Sociodemographic Characteristics

The follow-up study conducted a household visit to collect demographic, socioeconomic, health, and environmental characteristics. After providing verbal consent, the parent or primary caregiver was asked to respond to a survey covering socioeconomic, behavioral, and health conditions of the child (Table 1).

3.2.6 Waypoints

Waypoint is a set of coordinates (i.e., latitude and longitude) that identifies an exact location on the earth's surface. During the follow-up study, field researchers collected waypoints based on the residence location of each household using the Garmin eTrex 10/20 from November 2016 to December 2019. They also logged the longitude and latitude information in the follow-up survey record.

The Geographic Information System (GIS) officer then processed the global positioning system (GPS) data using the Garmin BaseCamp™ software. The GIS officer downloaded GPS data from the Garmin eTrex receivers, renamed waypoints with participant study identification numbers and sorted them into groups as needed and saved into .gpx files. Daily .gpx files were aggregated into monthly/yearly files for analysis. I compiled all the location data into one analytic file. As the field personnel may have made multiple attempts before they could locate the residential location of a child participant, for those participants with multiple waypoints, the latest record was used. If GPS data were not available, the longitudinal and latitude records from the follow-up survey were used. Then, I linked the geographic data to the follow-up survey data for each participant in a GIS.

3.3 Defining Neighborhood

The study area, initially segmented into 119 barangays based on existing political boundaries, posed limitations for detailed spatial analysis due to irregular shapes and varying sizes. To address these challenges and enable more precise spatial investigations, I employed a square grid methodology redefine neighborhoods. This approach provided standardized and geometrically uniform spatial units across the study area, facilitating consistent and comparable neighborhood definitions for analysis.

I created a square polygon grid over the study area and defined each grid cell as a neighborhood, which served as the geographic unit in this study (Figure 7). As an example, Figure 7a is a square polygon grid. The black dots in Figure 7b represent 8 child participants, and the square represents a neighborhood of 4 square kilometers. All the participants with a household waypoint within the square are counted as participants in this neighborhood. In Figure 7b, participants numbered 1, 2, 4, 6, 7 are participants within this neighborhood while participants numbered 3, 5, 8 are not. The neighborhood represents the geographic area surrounding each participant's residential location and it was defined by geography only.

To choose the neighborhood size for analysis, I created square polygon grids (Figure 7a) of varying sizes overlaying the study area (Figure 8a). The main study hospital, Gov. Celestino Gallares Memorial Hospital in Tagbilaran City (the red dot in Figure 7c and Figure 8), was used as the starting point of the grid, where the main study hospital was the centroid of a grid cell (Figure 8b). Each grid cell was defined as a neighborhood. Neighborhood was defined by geography only and served as the geographic unit for analysis.

Studies have used distances from 800 to 2,500 meters to define proximal neighborhood environment for children (101). A study evaluating the relationship between neighborhood design and rates of walking and biking to school among a sample of elementary students in California used circles with a radius of 0.5 miles (approximately 800 meters) as the immediate surrounding neighborhood of each school that all students must travel (102). A survey in Seattle on the association between environmental characteristics in the neighborhood and parents' concerns with active commuting to school used a 1000-meter radius around each participant's residential location as the unit to compute walkability index on individual level (103). A study on the correlation between access to recreational facilities and physical activity and body-mass index among about 800 young adolescents in California used 1 mile (approximately 1,600 meters) in street network as the size of the buffer to measure their built environment (104). Another multi-state study looking at the association between public park access and physical activity among adolescent girls used half-mile and 1 mile to define proximity (105). However, most of these studies were conducted in urban settings in high-income countries. The population density is lower in rural areas in a lower-income setting. Findings on vaccine efficacy from the parent study utilized 2.5 km as a buffer size (81). Thus, I examined grid sizes of 800 to 2,500 meters per side. The sides of the square increased in 100-meter intervals.

After the square polygon grids of each size were created overlaying the shapefile of points representing residential locations of all participants, a spatial join was used to identify which neighborhood each participant belongs to. As the study area includes a strait between Dauis and Tagbilaran City, the square grid covering both sides of the strait was divided into two neighborhoods, one on each side of the strait. Thus, for each participant, an identifier for the neighborhood was created by combining the grid number and dummy letters showing if the participant was on the island of Dauis and Panglao or not. For example, grid "AV68" (highlighted in Figure 9) was not on the island of Dauis and Panglao, so the unique identifier of the neighborhood was assigned as "AV68NDP". For each neighborhood, I calculated the percentage of participants with the outcome of interest, the percentage of vaccinated participants, and the total number of participants within the neighborhood. To avoid extreme values due to small sample size, only neighborhoods with 4 or more participants were retained for the analysis (Figure 10).

I further restricted the analysis to contain only neighborhoods connected to the main mass (Figure 11). I identified the neighborhood that contains the main study hospital, Gov. Celestino Gallares Memorial Hospital in Tagbilaran City, as the starting neighborhood (Figure 11a). Neighborhoods whose boundaries touch the starting neighborhood were selected layer by layer until no more neighborhoods intersected with the main mass, side or corner (Figure 11b-j).

For each grid size with sides varying from 800 to 2,500 meters, I ranked the number of neighborhoods and number of participants included and added up the two rankings. To achieve greater granularity than the readily available 119 political geographic units, I only considered grid sizes that yielded a larger neighborhood-level sample. I chose the grid size with the lowest sum of rankings to maximize both the number of participants and the number of neighborhoods. When multiple grid sizes had the same sum of rankings, I prioritized the one with the largest variation in percentages of participants with hearing loss. Once the neighborhood size was chosen, I aggregated all individual and family characteristics and the outcomes of interest to neighborhood level. I calculated the means for continuous variables and percentages for categorical variables.

3.4 Global Moran's I

To examine the global spatial autocorrelation of the outcomes of interest and primary independent variables, I used global Moran's I index with the queen's case contiguity weight matrix to summarize the degree to which similar observations tended to be near each other (106). The null hypothesis for Moran's I is that the distribution of a certain value is random across the entire study area. The index ranges from -1 to 1, with positive values indicating clustering and negative values indicating dispersion. Such clustering is a characteristic of the complete spatial pattern over the study area and does not provide an indication of the location of the clusters.

3.5 Local Indicator of Spatial Association

To investigate the clusters on a local level and identify their locations, I created location indicators of spatial association (LISA) maps for outcomes of interest. These maps provide a measurement of local similarity between the value of a region and those of nearby regions (107). The null hypothesis for LISA mirror that for general indicator of spatial association, which is the value of interest at a location is independent from its neighbors. In LISA maps, areas with significant local correlation at 0.05 level are highlighted in different colors based on their correlation with neighboring regions.

3.6 Spatial Models

After fitting a generalized linear (GLM) model, I assessed if spatial pattern distorted the GLM model by running Moran's I on the residuals and comparing to the Moran's I of the outcome of interest. In presence of spatial autocorrelation, I used spatial regression models to account for spatial dependence in the error term. The Lagrange multiplier (LM) tests and robust LM tests helped to determine which spatial model to be used for analysis (Figure 12) (108). Spatial lag model works with the assumption that dependent variable in a certain area is influenced by those from areas associated with it, while spatial error model considers the dependency of error value of an area with error values of other areas associated with it.

3.7 Geographically Weighted Regression Model

To determine if the association between the key characteristics identified and outcomes of interest were spatially homogenous across the study area, I employed geographically weighted regression (GWR) modeling. GWR assumed that the relationship between the dependent variable and independent variables varied by location and estimated one set of coefficients for each areal unit. Effectively, a subset of observations was used to estimate each coefficient. GWR generated a continuous surface of parameter values at each local observation to denote the spatial variations. For continuous outcomes of interest, I determined the bandwidth by minimizing the corrected Akaike Information Criterion (AICc) value for optimal tradeoff between bias and variance. For count outcome of interest, I obtained the global bandwidth using R package spgwr (109). The Monte-Carlo significance test assessed the statistical significance of the estimated coefficients. If some characteristics had little spatial non-stationarity while others varied statistically significantly across the study area, a mixed GWR was performed listing the ones with little spatial non-stationarity as a fixed effect. The coefficients and significance level in each neighborhood from GWR were mapped to present the results.

Models were evaluated with variance inflation factor (VIF), adjusted R^2 and AICc as appropriate. All statistical analyses were performed using R Statistical Software (v4.3.2; R Core Team 2023) and ArcGIS Pro 3.1.3. Statistical significance was decided on a 0.05 level unless otherwise specified.

Figure 3. The study area of the randomized placebo controlled pneumococcal conjugate vaccine (PCV) trial and its follow-up assessment in Bohol, Philippines (ISRCTN: 62323832).

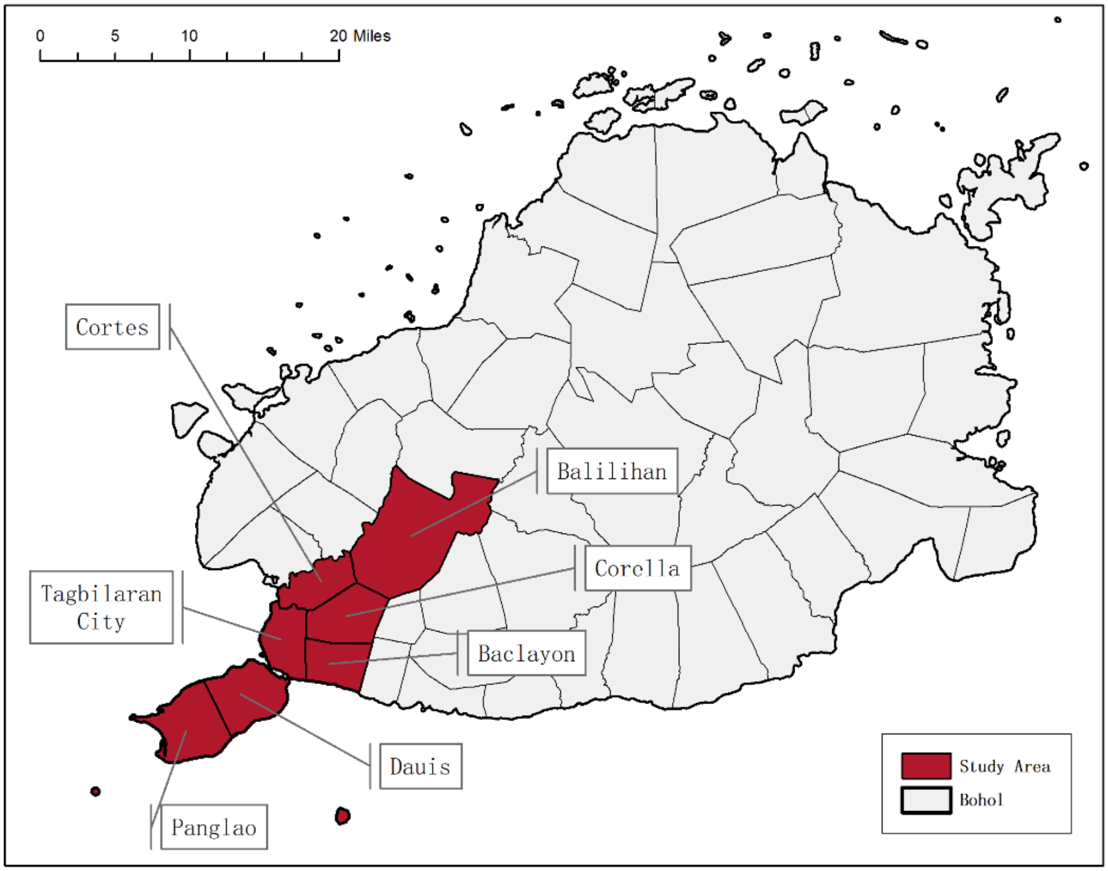


Figure 4. Land use information of Southwestern Bohol, Philippines.

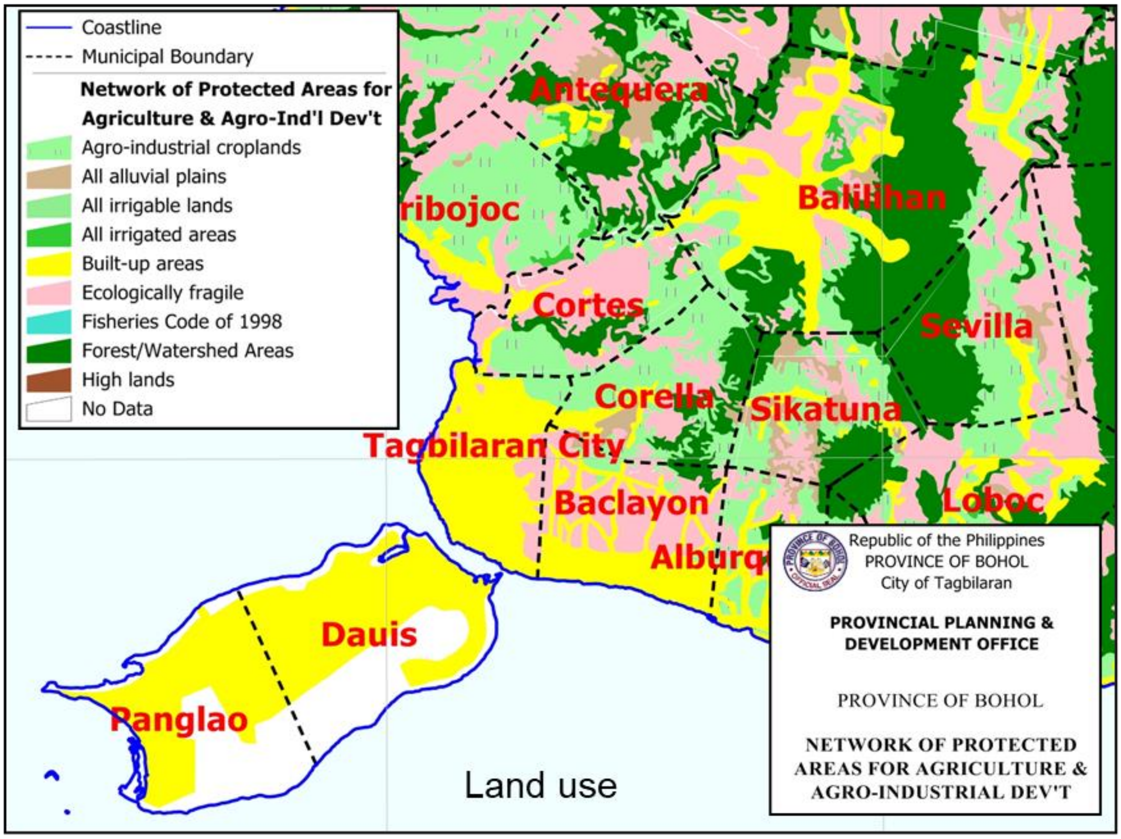


Figure 5. National and provincial roads in Bohol, Philippines.

Figure 6. Pictures of Tagbilaran Airport.

(a) The airport is closely surrounded by residential homes. Source: https://www.boholchronicle.com.ph/2022/11/14/convention-center-it-park-eyed-at-old-tagbilaran-airport/ (b) The airport serving as the revenue for a political campaign rally in April 2022.

(a)

(b)

Figure 7. The neighborhood was defined with a square polygon grid over the study area.

(a) A square polygon grid. Each gird cell represents one neighborhood. (b) One example neighborhood with the size of 2,500 meters per side. (c) Example of a square polygon grid with side of 2,500 meters overlaying the study area.

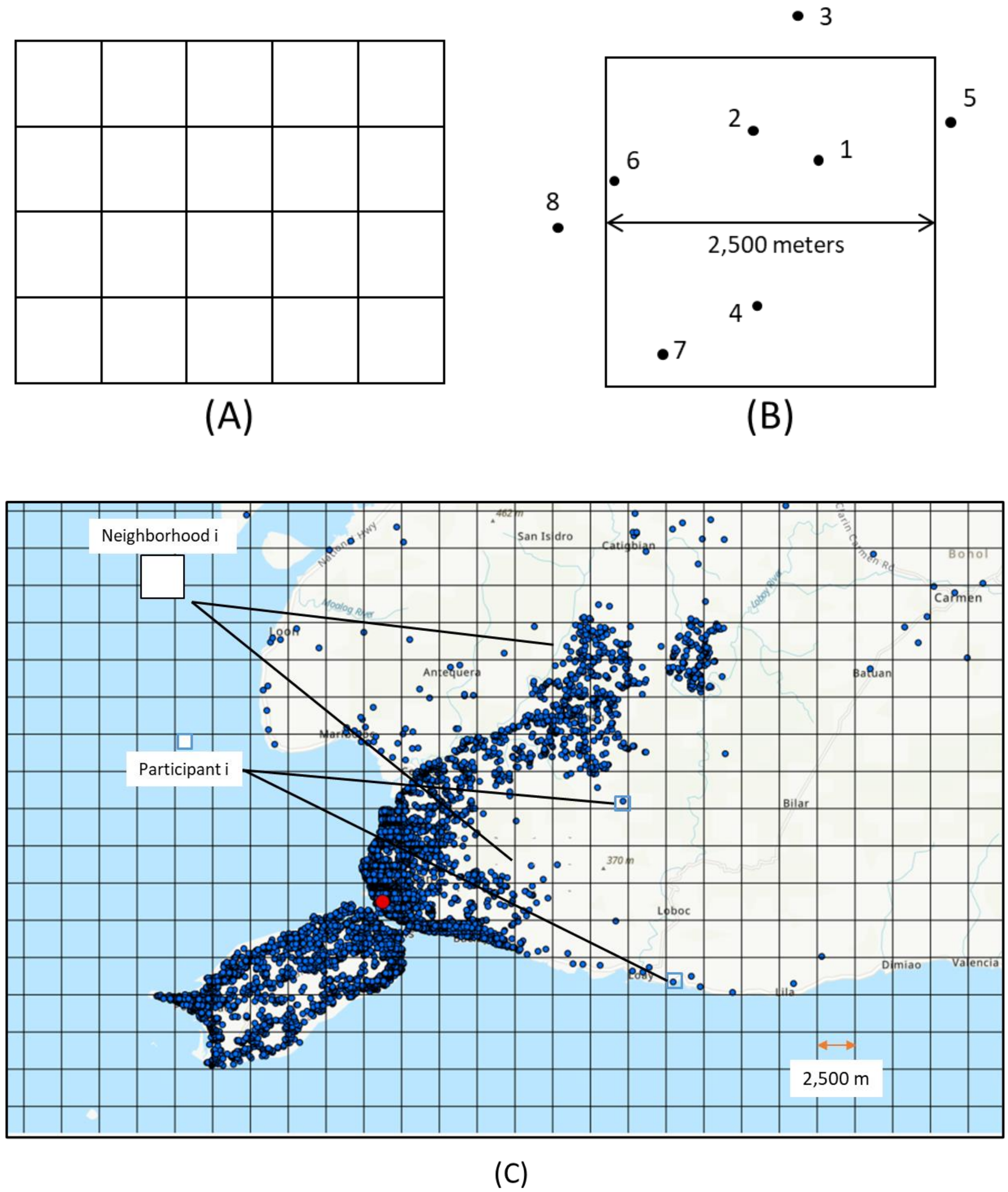
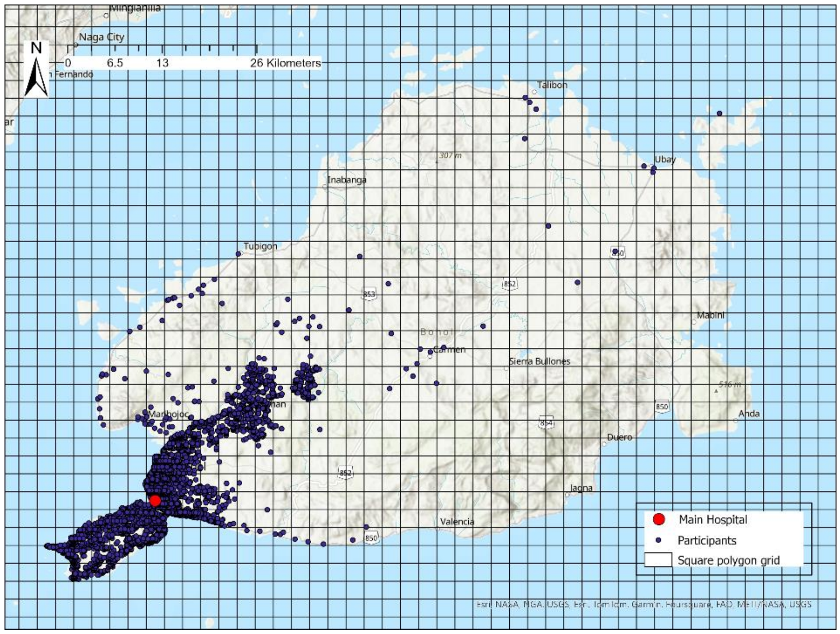
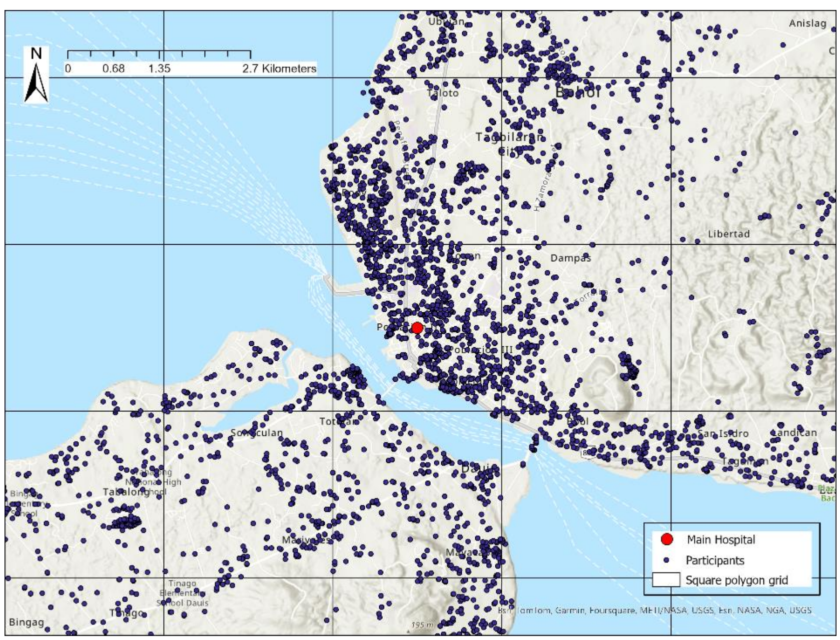


Figure 8. Square polygon grids were created over the study area to define neighborhoods.

Grids with sides of 2,500 meters are presented here as an example. (a) Grids overlaying the entire study area. Each grid cell is defined as one neighborhood. (b) The main study hospital was the centroid of the initial neighborhood.



(a)



(b)

Figure 9. Example of the naming of each neighborhood.

To identify if the neighborhood is on the island of Dauis and Panglao, additional letters were added to the neighborhood id. The highlighted neighborhood was not on the island of Dauis and Panglao, so it was assigned as “AV68NDP”.

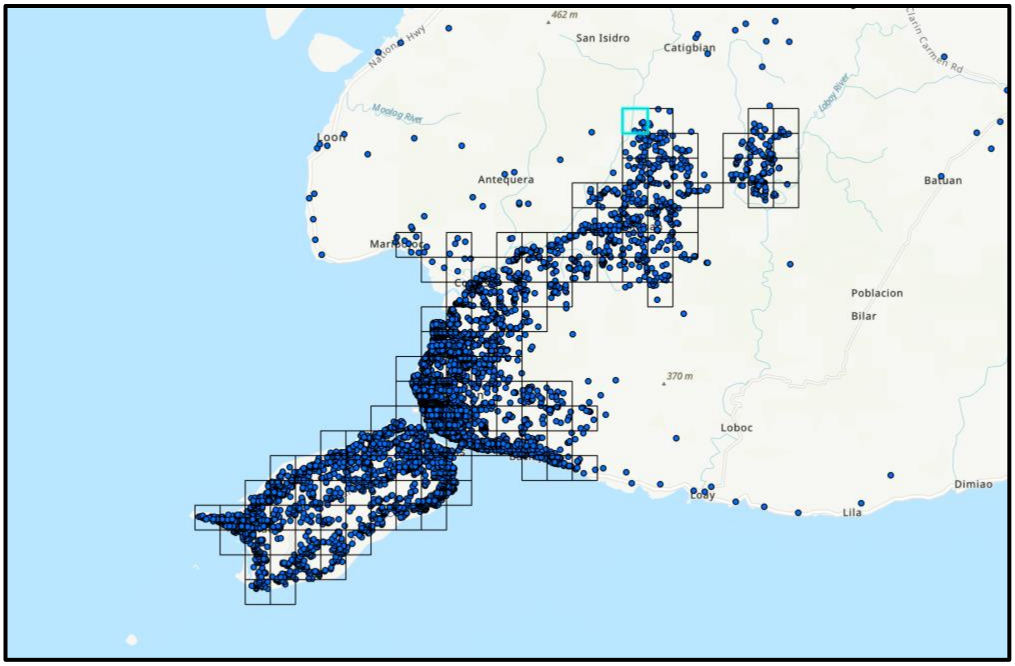
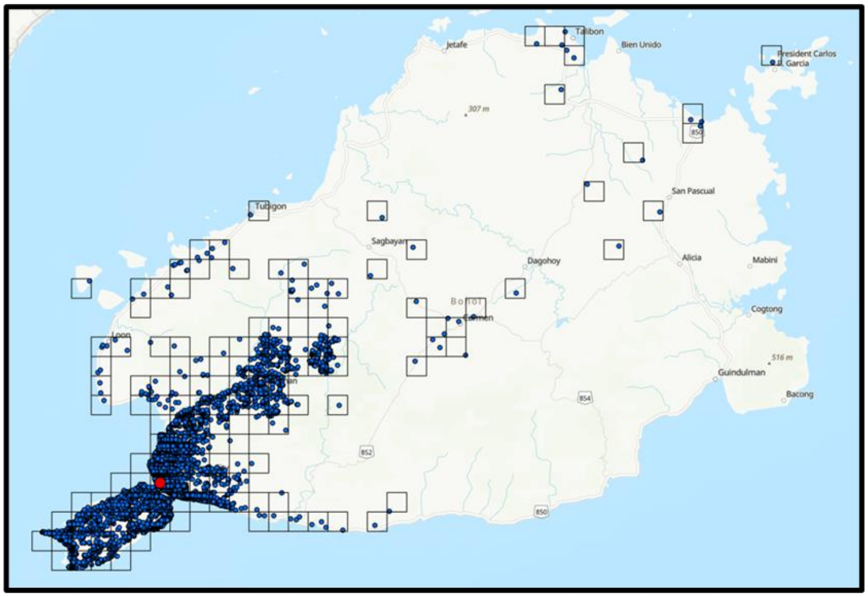
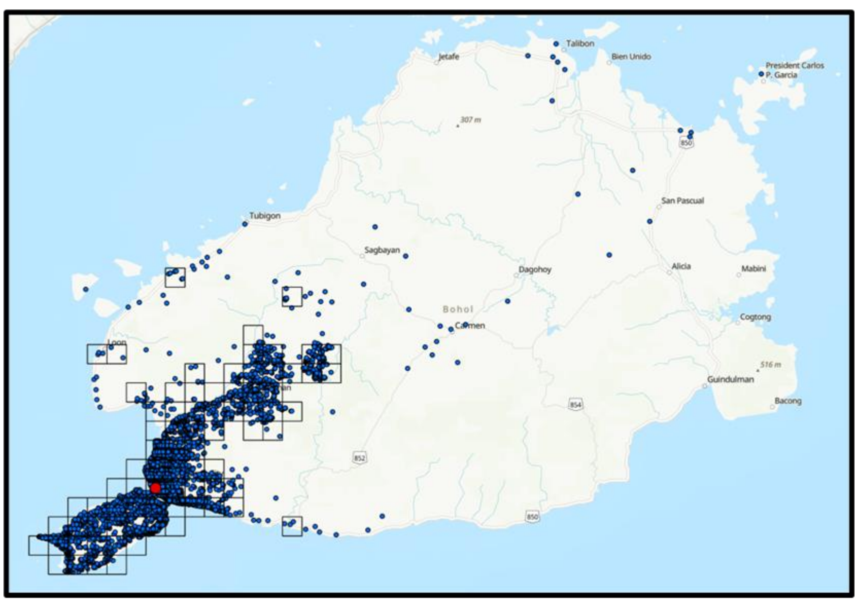


Figure 10. Neighborhoods including four or more participants were retained for the analysis.

(a) All neighborhoods created. (b) Neighborhoods with four or more participants were retained.



(a)



(b)

Figure 11. Neighborhoods not connected to the main mass were excluded from the analysis.

(a)-(j) An example process selecting neighborhoods connected to the main mass. (j) The neighborhoods highlighted in teal were included in the final selection.

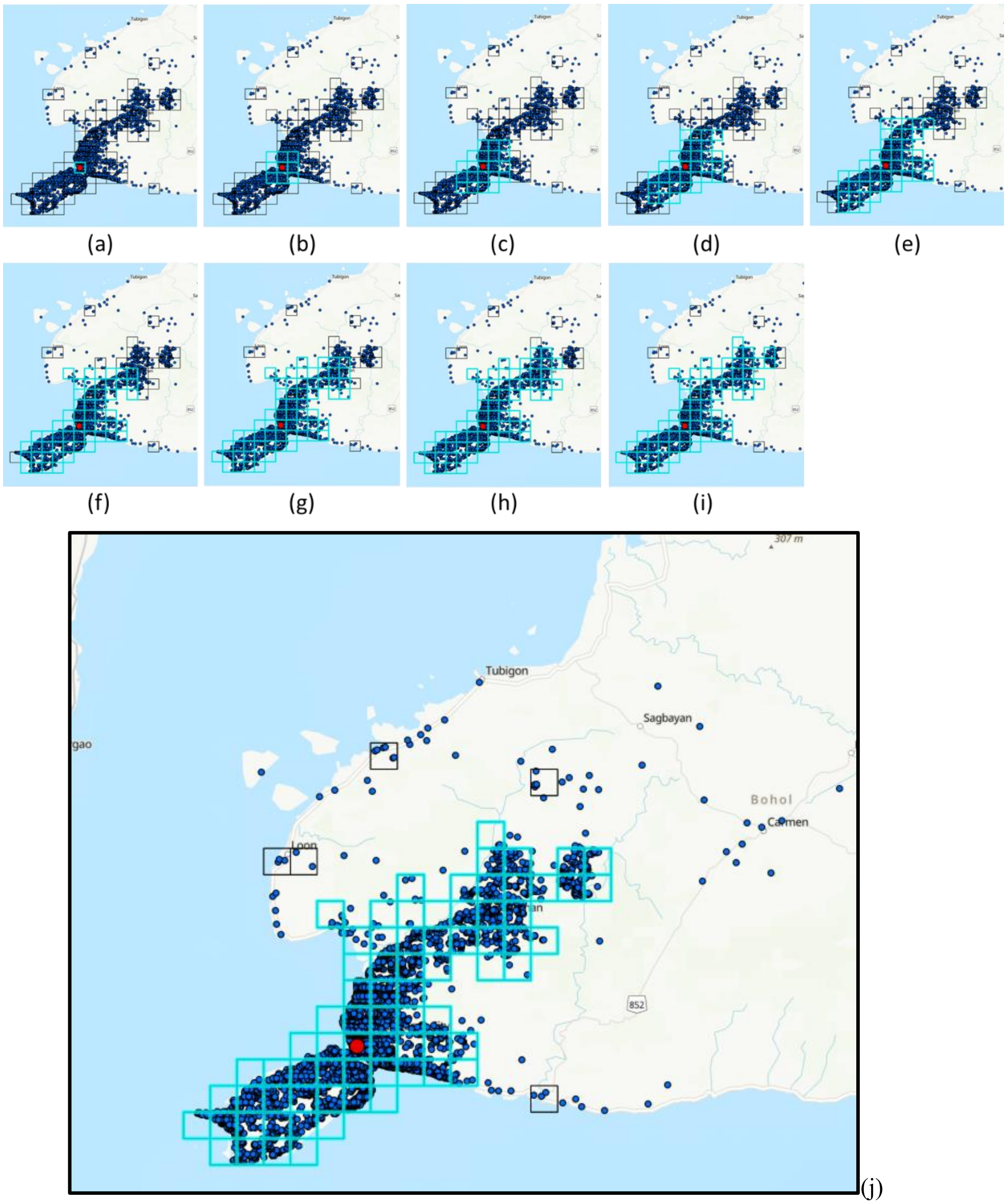


Figure 12. Flow chart of statistical modeling.

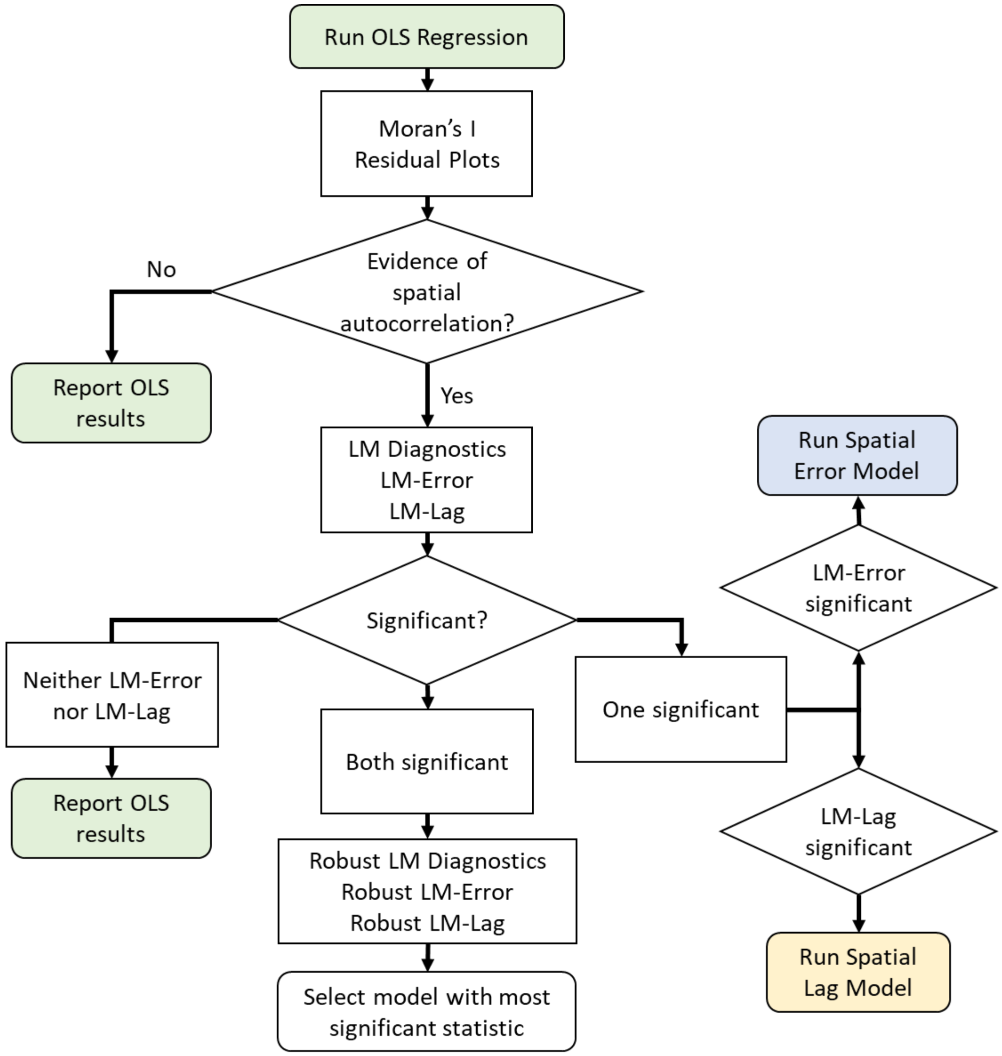


Table 1. Characteristics collected in a follow-up assessment of the randomized controlled trial (RCT) on a 11-valent pneumococcal conjugate vaccine (PCV) in Bohol, Philippines (ISRCTN: 62323832).

Characteristics	**Range**
Child's birthweight (gram)	500 - 9000
Number of children <15 years in the household	0 - 10
Number of adults >15 years in the household	1 - 22
Number of people in the household	1 - 28
Parity of mother	1 - 18
Household crowding index (Number of people per room)	0.3 – 19.0
Household wealth index (110)	-3.1 – 3.6
Child's age at follow-up assessment	12.9 – 19.5
Mother's age at follow-up assessment	28.7 – 73.7
Number of household members regularly smoke in the house	0 - 5
Characteristics	**Categories**
Child sex	Female/Male
Child has a chronic health condition	Yes/No
Child attended daycare	Yes/No
Child attended preschool	Yes/No
Mother has health insurance	Yes/No
Child's birth order	• First • Second to fourth • Fifth or more
Parent's marital status	• Never married • Separated/divorced • Married
Parental education (highest)	• College or post grad • Some college • High school or Vocational school grad • Elementary school or less
Parental employment (highest)	• Manager/Professional/Technical • Clerical/Service/Armed Forces • Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler • Unskilled manual labor/Farmer

Continued

Table 1 Continued

Characteristics	Categories
Mother or father is deceased	Yes/No
Child lives with	• One parent • Both parents • No parent. Foster or grandparent(s), aunt/uncle, sibling, or other
Breastfeeding during the first 6 months of life	• Breastfed only • Milk formula only • Mixed including breastmilk • Mixed excluding breastmilk
History of disease diagnosed by a medical professional	
Tuberculosis	Yes/No
Malnutrition	Yes/No
Respiratory disease	Yes/No
Allergy	
Animals	Yes/No
Medication	Yes/No
Bee/Wasp sting	Yes/No
Food	Yes/No
Latex	Yes/No

Chapter 4. Key Characteristics Associated with Otitis Media

4.1 Introduction

Otitis media (OM), a common inflammatory disease of the middle ear, continues to be one of the most prevalent pediatric illnesses globally (1, 3). The burden of OM is especially high among children in low- and middle-income countries (LMICs), where access to healthcare is often limited and complications are more common (5, 53, 111). OM not only causes acute discomfort and hearing loss but can also lead to chronic hearing impairment and other long-term sequelae (1-3, 5, 55). These consequences highlight the necessity for effective public health strategies, particularly in LMICs where the burden is most substantial.

Various factors have been associated with risk of OM, including genetic predispositions, socioeconomic status, and environmental exposures (1-3, 17, 25-28, 30, 68, 69, 112-115). The pneumococcal conjugate vaccine (PCV) has shown potential in reducing the incidence of OM, although its effectiveness varies based on regional healthcare access and other sociodemographic factors (53, 112). Despite the recognized burden of OM and efforts to mitigate this condition, little is known about the spatial distribution of OM cases and the key factors associated with them in LMICs. Understanding these patterns is crucial for developing targeted interventions.

This study aims to investigate the spatial distribution of OM among children in Bohol, Philippines, and to identify the key characteristics associated with prevalence of OMs on neighborhood level, including proximity to healthcare facilities. By clarifying the spatial dynamics of OM and identifying relevant key factors, this study seeks to inform more effective public health interventions and resource allocation strategies, ultimately aiming to reduce the burden of OM among vulnerable populations.

4.2 Methods

4.2.1 Data Source

The study utilized secondary data from a follow-up study of a double-blind randomized controlled trial (RCT, International Standard Randomized Controlled Trial Number [ISRCTN] 62323832) investigating the efficacy of an 11-valent PCV in Bohol, Philippines, among children under two years of age (50). The parent trial included 12,191 infants born between July 2000 and December 2004, with 8,926 children (73.2%) participating in the follow-up study conducted from September 2016 to February 2020 (50). The study area is in the Central Visayas region and encompasses seven districts in Southwestern Bohol: Tagbilaran City, Baclayon, Balilihan, Corella, Cortes, Dauis, and Panglao. This predominantly rural agricultural area covers 397 km^2 and had a population of 175,000 in 2000 (50, 81).

In the parent trial, researchers enrolled and vaccinated participants in 48 government primary health care centers. The PCV, prepared by Sanofi Pasteur, included specific concentrations of *S. pneumoniae* capsular polysaccharide conjugated to either tetanus or diphtheria toxoid, while saline served as a placebo (50). Researchers conducted allocation via individual-level block randomization, with nurses who administered the allocated vaccine or placebo, participants, and clinical team who reviewed the participant data blinded to treatment assignments.

For the follow-up assessment, field personnel conducted home visits to locate participants. Upon finding a participant, field personnel obtained verbal parental consent and child assent (for those under 18 years of age) or consent (for those 18 years of age or older). Parents or primary caregivers completed a questionnaire covering demographics, socioeconomic, behavioral and health conditions. After that, children underwent otoscopic screening, tympanometry, distortion product otoacoustic emissions, and audiologic screening at the study office in Tagbilaran city (90). Geographic data, including shapefiles of political boundaries, roads and healthcare facilities were obtained from the Bohol Provincial Planning and Development Office (https://ppdo.bohol.gov.ph/) and the Philippine Geoportal (https://www.geoportal.gov.ph).

4.2.2 Variable Definitions

4.2.2.1 OM (ear disease)

During the follow-up assessment, researchers classified ear disease into four categories using an algorithm that integrated findings from otoscopic examinations, tympanometric measurements, video otoscopy recordings assessments by ear, nose, and throat (ENT) specialists (91). Categories included normal, mild ear disease (acute OM [AOM], OM with effusion [OME], myringosclerosis, or healed tympanic membrane

[TM] perforation), moderate ear disease (dry TM perforation or adhesive OM), and severe ear disease (chronic suppurative OM [CSOM]). For this analysis, participants were grouped into two categories: no and any ear disease.

4.2.2.2 Vaccine Coverage in the Neighborhood

I defined vaccine coverage (VC) in each neighborhood as $VC_i = \frac{NV_i}{N_i}$, where VC_i stands for VC in neighborhood i, NV_i is the number of children who received PCV in the parent RCT, and N_i is the total number of children enrolled in that neighborhood (81, 96).

4.2.2.3 Distance to Healthcare

I measured distance to healthcare by first calculating the Euclidean distance in kilometers (km) from each participant's residence to the nearest hospital. I then calculated the mean distance for all participants within each neighborhood to represent distance to healthcare for that neighborhood.

4.2.2.4 Traffic-related Air Pollution

Local agencies categorized roads into national, provincial, municipal, barangay, private, and trial roads (97). I quantified traffic-related air pollution using the total length of national and provincial roads within each neighborhood, as these roads are the major thoroughfares in the area.

4.2.2.5 Other Sociodemographic Characteristics

The follow-up study collected demographic, socioeconomic, health, and environmental data during the household visit. After proving verbal consent, the parent or primary caregiver was asked to respond to a survey covering various conditions. Variables included child's age and sex, birthweight, household size, crowding index (number of people per room), mother's parity and health insurance status, child's birth order, breastfeeding history, daycare and preschool attendance, smoking exposure, parental education and employment, child's chronic health conditions (e.g., asthma, heart condition, gastrointestinal, kidney and blood conditions, etc.), history of malnutrition or respiratory disease diagnoses, allergy symptoms, and a household wealth index developed with the Demographic and Health Surveys Program (DHS) methodology (110). The index is a composite measure that combines multiple indicators reflecting household assets, such as housing characteristics and ownership of selected consumer goods. For each household, a wealth score was generated using principal component analysis (PCA), with higher scores indicating wealthier households. For the Philippines, the household wealth index includes indicators such as types of roofing and flooring materials, access to electricity, ownership of appliances such as televisions and refrigerators, and access to improved water sources and sanitation facilities. The localized approach ensures the index accurately reflects the socioeconomic status variations within the country.

4.2.3 Location Information

4.2.3.1 Waypoints

Waypoints, defined as coordinates identifying exact locations, were collected using Garmin eTrex devices during the follow-up study. The Geographic Information System (GIS) officer processed the global positioning system (GPS) data of the residential location of each participant using the Garmin BaseCamp™ software, aggregating daily .gpx files into monthly and yearly files for analysis. I compiled all geographic data for each participant and linked them to follow-up survey data.

4.2.3.2 Defining Neighborhoods

I constructed a square polygon grid overlaying the study area, defining each grid cell as a neighborhood. These neighborhoods were defined solely by geography. To determine the optimal neighborhood size for analysis, I generated grids with cell sizes ranging from 800 to 2,500 meters per side, increasing in 100-meter increments, with the main study hospital, Gov. Celestino Gallares Memorial Hospital, as the centroid of a grid cell. Participants on different sides of the strait were assigned to different neighborhoods. I then assigned participants to their respective neighborhoods with a spatial join. To ensure robustness, only neighborhoods containing four or more participants were retained. I further restricted the analysis to neighborhoods connected to the main mass. I chose the final neighborhood size based on the lowest combined rankings of neighborhood and participant counts to maximize both numbers. In presence of a tie, I prioritized the one with the greatest variability in areal prevalence of OM.

4.2.3.3 Neighborhood Level Variables

For each neighborhood of designated size, I aggregated individual and family characteristics and calculated the areal OM prevalence. I calculated the percentages for categorical variables and means for continuous variables.

4.2.4 Inclusion and Exclusion Criteria

4.2.4.1 Inclusion Criteria

a. Children who participated in the parent RCT on a PCV from 2000 to 2004.

b. Provided verbal consent for the parent trial and follow-up assessments.

4.2.4.2 Exclusion Criteria

a. Unwilling to participate in surveys and assessments.

b. Deceased participants before follow-up assessment completion.

c. Inability to locate participants.

d. Lack of ear disease examination results.

4.2.5 Analysis

After identifying the neighborhood size, I compared individual characteristics from the entire sample with those included in the final neighborhoods using t-test for continuous characteristics and chi-squared test for categorical characteristics. I then aggregated these characteristics to the neighborhood level and created maps to visualize the spatial distribution of OM, vaccine coverage, distance to the closest hospital, and total road length. I used global Moran’s I index with the queen’s case contiguity weight matrix to assess the global spatial autocorrelation and created location indicators of spatial association (LISA) maps to identify local clusters (106, 107).

For the statistical modeling, I began with bivariate analysis to identify covariates with p-values less than 0.20. Starting with a full multivariable ordinary least squares (OLS) model, I applied backward selection to optimize AIC and build the final model. I evaluated the final model using the overall F-test of significance and R-squared values. To detect potential multicollinearity, I examined the variance inflation factor (VIF), with a threshold of 5, and used the correlation matrix to decide which variables to include in the presence of multicollinearity. Residual plots helped examine heteroskedasticity, outliers and curvature. I assessed if spatial pattern distorted the OLS model by running Moran’s I on the residuals and comparing it to the Moran’s I of the areal OM prevalence. In the presence of spatial autocorrelation, I employed spatial regression models to account for spatial dependence in the error term. The Lagrange multiplier (LM) tests and robust LM tests guided the selection of the appropriate spatial model (108).

To evaluate whether the association between the key characteristics identified and OM were spatially homogeneous across the study area, I employed geographically weighted regression (GWR) modeling, using the bandwidth that minimizes the corrected Akaike Information Criterion (AICc) value for optimal tradeoff between bias and variance. The Monte-Carlo significance test assessed the statistical significance of the estimated coefficients. I evaluated the models using VIF, adjusted R-squared and AICc values.

All statistical analyses were performed using R v4.3.2 and ArcGIS Pro. Statistical significance was determined at the 0.05 level unless otherwise specified.

4.3 Results

Among the 12,191 participants in the parent RCT, 8,926 (73.2%) were enrolled in the follow-up study and their parent or primary caregiver completed the parental questionnaire (Figure 13). Among those, 564 participants did not return for the ear examination, 1 child was not able to comprehend instructions, and the ear disease status was not classifiable for 40 children. After excluding those participants, 157 children did not have waypoints of their residential location documented, yielding 8,164 enrolled participants with a valid ear exam and their residential location recorded.

4.3.1 Define the Neighborhood

For each grid size from 800 meters to 2,500 meters, I listed the number of neighborhoods, number of participants covered, mean percentage of participants within each neighborhood with ear disease and its variance, and the number of neighborhoods with no participants with ear disease to help decide the optimal neighborhood size for analysis (Table 2). Table 2 also presents the total number of neighborhoods needed to cover all participants and the reasons some neighborhoods were excluded from the analysis. As grid size increased, the number of neighborhoods included for the analysis decreased while the number of participants included increased. How the number of neighborhoods and number of participants changed as the grid size increased was also presented in Figure 14. The existing political boundaries in the study area divide the area into 119 barangays (villages). For increased spatial granularity, I did not consider grid sizes that lead to fewer than 119 neighborhoods, which were grid sizes equal to or larger than 1,800 meters. Considering the trade-off between obtaining most information from the data and a larger neighborhood level sample size, I selected 1,600 meters as the grid size for analysis. This grid size allowed the analysis to include data from 98.1% of the enrolled participants with complete parental questionnaire, ear examination, and residential location records (8,011 out of 8,164) and almost 58% of the neighborhoods created (137 out of 238). To better understand the difference between the available sample and those included in the final analysis, I compared all characteristics between the two groups with chi-squared tests for categorical variables and t-tests for continuous variables (Table 3). No statistically significant difference at 0.05 level was identified between the two groups for any of the study characteristics.

4.3.2 Neighborhood Level Characteristics and Neighborhood Maps

Using the neighborhood size of 1,600 meters, I aggregated each characteristic to neighborhood level for analysis (Table 4). The mean percentage of participants with ear disease for each neighborhood was 41% and the mean percentage of participants vaccinated in the parent trial was 50%. The mean Euclidean distance from the closest hospital ranged from 0.36 to 15.00 kilometers (km) with an average of 7.16 km. Twenty-four neighborhoods had no national or provincial road within them and the neighborhood with the longest national or provincial road had a total of 5.76 km.

To spatially visualize the distribution of participants across the study area and their characteristics, I created neighborhood level maps, presenting each characteristic in quintiles. Among the final sample of 137 neighborhoods with sides of 1,600 meters, the number of participants within each neighborhood ranged from 4 to 540 (Figure 15). Neighborhoods with more participants tended to cluster around the main study hospital (Gov. Celestino Gallares Memorial Hospital in Tagbilaran city) and along the north shore of the island of Panglao and Dauis (Figure 15). Neighborhoods in Panglao and Dauis also tended to have higher percentage of participants with OM, as well as the neighborhoods along the coastline of the main island (Figure 16). Percentage of participants vaccinated during the parent PCV trial did not seem to have clusters across the study area (Figure 17). Since most hospitals in or near the study area are located along the coastline of the larger island, neighborhoods closer to the central region tended to have shorter mean distances (Figure 18a). Neighborhoods along the south shore of the island of Panglao and Dauis and those in the North had clear spatial clustering of longer distances to the nearest hospital except for a couple of neighborhoods in the northeast, showing a shorter distance due to a hospital in the north (Catigbian District Hospital). For the total length of national and provincial roads, the central area surrounding the main hospital seemed to have a cluster of neighborhoods with more national and provincial roads, but the overall pattern did not indicate clear spatial autocorrelation (Figure 18b). Insurance coverage of the participant mothers was comparatively higher in the northeast and lower around Tagbilaran city center and most parts of the island of Panglao and Dauis (Figure 19). Neighborhood level mean household wealth index and percentage of participants whose parents' highest education level was some college or above shared similar spatial pattern where those within the highest quintile were mostly close to Tagbilaran city center (Figure 20).

4.3.3 Spatial Autocorrelation

To quantify the strength of the possible spatial clustering of the neighborhood level prevalence of OM, vaccine coverage, mean distance to the nearest hospital, and total length of national and provincial roads, I examined their spatial autocorrelation both globally and locally. Using the queen's case contiguity weight matrix, the global Moran's I for areal OM prevalence was 0.31, with a Z-value of 6.47 ($p<0.001$), indicating a statistically significant considerable tendency toward clustering of neighborhoods with similar prevalence of OM across the study area (Table 5). The Moran's scatterplot (Figure 21) illustrated neighborhood level OM prevalence (x-axis) in relation to the spatially lagged OM prevalence for the neighbors (y-axis), using queen's case contiguity weight matrix. Points clustered in the upper right and lower left quadrants of the Moran's scatterplot indicated positive spatial autocorrelation, which means neighborhoods with lower OM prevalence that were surrounded by neighborhoods with lower OM prevalence, and those with higher rates were surrounded by neighborhoods with higher rates. The global Moran's I index for vaccine coverage was close to zero at -0.037, with a Z-value of -0.61 ($p=0.73$), which was not statistically significant at the 0.05 level. I failed to reject the null hypothesis that the vaccine rate was randomly distributed across the study area and no significant spatial autocorrelation was present. The magnitude of spatial clustering of the neighborhood level mean distance to the closest hospital was high (Moran's I=0.94) and statistically significant ($p<0.001$). The spatial autocorrelation of total length of national and provincial roads in each neighborhood was not significant with a small global Moran's I index of 0.08 ($p=0.06$).

The LISA maps were utilized to evaluate the local spatial heterogeneity and detect any local instability in the four characteristics of interest: prevalence of OM, vaccine coverage, mean distance to the closest hospital, and total length of national and provincial roads (Figure 22). The cluster maps can help identify local clusters, where similar values are clustered together, and outliers, where certain neighborhoods are surrounded by dissimilar values (26). In LISA maps (Figure 22), pink highlighting indicates a region with high value surrounded by neighbors with high values (high-high). Following this scheme, light blue regions indicate low-low, red regions were for high-low, and dark blue regions were for low-high. The southern part of the island of Panglao and Dauis had a hotspot of high prevalence of OM, and the northern part of the study area as a whole had a cluster of neighbors with low OM prevalence (Figure 22a). For vaccine coverage, few neighborhoods were identified to have significant local spatial heterogeneity in the LISA analysis (Figure 22b). Validating what was observed in the map of neighborhood level mean distance to the closest hospital (Figure 18a), the central area around the main study hospital had local clusters of low values, indicating close access to healthcare facilities (Figure 22c). The southwestern part of the island of Panglao and Dauis and an area in the northeast of the main study hospital had local clusters of higher values.

4.3.4 Statistical Modeling

Based on the bivariate analysis results, covariates considered for multivariable models included percentage of participants vaccinated in the parent trial, traffic-related air pollution exposure measured by the total length of national and provincial roads in km, mean household size, mean parity of mothers in the household, mean household wealth index, mean age of the child participants, percentage of female participants, percentage of participants whose mothers had health insurance, percentage of participants that were firstborn in the family, percentage of participants whose parents' highest education level is college or post grad, percentage of participants who were exclusively breastfed in the first 6 months of life, and percentage of participants ever diagnosed with respiratory disease (Table 6).

I included the above characteristics in the full multivariable OLS model. After backward selection, 6 characteristics were associated with higher neighborhood level OM prevalence: less traffic-related air pollution exposure measured by shorter total length of national and provincial road, fewer people in the household on average, lower percentage of female participants, lower percentage of participants whose mothers had health insurance, lower percentage of participants that were firstborn in the family, and lower percentage of participants who were exclusively breastfed in the first 6 months of life (Table 7). The F-statistics for overall significance of the final model was 11.99 on 6 independent variables and 132 degrees of freedom. The significance test result indicated the final model provided a better fit than the null model ($p<0.001$). The adjusted R-squared of the final model was 0.3232, suggesting the final model explained 32.32% of the variance in the outcome of interest. An analysis of variance (ANOVA) test comparing the full model including all the key characteristics identified in the bivariate analysis and the final model failed to reject the null hypothesis (F=0.61, DF=7, p=0.75). Thus, the full model was not significantly better than the final model and the final model was favored due to the principle of parsimony. No multicollinearity was identified with the VIF threshold of 5. Compared to the Moran's I for OM prevalence (Moran's I=0.312, p<0.001), the Moran's I for the residuals decreased to 0.123 (Figure 23a, p=0.004). The reduction in Moran's I implied some of the spatial autocorrelation presented in the prevalence of OM was explained by the OLS model. However, the residuals were still moderately positive spatial autocorrelated, showing that certain spatial patterns remained unexplained by the OLS model.

To account for the spatial dependence in the error term, spatial regression models were utilized. Based on the Lagrange multiplier diagnostic tests, the statistics for robust LM-error model (RLMerr=1.7651, df=1, p=0.184) was smaller than that for robust LM-lag model (RLMlag=9.2417, df=1, p=0.002), suggesting the use of a spatial lag model (SAR) (Table 7). Compared to the OLS model, the SAR model performed better as it had higher adjusted R-squared statistics, accounting for 40.69% of the variation in the outcome of interest and had lower AICc (-175.51 compared to -164.13 for the OLS model). The SAR also yielded lower spatial dependency in residuals, both in terms of significance and magnitude (Figure 23, Moran's I=-0.035, p=0.57). All the characteristics in the final OLS model were still statistically significant in the SAR model. None of the estimated effects changed direction. The SAR model drawn most of the estimated effects towards the null compared to OLS results, with the exception of percentage of female participants. In the OLS model, one percent increase in percentage of female participants in the neighborhood was associated with 0.279 percent decrease in local OM prevalence. While in the SAR model, the effect was a 0.290 percent decrease. Both associations were statistically significant ($p<0.01$).

To address the potential spatial non-stationarity within the study area, I used a GWR model (Table 7). The GWR model performed better than the OLS model based on both adjusted R-square (0.4102) and AICc (-173.65). The GWR showed comparable performances to the SAR model according to adjusted R-square (0.4102 compared to 0.4069), and AICc (-173.65 compared to -175.51). The direction of effects of the 6 characteristics remained consistent with those observed in the OLS model (Table 7 and Figure 24). Higher percentage of female participants was statistically significantly associated with lower prevalence of OM in the inland area in the North (Figure 24a), and higher percentage of participants whose mothers had health insurance was also associated with lower OM prevalence in the majority of the study area, except for the southern part of the island of Panglao and Dauis (Figure 24b). However, none of the key characteristics were statistically significant according to the Monte-Carlo significance test for the spatial variation of the local parameter estimates, indicating little spatial non-stationarity, leaving SAR as the preferred model for this analysis.

4.4 Discussion

This study identified key characteristics associated with a higher prevalence of OM in Bohol, Philippines neighborhoods, including a lower percentage of female participants, fewer of the participants were firstborn in their families, more people in the household on average, lower percentages of participants exclusively breastfed in the first 6 months of life, lower percentages of participants whose mothers had health insurance, and less exposure to traffic-related air pollution, indicated by a shorter total length of national and provincial roads. These neighborhood-level risk factors are consistent with the individual-level risk factors identified in previous studies. Studies from different parts of the world have consistently shown that OM occurs less frequently among females. Studies in North America reported higher odds of having OM among boys with odds ratios ranging from 1.23 (95% CI, 1.19-1.27) to 1.96 (95% CI, 1.46-2.64) (116-118). Studies in Europe (119-121) and Asia (122, 123) also showed an increased odds associated with male gender during the first few years of life.

While OM itself is not contagious, the virus and bacteria responsible for causing OM can be transmissible. As is true for most childhood infectious diseases, reducing exposure to respiratory pathogens can be preventive against OM. Being a firstborn and a smaller family size reduce exposure on individual level (3, 30, 124). On a neighborhood level, since the parent trial reached out to all children born into the area during the recruitment period, a higher percentage of the participants being firstborn in the neighborhood may indicate fewer young children. A smaller family size on average may indicate reduced exposure to young children, who are often carriers of the virus and bacteria that can lead to OM. Smaller family sizes may also be associated with higher socioeconomic status, which has been linked to lower risk for OM (2, 3, 114, 125).

Breastfeeding has long been considered protective against OM, and the present analysis added to the literature by providing a neighborhood level perspective (2, 3, 17, 30, 68, 126). About 62% of the participants in the present study were exclusively breastfed during the initial 6 months of life. The United Nations International Children's Emergency Fund (UNICEF) estimates for the Philippines in 2003 on percentage of children exclusively breastfed in the first 5 months of life was much lower at 34.0% (95% CI: 30.2% - 38.0%) nationally and 26.9% (95% CI: 16.6% - 40.3%) in Central Visayas, where Bohol locates (127). According to the estimates, breastfeeding behavior varies by geography; urbans area had a lower percentage of children exclusively breastfed, and our study area was a predominantly rural area.

This analysis revealed that a higher percentage of participants whose mother had health insurance was associated with a lower OM prevalence in the neighborhood. In the current study, the parental questionnaire assessed maternal health insurance coverage with the question: “Do you (mother) have health insurance?” and requested specification of the insurance type if the answer was affirmative. In our sample, approximately 68% of the participants’ mothers were insured with the Philippine Health Insurance Corporation (PhilHealth) only, 0.5% with private health insurance only, and 2% with both PhilHealth and private health insurance, resulting in a 70% overall PhilHealth coverage. Due to the small number enrolled with private health insurance, the association identified are probably all attributable to PhilHealth. PhilHealth, founded in 1995, represents the

Philippine's approach to universal health coverage (UHC) with an initial mission to achieve UHC by 2010 (128). However, a survey in 2010 showed only 36% coverage, which increased to 61% by 2017 (129, 130). In our study area, the neighborhood level maternal health insurance coverage ranged from 17.6% to 100%, and was much higher in the northeast, whereas coverage was lower in Tagbilaran city center and most of the island of Panglao and Dauis (Figure 19). Prior research has established an association between increased PhilHealth coverage and higher wealth index and educational attainment (130, 131). However, our findings diverge from these results, as the spatial distribution of neighborhood insurance coverage differed from that of household wealth index and education attainment (Figure 19 and Figure 20). Specifically, insurance coverage appeared to play a protective role against OM on neighborhood level, independent of wealth and education factors. Health insurance can improve access to healthcare services, including routine check-ups and early interventions for minor illnesses, potentially preventing complications such as OM. Insured mothers might also have better health literacy thanks to more frequent interactions with healthcare providers, leading to improved health practices and preventive care for their children. In addition, insurance coverage can alleviate financial barriers, allowing families to seek timely medical treatment. These factors collectively contribute to lower OM prevalence in neighborhoods with higher insurance coverage.

Health insurance plays a critical role in improving access to healthcare, with proximity to healthcare facilities also being a crucial component. The previous analysis of the parent trial revealed an intriguing finding that children living near the main study hospital did not exhibit significant benefits from PCV vaccination, whereas those resided farther away experienced a substantial reduction in radiographic pneumonia diagnoses following vaccination (132). This finding highlighted the potential impact of healthcare accessibility, as measured by proximity to care, on health outcomes within this population. Building upon this, the current study integrated the Euclidean distance from the closest hospital to further explore spatial dynamics and evaluate whether closer proximity to healthcare facilities correlates with decreased rates of OM. Examination of LISA maps revealed a noteworthy pattern that a hotspot indicating longer distances to the closest hospital (Figure 22c) coincided with a hotspot of elevated prevalence of OM (Figure 22a) in the southwest part of the study area. This alignment suggests a plausible association between access to healthcare and areal OM prevalence in this specific area. However, our bivariate analysis did not identify a statistically significant association between Euclidean distance from the closest hospital and neighborhood-level OM prevalence ($p=0.46$). This indicates that while proximity to healthcare facilities may indeed be associated with certain health outcomes, it may not be directly associated with prevalence of OM within this population. The association between health insurance coverage and healthcare accessibility, including proximity to healthcare facilities, emphasizes the importance of a multifaceted approach to improve health outcomes. Notably, in the rural north of the study area, where both mean Euclidean distance to the nearest hospital and maternal insurance coverage were relatively high, there may be a different dynamic at play. Therefore, I advocate for targeted initiatives to expand insurance coverage, particularly in areas with lower coverage rates, such as the Tagbilaran city center, Panglao, and Dauis (Figure 19).

The present study found that greater exposure to traffic-related air pollution was associated with a lower neighborhood level OM prevalence. However, the study did not directly measure air pollution; instead, I used the total length of national and provincial roads within each neighborhood as a proxy for traffic-related air pollution. This approach has its limitations, as the proxy variable does not directly quantify air pollution. In urban settings, previous studies have measured air pollution using direct measurements of specific pollutants (e.g., nitrogen dioxide, fine particulate matter, sulfur dioxide) or reported values from local agencies (25, 113). Unfortunately, air pollution data were not available for this study, either publicly or through local agencies. Using the total length of national and provincial roads as a proxy for traffic-related air pollution may not be an accurate estimate, as it lacks specificity for the intended interpretation. Proxies can be useful when direct measurements are unavailable, but the effectiveness depends on how well the proxy correlates with the actual measurement of interest. In this case, assuming a perfect correlation between air pollution and road length could introduce measurement error or potential misclassification. The observed inverse association between road length and OM prevalence might reflect that. Major roads are typically associated with more traffic and, therefore, higher exposure to pollutants; however, airborne particles also contribute to OM, and not including more local roads may lead to an underestimate of exposure to dirt or gravel (133, 134). By 2019, less than half of provincial roads in Bohol were paved, with particle exposure measured primarily for these roads but not for more local, unpaved roads (135). Additionally, air pollution in the study area may originate from various sources beyond vehicle emissions, including agricultural activities, residential emissions, construction activities, and marine and shipping activities. Thus, the proxy of road length may have failed to capture the complex and multifactorial nature of air pollution in the study area. This misalignment might explain why we found an association opposite to previously reported from studies using direct measurements of air pollution. Based on results from the GWR model (Figure 24f), neighborhoods with statistically significant clusters of this association were located in the northeast of the study area, separated by a forest/watershed area (Figure 4). Notably, no hospital was located on that side of the forest/watershed area. An alternative explanation of the observed association is that, for those neighborhoods, the total length of national and provincial roads does not represent exposure to traffic-related air pollution. Instead, it measures access to healthcare. Future research should aim to incorporate direct measurements of air pollution to better understand the relationship between traffic-related air pollution and OM prevalence.

Contrary to my hypothesis, the Monte-Carlo significance test for the spatial variation of local parameter estimates from the GWR model indicated that key characteristics did not vary significantly across the study area. Despite this, the GWR model achieved the highest adjusted R-squared (0.4102) and identified some localized patterns and clusters of significance within the study area (Figure 24). However, GWR may not have been the most appropriate method for this analysis, as it performs best with a sample size of at least 160 neighborhoods, which allows for each parameter to be spatially heterogeneous (136, 137). The current study included only 137 neighborhoods. Increasing the sample size of neighborhoods would have required decreasing the neighborhood size (i.e., the number of participants within a neighborhood), which would have reduced the number of participants included in the final analysis and potentially impacted the representativeness of the results (Table 2 and Figure 14). However, representativeness does not solely depend on sample size. It also depends on the inclusion and exclusion criteria and whether certain groups are systematically underrepresented or missing from the analysis. The neighborhood size used in this study was chosen after careful consideration of the trade-offs between having a larger sample size of neighborhoods and maximizing the information obtained from the study data. The chosen neighborhood size aimed to capture sufficient variability while maintaining a robust sample. The smaller number of neighborhoods may have hindered the performance of GWR in this study, affecting its ability to detect spatial heterogeneity. Therefore, while GWR provides valuable information on general patterns and local estimates, the results from SAR are the preferred estimates for the identified associations. Future studies should aim for a larger sample size of neighborhoods while ensuring a representative sample to better utilize the strengths of GWR and ensure robust spatial analysis.

Higher vaccine coverage in the neighborhood was associated with a lower prevalence of OM in bivariate analysis, although this association was not statistically significant (p=0.12). Therefore, the results did not support a long-term secondary impact of PCV coverage on OM prevalence among the study population. In the present study, 44% of participants had OM, and the neighborhood level OM prevalence averaged 41%

(95% confidence interval [CI]: 38% - 44%). This rate is close to the higher bound of previous OM prevalence estimates from different regions around the world (53, 111, 138). The present study included all stages of OM, from AOM to CSOM, while some previous studies only included certain stages. Additionally, this study used data from robust physical exams performed by medical professionals, including otoscopy, tympanometry, otoacoustic emission, and audiometry. In contrast, some previous studies relied on survey data or did not utilize as many methods for examination (111). The comprehensive diagnostic approach employed in the current study provided a more accurate assessment of OM prevalence, potentially explaining the higher observed rates compared to other studies.

Except for OM status, most characteristics assessed in this study were collected from the parental questionnaire, potentially introducing self-report bias. As the study utilized secondary data, the key characteristics explored were limited to those that had been collected or were publicly available. To address gaps and validate the data, I consulted with other researchers who had visited the study area and searched for local information from government websites. This study, like all others working with grouped data, is susceptible to the ecological fallacy and its geographic manifestation, modifiable areal unit problem (107). Therefore, extrapolating the findings to individual levels or other neighborhood sizes should be done with caution.

This study is the first to explore spatial variation of OM and its associated characteristics at the neighborhood level in LMICs. Using ear examination data collected through multiple methods by medical professionals, we found that the prevalence of OM was comparatively high among study participants, confirming the elevated burden of the disease in LMICs. Additionally, this present study demonstrated the utility of spatial methods in public health research to identify target neighborhoods for interventions. Our findings revealed that maternal health insurance coverage, particularly through PhilHealth, is associated with lower OM prevalence at the neighborhood level. This underscores the importance of health insurance in improving access to healthcare services, leading to early intervention and prevention of conditions like OM. Despite the lack of significant spatial variation in key characteristics across the study area, the GWR model identified localized patterns and clusters, suggesting potential areas for targeted interventions. Furthermore, the unexpected association between traffic-related air pollution and OM prevalence highlights the need for more precise measurement of environmental factors in future research. Given these findings, I advocate for initiatives to expand PhilHealth coverage in Dauis, Panglao, and Tagbilaran city to protect children from OM and improve their overall well-being. This targeted approach could mitigate the high prevalence of OM observed and enhance health outcomes in vulnerable communities.

Figure 13. CONSORT diagram.

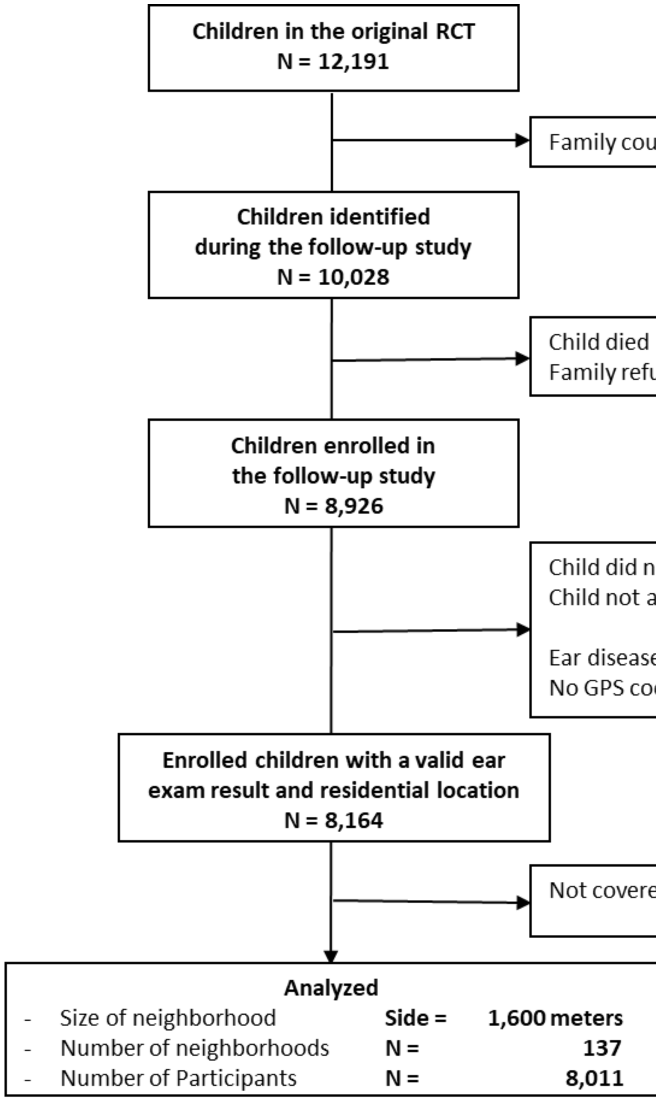


Figure 14. Changes in number of neighborhoods and number of participants covered for different grid sizes.

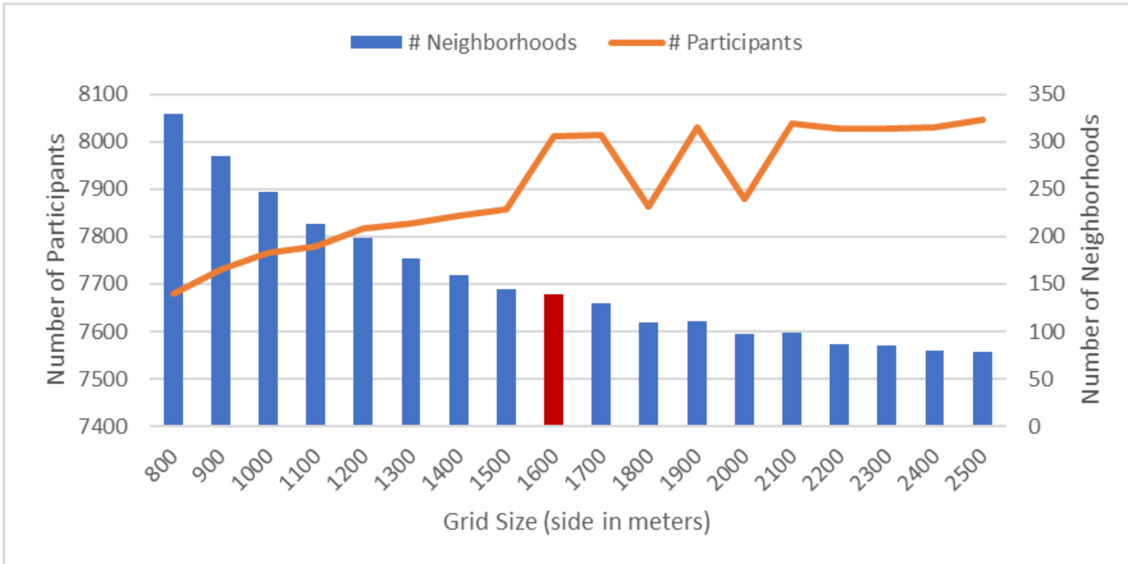
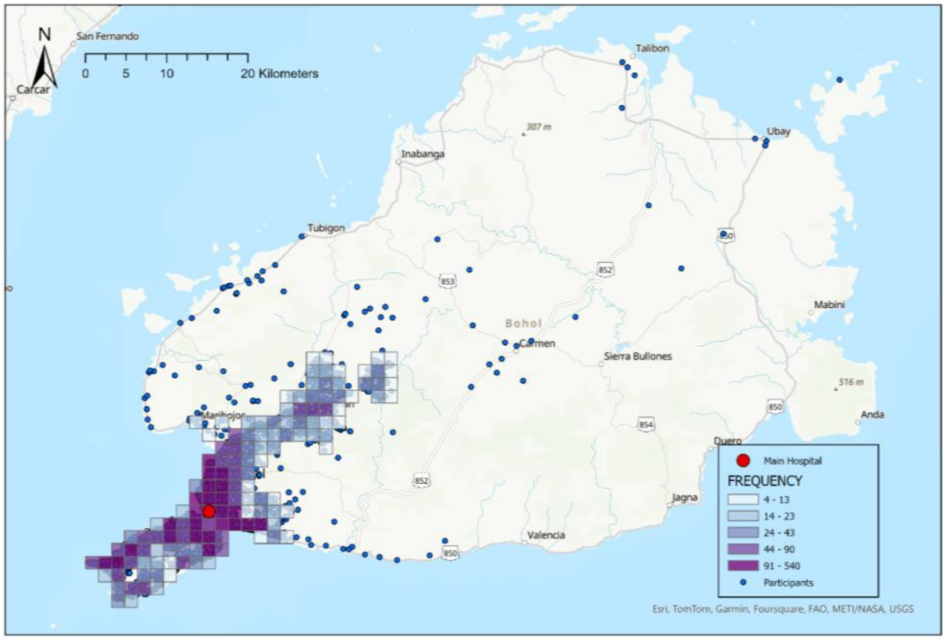
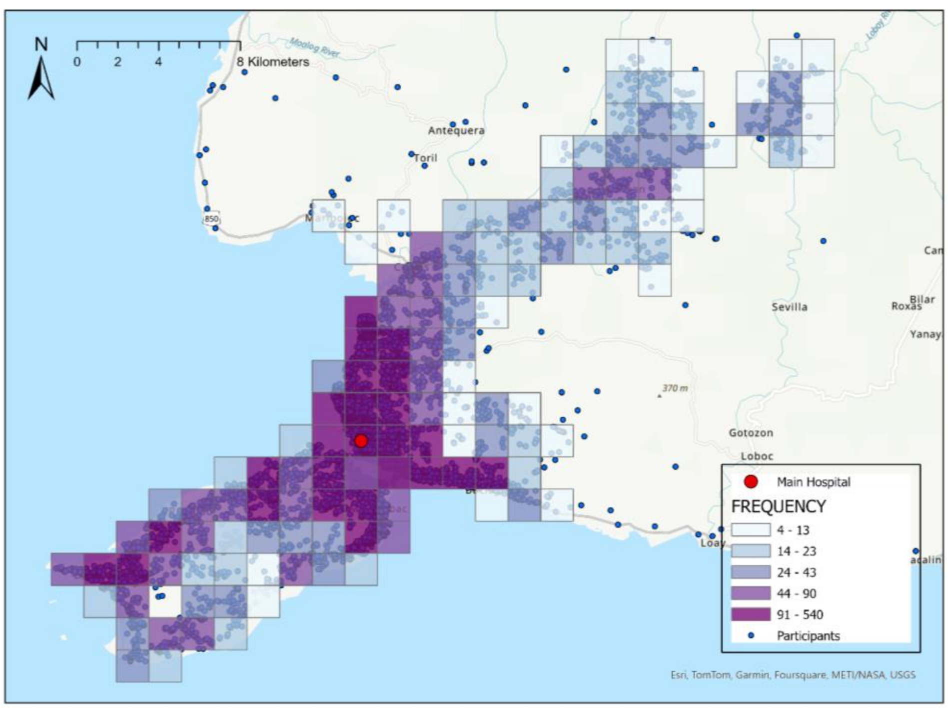


Figure 15. Number of participants in each neighborhood (a) in Bohol, Philippines and (b) across the study area (neighborhoods size: 1,600 meters).



(a)



(b)

Figure 16. Neighborhood level percentage of participants with ear disease (neighborhood size: 1,600 meters).

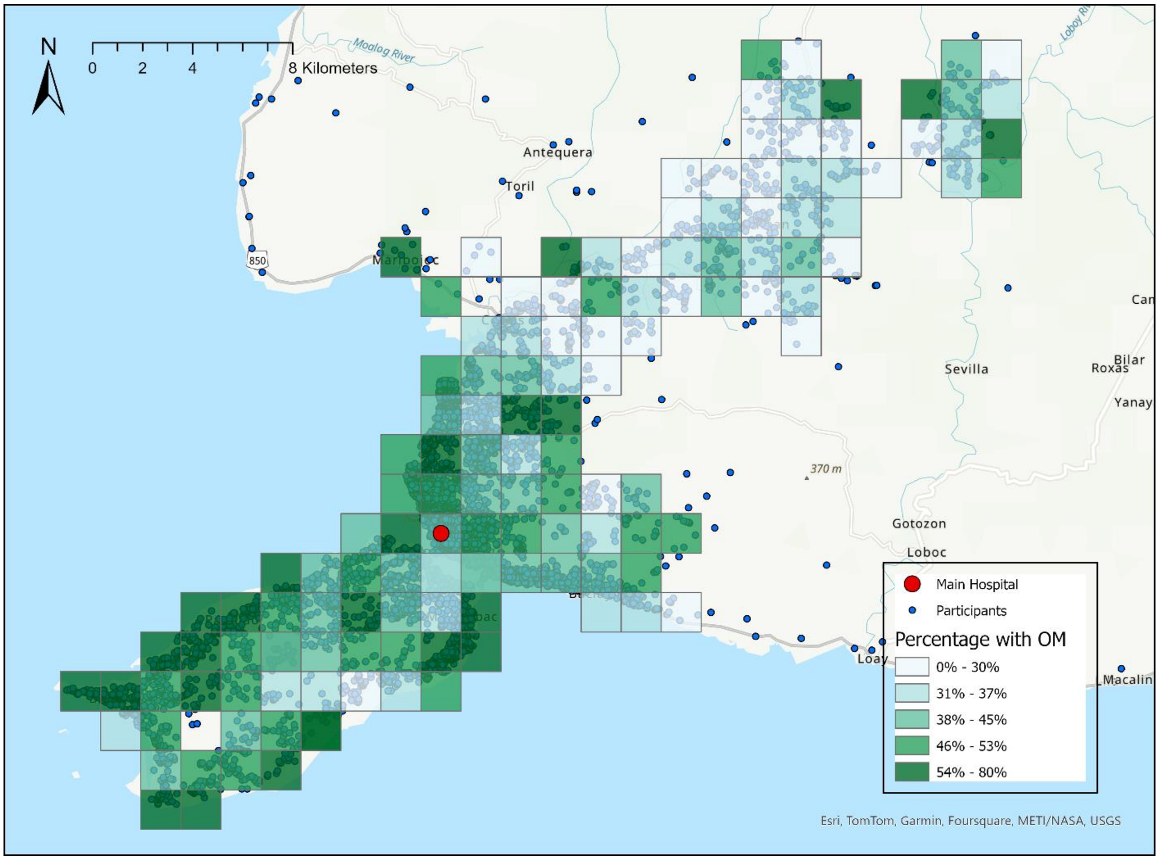


Figure 17. Neighborhood level percentage of participants vaccinated during the parent trial (ISRCTN: 62323832) (neighborhood size: 1,600 meters).

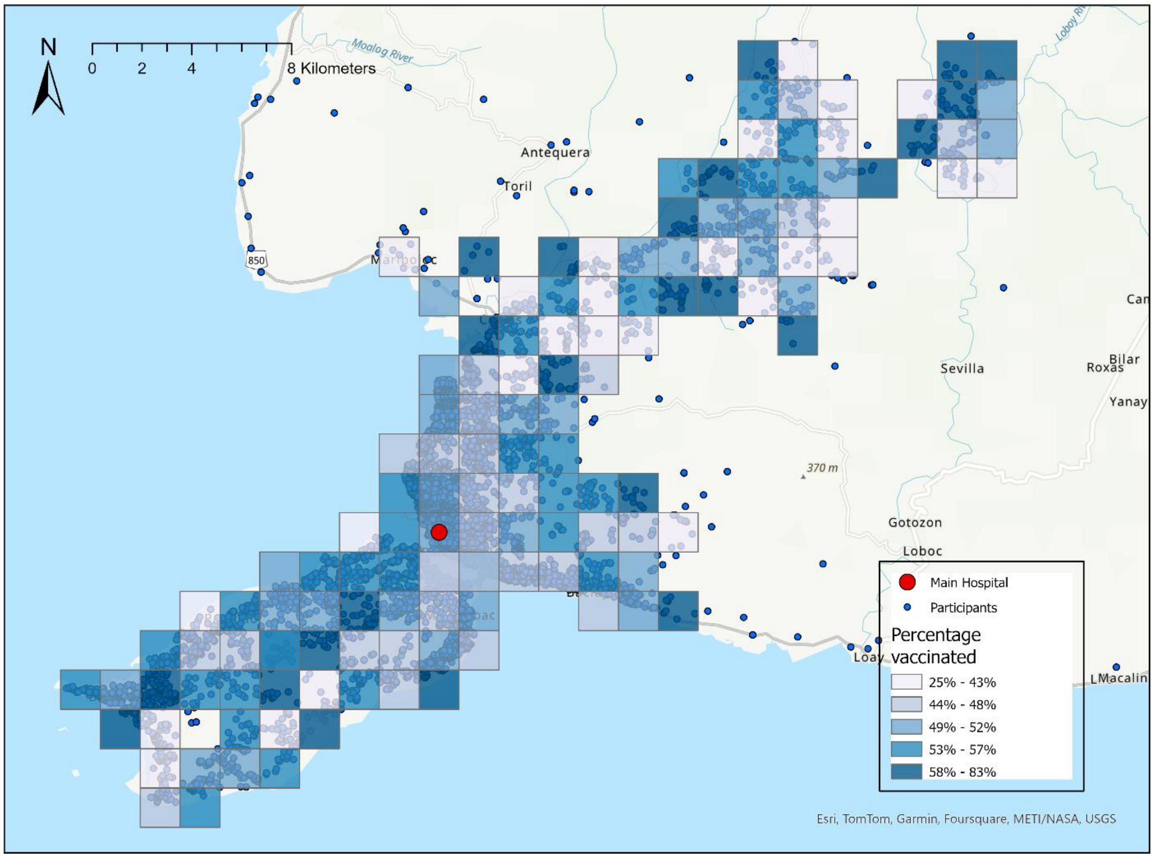
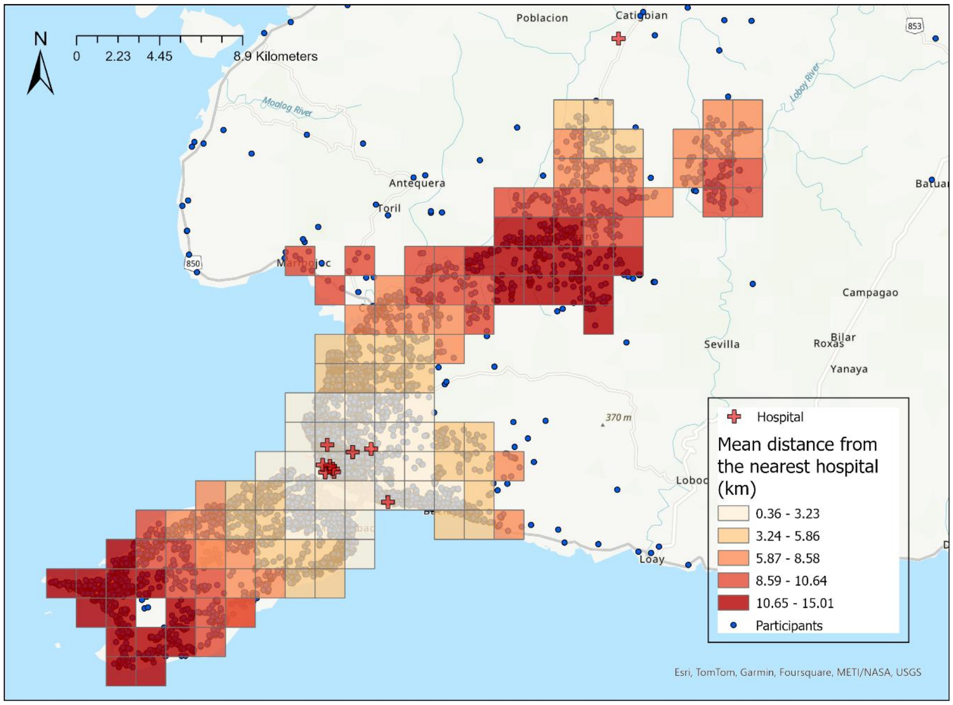
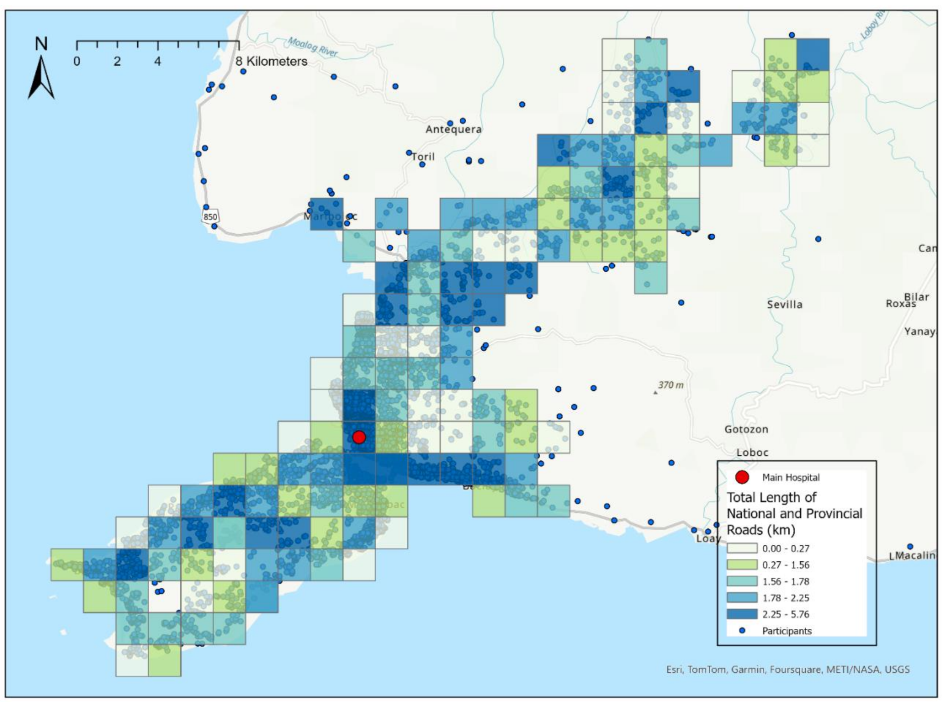


Figure 18. Neighborhood level (a) mean distance to the closest hospital in km and (b) total length of national and provincial roads in km (neighborhood size: 1,600 meters).



(a)



(b)

Figure 19. Health insurance status among participants' mothers and neighborhood level percentage of participants whose mothers had health insurance.

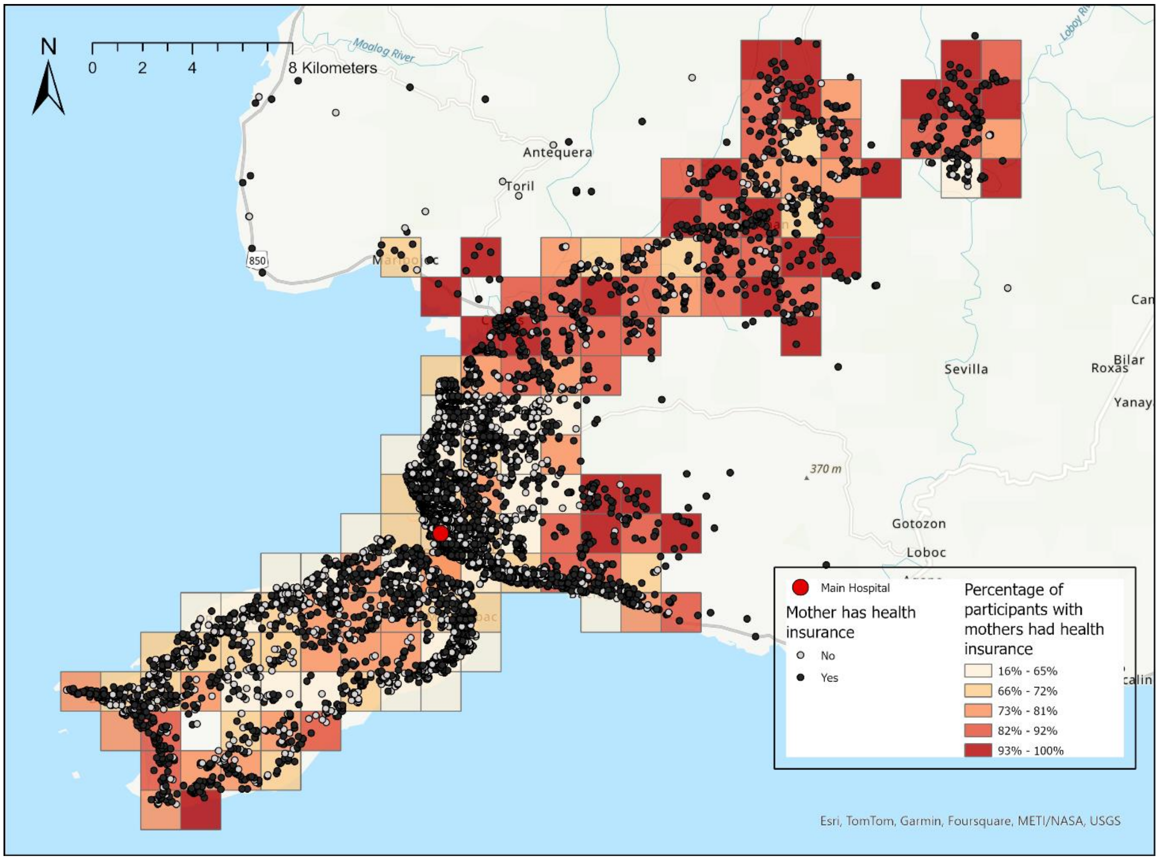
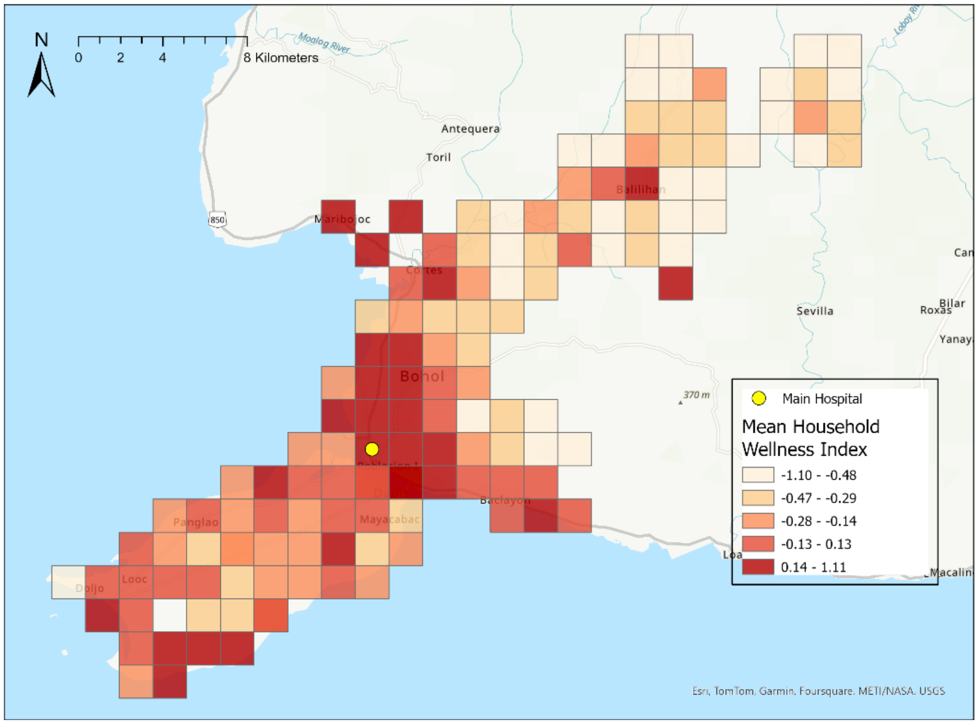
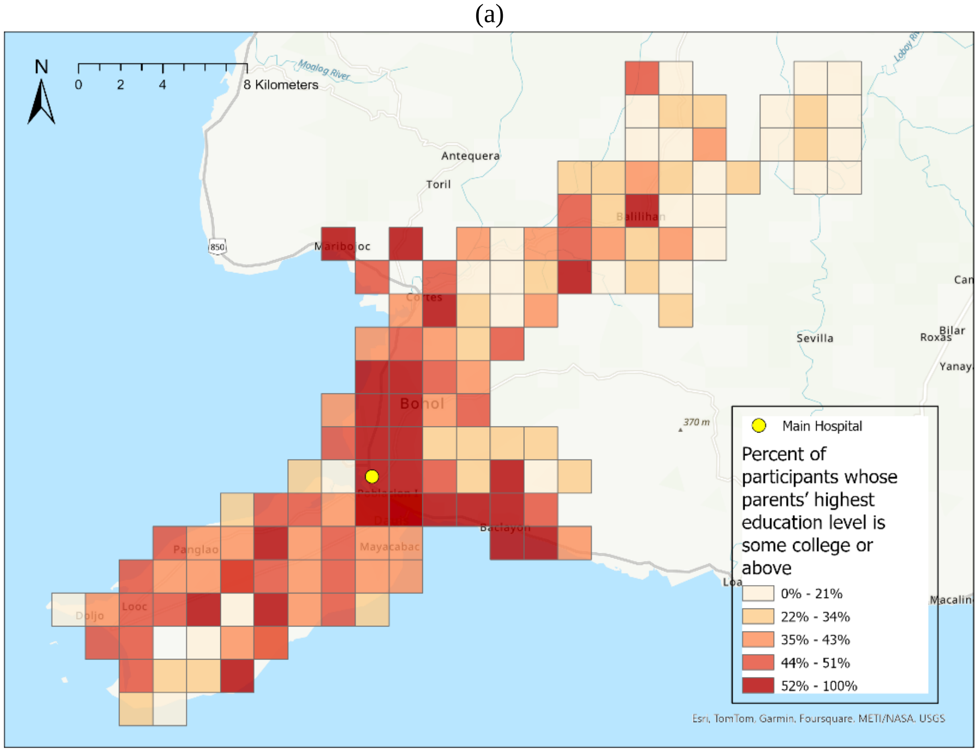


Figure 20. Neighborhood level (a) mean household wealth index and (b) percentage of participants whose parents' highest education level is some college or above.



(a)



(b)

Figure 21. Moran scatterplot of neighborhood level otitis media (OM) prevalence.

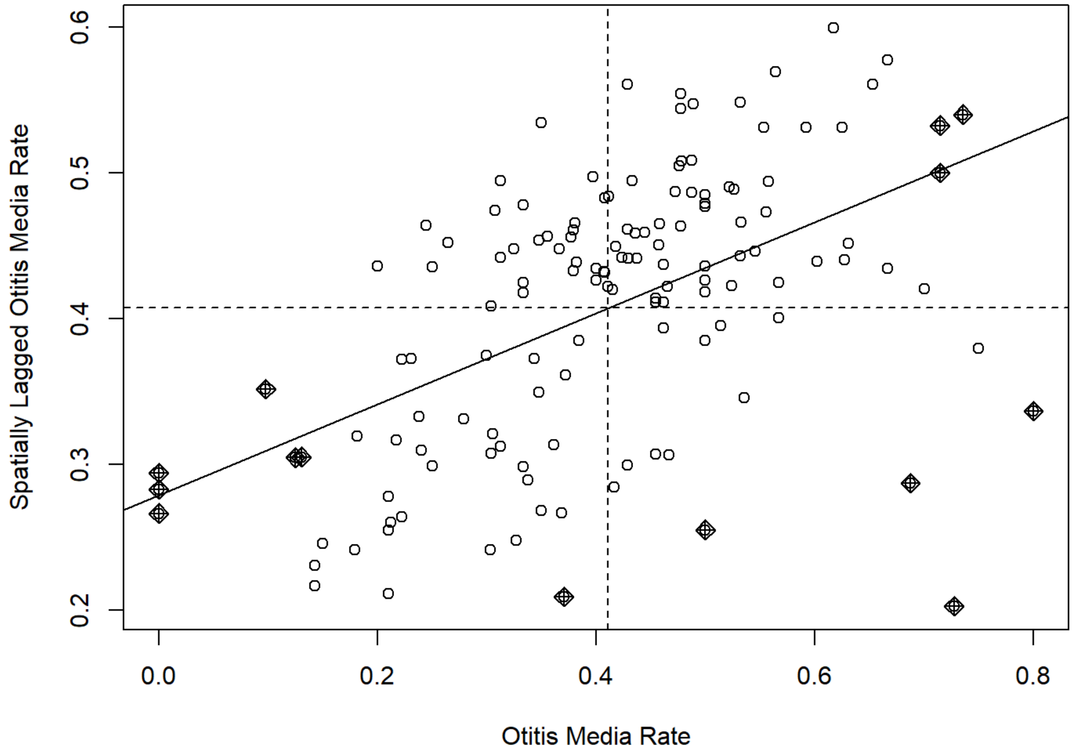
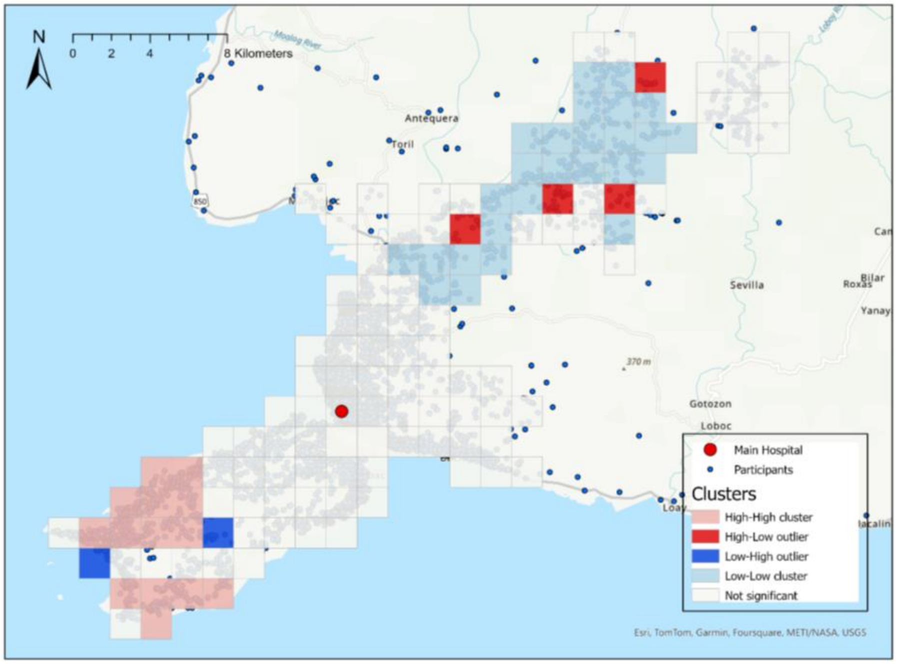
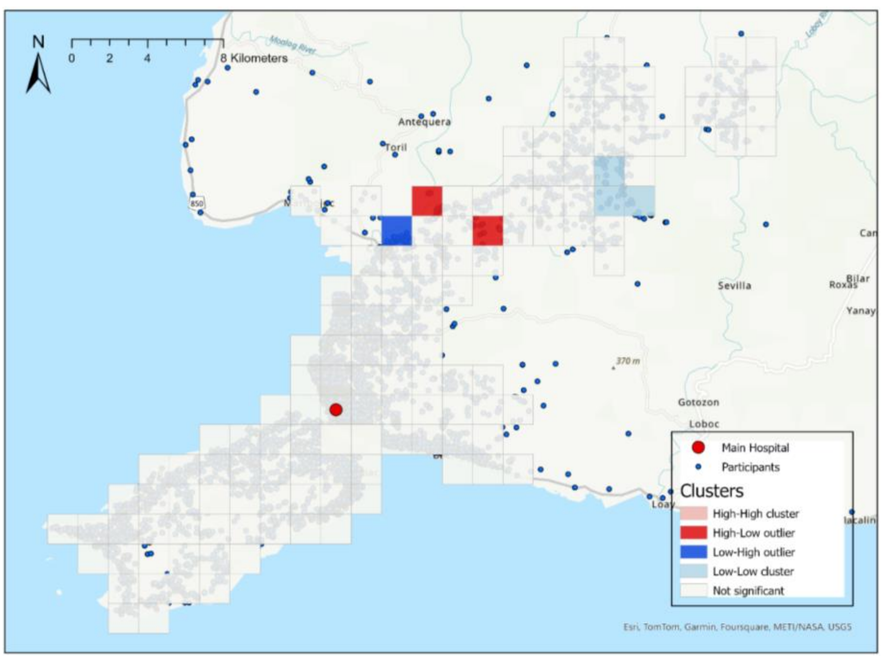


Figure 22. Local indicators of spatial association (LISA) maps on neighborhood level of (a) otitis media (OM) prevalence, (b) vaccine coverage, (c) mean distance to the closest hospital, and (d) total length of national and provincial roads in Bohol, Philippines (neighborhood size: 1,600 meters).



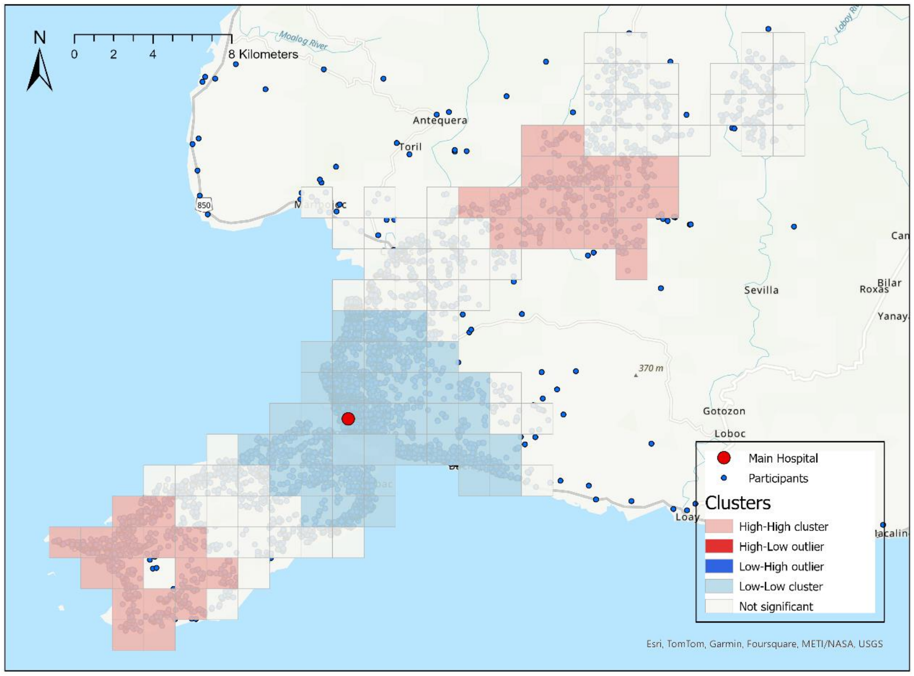
(a)



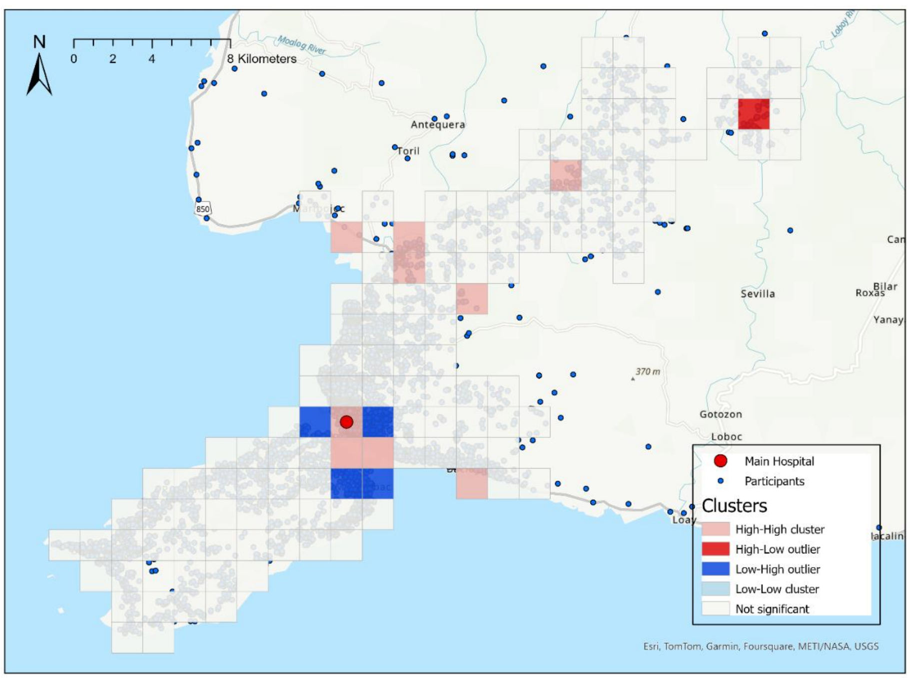
(b)

Continued

Figure 22 Continued

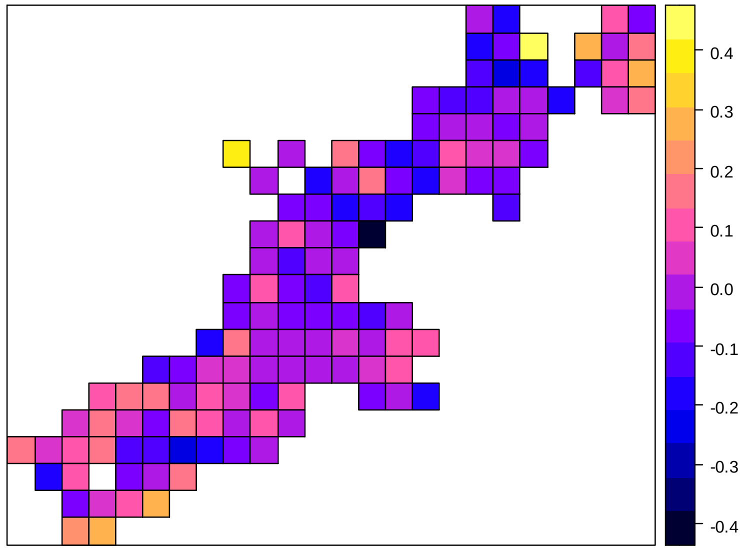


(c)

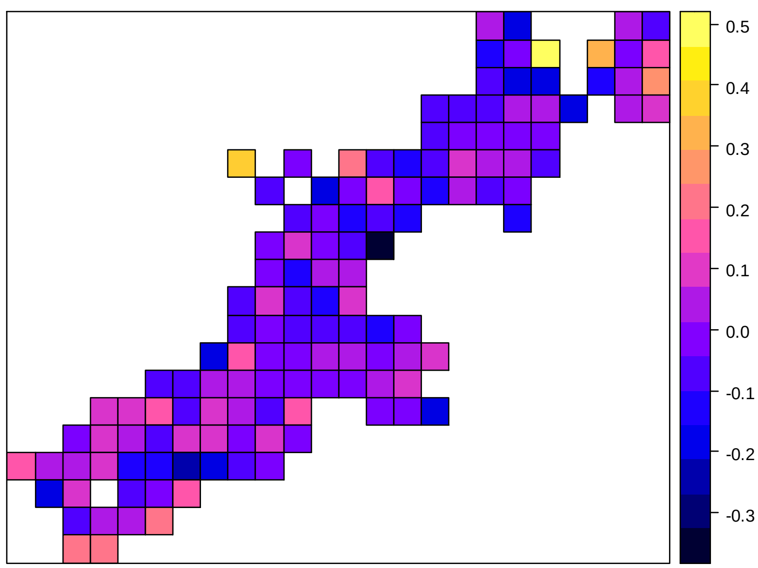


(d)

Figure 23. Residual plot of (a) the final ordinary least square (OLS) model and (b) the spatial lag model (SAR) model.



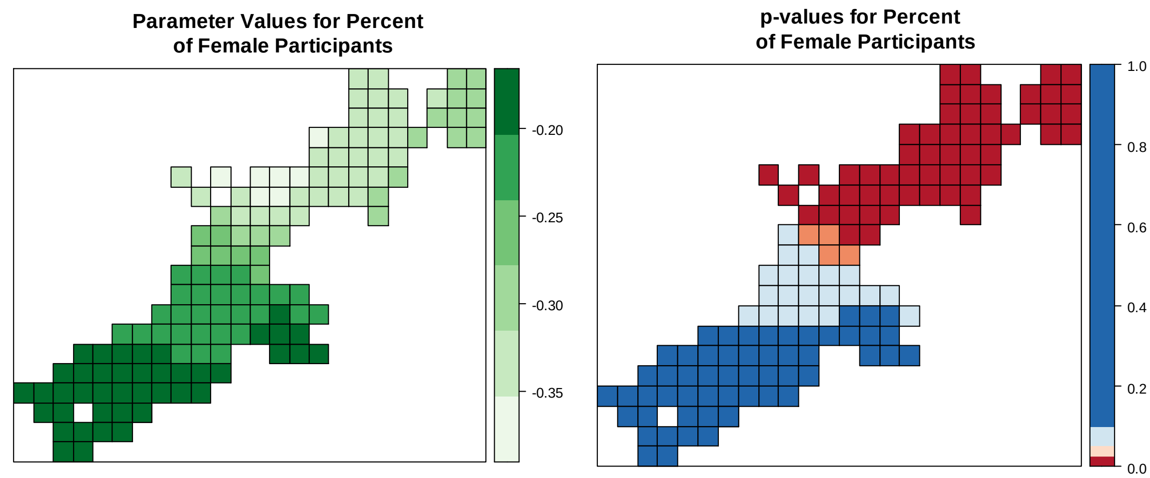
(a)



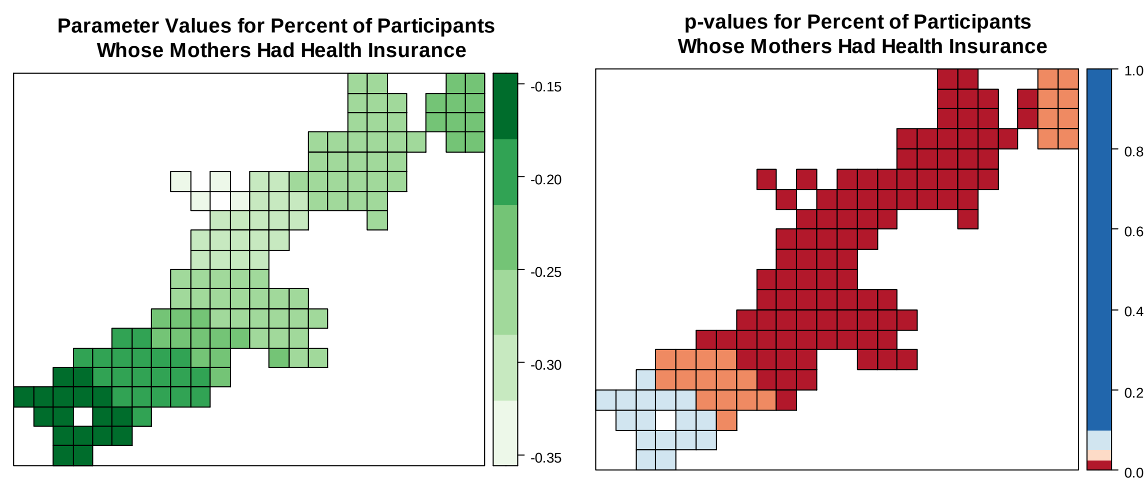
(b)

Figure 24. Parameter values and p-values from the geographically weighted regression (GWR) model for each key characteristic.

(a) Percentage of female participants, (b) Percentage of participants whose mothers had health insurance, (c) Percentage of participants that were firstborn in the family, (d) Percentage of participants who were exclusively breastfed in the first 6 months of life, (e) Mean number of people in the household, and (f) Air pollution exposure measured in total length of national and provincial roads in km.



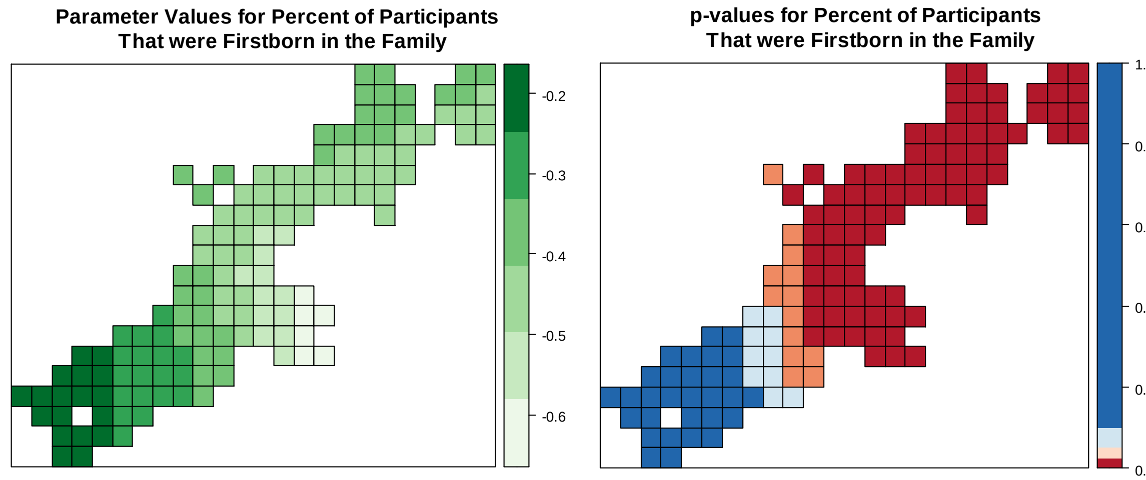
(a)



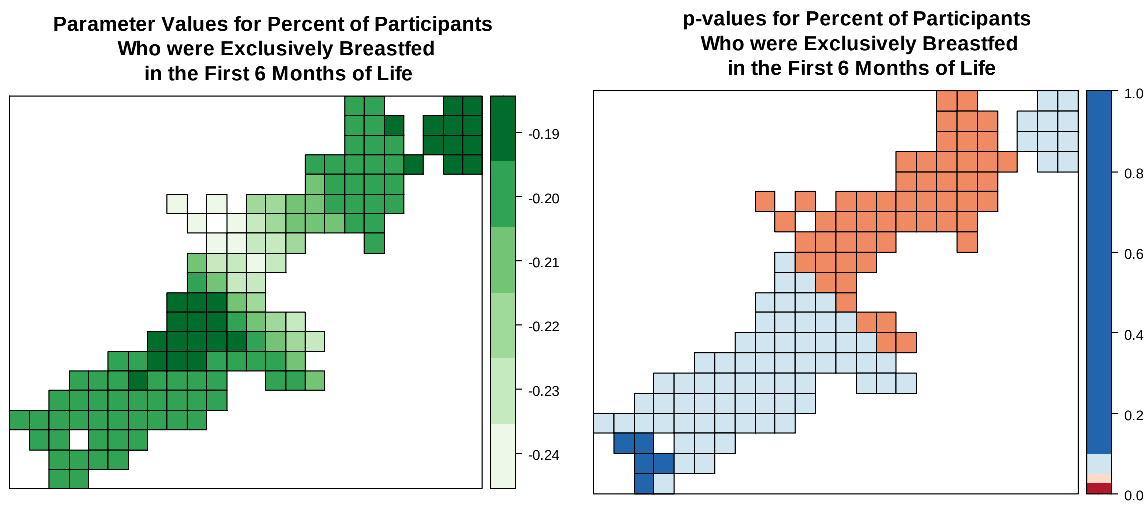
(b)

Continued

Figure 24 Continued



(c)



(d)

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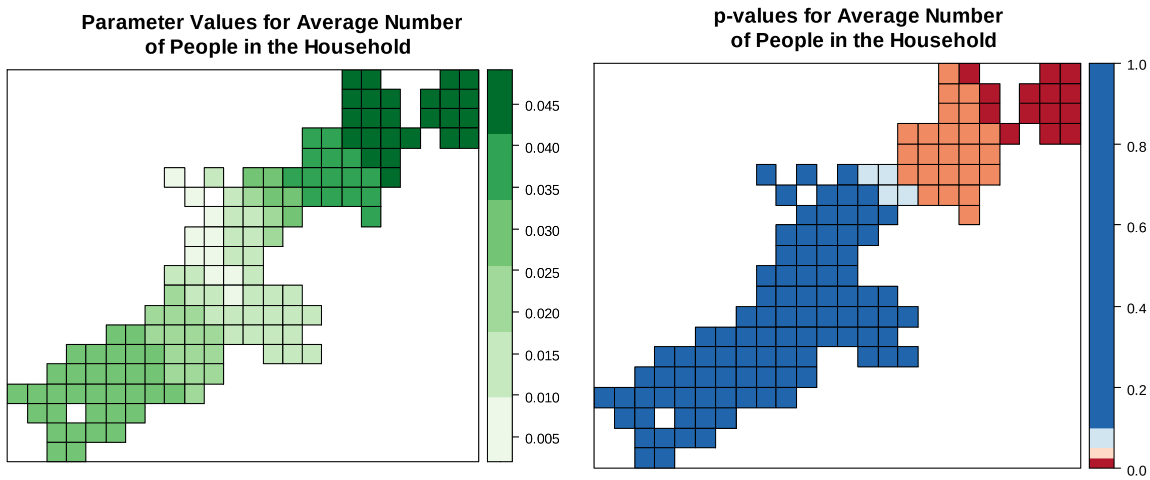
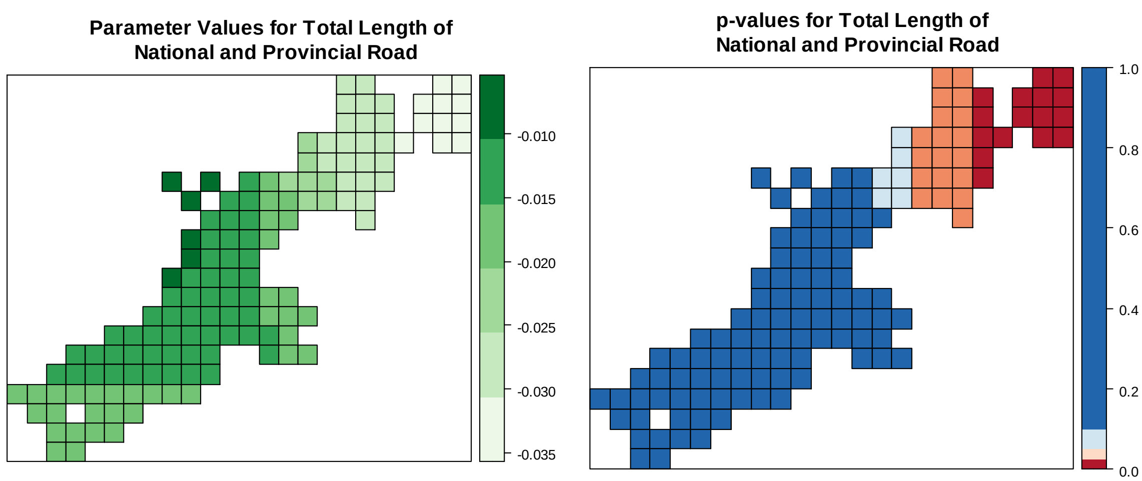
Figure 24 Continued



(e)



(f)

Table 2. Metrics used to determine the optimal neighborhood size to identify key characteristics associated with the areal otitis media (OM) prevalence.

Using the main study hospital as the centroid of the first grid cell, grids of varying sizes were overlayed on the study area. For each grid size ranging from 800 to 2,500 meters per side, the table lists the number of neighborhoods (NB) in the final sample, the number of participants included, the mean percentage of participants with OM and its variance, the number of neighborhoods with no OM cases, the total number of neighborhoods created, and the reasons for excluding some neighborhoods. This information guided the decision on the optimal neighborhood size.

							Removed due to	
Grid size (m)	**Number of NB***	**Number of Participants**	**Mean % with OM**	**Variance**	**Number of NB with no participants with OM**	**Original sample size (NB)**	**Small sample size**	**Not connected to main mass**
800	329	7679	0.414	0.035	13	562	216	17
900	284	7731	0.400	0.033	14	476	174	18
1000	247	7765	0.411	0.034	7	420	155	18
1100	213	7780	0.399	0.029	5	374	149	12
1200	198	7816	0.407	0.030	4	336	122	16
1300	177	7829	0.411	0.028	4	306	119	10
1400	159	7844	0.401	0.027	2	281	114	8
1500	144	7857	0.403	0.027	3	251	99	8
1600	**137**	**8011**	**0.411**	**0.025**	**3**	**234**	**97**	**0**
1700	129	8015	0.404	0.021	1	223	93	1
1800	109	7864	0.419	0.025	1	206	88	9
1900	111	8029	0.410	0.022	0	200	87	2
2000	97	7880	0.396	0.022	1	185	81	7
2100	98	8038	0.401	0.022	2	180	81	1
2200	86	8026	0.413	0.022	1	170	80	4
2300	85	8026	0.434	0.024	0	165	77	3
2400	80	8030	0.413	0.021	0	159	76	3
2500	78	8047	0.408	0.024	1	145	64	3

* NB: neighborhoods

Table 3. Descriptive statistics of the participants of a randomized controlled trial (RCT) on pneumococcal conjugate vaccine (PCV) in Bohol, Philippines who completed the follow-up study (n=8,164) and those lived within the final neighborhoods with a grid size of 1,600 meters (n=8,011). All characteristics were evaluated at the follow-up.

	Participants completed the follow-up study N=8,164			**Analyzed participants (Grid size: 1,600m) N=8,011**				
Categorical characteristics	**N**	**n**	**%**	**N**	**n**	**%**	**$\chi2$**	**P[1]**
Child has ear disease	8164			8011			0.06	0.81
Yes		3581	43.9		3529	44.1		
No		4583	56.1		4482	56.0		
Vaccinated in the parent trial	8164			8011			0.04	0.84
Yes		4106	50.3		4016	50.1		
No		4058	49.7		3995	49.9		
Child sex	8164			8011			0.01	0.96
Male		4147	50.8		4066	50.8		
Female		4017	49.2		3945	49.2		
Child has a chronic health condition	8151			7998			0.01	0.94
Yes		240	2.9		234	2.9		
No		7911	97.1		7764	97.1		
Daycare attendance	8151			7998			0.01	0.95
Yes		6878	84.4		6752	84.4		
No		1273	15.6		1246	15.6		
Preschool attendance	8154			8002			0.03	0.85
Yes		3252	39.9		3179	39.7		
No		4902	60.1		4823	60.3		
Mother had health insurance	8060			7909			0.05	0.82
Yes		5820	71.3		5698	71.1		
No		2240	27.4		2211	27.6		
Child's birth order	8162			8009			0.08	0.96
First		2241	27.5		2185	27.3		
Second to fourth		4425	54.2		4347	54.3		
Fifth or more		1496	18.3		1477	18.4		
Member(s) in the household regularly smoke	8158			8005			0.07	0.79
Yes		3012	36.9		2972	37.1		
No		5146	63.1		5033	62.9		
Child smokes cigarettes	6420			6293			0.01	0.93
Yes		135	2.1		131	2.1		
No		6285	97.9		6162	97.9		
Child ever diagnosed with malnutrition	8149			7996			0.31	0.58
Yes		473	5.8		466	5.8		
No		7676	94.2		7530	94.2		

Continued

Table 3. Continued

	Participants completed the follow-up study N=8,164			Analyzed participants (Grid size: 1,600m) N=8,011				
Categorical characteristics	**N**	**n**	**%**	**N**	**n**	**%**	**χ2**	**P[1]**
Parental education (highest)	8152			8000			0.04	1.00
College or post grad		2605	32.0		2546	31.8		
Some college		1349	16.6		1324	16.6		
HS or Vocational school grad		3184	39.1		3131	39.1		
Elementary school or less		1014	12.4		999	12.5		
Parental employment (highest)	7503			7363			0.05	1.00
Manager/Professional/Technical		1269	15.5		1237	15.4		
Clerical/Service/Armed Forces		3462	42.41		3401	42.5		
Agriculture/Crafts/Skilled labor/Plant or machine operator or assembler		1536	18.8		1505	18.8		
Unskilled labor/Farmer		1236	15.1		1220	15.2		
Breastfeeding status in the first 6 months of life	8148			7995				
Breastfed only		5052	62.0		4950	61.9		
Milk formula only		937	11.5		920	11.5		
Mixed including breastmilk		2151	26.4		2117	26.5		
Mixed excluding breastmilk		8	0.1		8	0.1		
Child has one or more allergy symptoms, often or always	8164			8011			0.02	0.90
Yes		354	4.3		344	4.3		
No		7810	95.7		7667	95.7		
Child ever diagnosed with respiratory disease	8151			7998			0.02	0.88
Yes		135	1.7		130	1.6		
No		8016	98.3		7868	98.4		
Continuous characteristics	**N**	**Mean**	**SD[2]**	**N**	**Mean**	**SD[2]**	**t**	**p**
Child's age	8164	16.04	1.3	8011	16.02	1.3	0.98	0.33
Child's birthweight	8144	2928.61	606.0	7991	2927.68	604.1	0.10	0.92
Euclidean distance from the closest hospital (km)	8164	4.82	4.13	8011	4.74	4.08	1.16	0.25
Crowding	8140	2.79	1.7	7987	2.79	1.7	0	1
Household Wealth Index	8164	0.01	1.0	8011	0.01	1.0	0	1
Number of people in the household	8163	6.45	2.6	8010	6.45	2.6	0	1
Parity of mother	8162	4.43	2.3	8009	4.43	2.3	0	1

[1] p-value is for the difference between all enrolled participants with valid ear exam and residential location records and participants included in the final analysis from t-tests (continuous variables) or chi-squared tests (categorical variables)
[2] SD: standard deviation.

Table 4. Description of neighborhood level characteristics among participants of a randomized controlled trial (RCT) on pneumococcal conjugate vaccine (PCV) in Bohol, Philippines who completed the follow-up assessment between 2016 and 2020 and lived within the final neighborhoods with grid size of 1,600 meters (n=137).

Continuous characteristics	**Mean (SD[1])**	**Median (IQR[2])**
Mean age of the child participants	16.56 (0.64)	16.62 (0.83)
Mean number of people in the household	6.32 (0.80)	6.31 (0.92)
Mean parity of mothers in the neighborhood	4.55 (0.77)	4.50 (0.89)
Mean crowding index	2.80 (0.50)	2.78 (0.63)
Mean household wealth index	-0.19 (0.37)	-0.22 (0.48)
Mean Euclidean distance from the closest hospital (km)	7.16 (3.85)	7.17 (6.06)
Total length of national and provincial roads (km)	1.54 (1.12)	1.70 (1.71)
Categorical characteristics	**Mean %**	**95% CI[3]**
Percentage of participants with ear disease	41.08	38.46, 43.70
Percentage of participants vaccinated in the parent trial	50.43	48.77, 52.09
Percentage of participants with birth weight less than 2500 grams	22.32	20.17, 24.49
Percentage of participants with members in the house regularly smoke	41.12	38.82, 43.42
Percentage of participants that smokes cigarettes	2.72	1.96, 3.48
Percentage of female participants	48.87	46.97, 50.77
Percentage of child participants with at least one chronic health condition.	2.18	1.54, 2.82
Percentage of participants attended daycare	90.14	88.52, 91.76
Percentage of participants attended preschool	34.45	31.25, 37.65
Percentage of participants whose mothers had health insurance	77.05	74.29, 79.81
Percentage of participants that were firstborn in the family	27.59	25.97, 29.21
Percentage of participants whose parents' highest education level was		
High school or vocational school grad or above	81.92	79.79, 84.05
Some college or above	38.15	34.98, 41.32
College or post grad	23.64	20.86, 26.42
Percentage of participants whose parents' highest employment level was		
Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler or *Clerical/Service/Armed Forces* or *Manager/Professional/Technical*	80.15	77.56, 82.74
Clerical/Service/Armed Forces or *Manager/Professional/Technical*	57.51	54.55, 60.47
Manager/Professional/Technical	12.85	10.94, 14.76
Percentage of participants who were exclusively breastfed in the first 6 months of life	68.55	66.04, 71.06
Percentage of participants with any allergy	3.26	2.57, 3.95
Percentage of participants ever diagnosed with malnutrition	5.11	4.15, 6.07
Percentage of participants ever diagnosed with respiratory disease	1.10	0.58, 1.62

[1]SD: standard deviation
[2]IQR: Inter-quartile range
[3]CI: confidence interval

Table 5. Global Moran's I statistics for neighborhood level prevalence of otitis media (OM), vaccine coverage, mean distance to the closest hospital in kilometers (km), and total length of national and provincial roads in km.

	Global Moran's I Index	Variance	z-score	p-value
OM prevalence	0.3125	0.0024	6.4741	<0.001
Vaccine coverage	-0.0371	0.0024	-0.6075	0.73
Mean distance to the closest hospital (km)	0.9379	0.0025	19.0624	<0.001
Total length of national and provincial roads (km)	0.0839	0.0024	1.8488	0.06

Table 6. Bivariate analysis of all the study characteristics.

	Bivariate Analysis		
Characteristics	**Estimate**	**Standard error**	**p value**
Percentage of participants vaccinated in the parent trial	-0.20882	0.13417	0.12*
Mean Euclidean distance from the closest hospital (km)	-0.00259	0.00349	0.46
Air pollution exposure (Total length of national and provincial roads in km)	0.03032	0.01177	0.01*
Percentage of participants with birth weight less than 2500 grams	0.02922	0.10617	0.78
Mean number of people in the household	0.04759	0.01638	0.004*
Mean parity of mothers in the neighborhood	0.04758	0.01697	0.006*
Mean crowding index	0.00355	0.02698	0.90
Mean household wealth index	0.06951	0.03575	0.05*
Mean age of the child participants	-0.08011	0.01995	<0.001*
Percentage of participants with members in the house regularly smoke	-0.05483	0.09753	0.58
Percentage of participants that smokes cigarettes	0.22660	0.29370	0.44
Percentage of female participants	-0.25160	0.11580	0.03*
Percentage of child participants with at least one chronic health condition	0.04293	0.35129	0.90
Percentage of participants attended daycare	-0.20120	0.13770	0.15*
Percentage of participants attended preschool	-0.08644	0.06978	0.22
Percentage of participants whose mothers had health insurance	-0.34146	0.07577	<0.001*
Percentage of participants that were firstborn in the family	-0.51194	0.13131	<0.001*
Percentage of participants whose parents' highest education level is			
high school or vocational school grad or above	0.06693	0.10496	0.53
some college or above	0.07061	0.07055	0.32
college or post grad	0.11123	0.08019	0.17*
Percentage of participants whose parents' highest employment level is			
Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler or *Clerical/Service/Armed Forces* or *Manager/Professional/Technical*	-0.00366	0.08650	0.97
Clerical/Service/Armed Forces or *Manager/Professional/Technical*	0.04434	0.07557	0.56
Manager/Professional/Technical	0.06657	0.11729	0.57
Percentage of participants who were exclusively breastfed in the first 6 months of life	-0.30802	0.08521	<0.001*
Percentage of participants with any allergy	0.27025	0.32331	0.41
Percentage of participants ever diagnosed with malnutrition	0.15364	0.23238	0.51
Percentage of participants ever diagnosed with respiratory disease	0.73633	0.43012	0.09*

* Significant at 0.20 level. Included in the multivariable analysis.

Table 7. Results from the ordinary least squares (OLS) model, spatial lag model (SAR), and geographically weighted regression (GWR) model.

	OLS	SAR				GWR			
Variable	β (SE)	β (SE)	Direct	Indirect	Total	Min	Median	Max	MC Sig. Test[1]
Percentage of female participants	-0.279 (0.099) **	-0.290 (0.090) **	-0.300	-0.186	-0.486	-0.407	-0.183	-0.109	0.40
Percentage of participants whose mothers had health insurance	-0.242 (0.073) **	-0.165 (0.069) *	-0.171	-0.106	-0.277	-0.381	-0.233	-0.072	0.26
Percentage of participants that were firstborn in the family	-0.337 (0.120) **	-0.331 (0.110) **	-0.343	-0.213	-0.555	-0.768	-0.419	-0.058	0.22
Percentage of participants who were exclusively breastfed in the first 6 months of life	-0.254 (0.081) **	-0.177 (0.076) *	-0.183	-0.114	-0.297	-0.256	-0.167	-0.098	0.84
Mean number of people in the household	0.044 (0.015) **	0.032 (0.014) *	0.034	0.021	0.054	-0.011	0.025	0.051	0.44
Air pollution exposure (Total length of national and provincial roads in km)	-0.022 (0.010) *	-0.019 (0.010) *	-0.020	-0.012	-0.032	-0.041	-0.017	-0.005	0.35
Intercept	0.758 (0.120) ***	0.554 (0.120) ***				0.537	0.742	1.200	0.27
Diagnostics									
Adj. R^2	0.3232	0.4069							0.4102
AICc	-164.13	-175.51							-173.65

* p<0.05 ** p<0.01 *** p<0.001

[1] Monte-Carlo significance test

Chapter 5. Key Characteristics Associated with Hearing Loss

5.1 Introduction

Hearing loss in children is a significant public health concern globally, with profound implications for social, educational, and cognitive development (139). In low- and middle-income countries (LMICs), the burden of pediatric hearing impairment is particularly high, often exacerbated by limited access to healthcare services, high prevalence of otitis media (OM), and socioeconomic disparities (5, 140). The island of Bohol in the Philippines presents a pertinent case study for examining these issues, given its diverse geographic and socioeconomic landscape.

Previous research has established a strong link between OM, particularly chronic suppurative otitis media (CSOM), and hearing loss among children (5, 7, 55, 58). CSOM is often a consequence of untreated acute otitis media (AOM), a common condition in LMICs where healthcare access is limited (141). In addition, socioeconomic factors such as household wealth, parental education, and exposure to environmental pollutants, including household smoke, have been identified as significant determinants of hearing loss (29, 31, 142).

Despite the known associations between these factors and hearing loss, there remains a gap in understanding the spatial variability of these relationships within specific geographic contexts. Most studies have focused on individual-level data, with limited attention to neighborhood-level analyses that could reveal localized patterns and inform targeted public health interventions (143). Furthermore, while spatial epidemiology has been increasingly utilized to explore health outcomes, its application to pediatric hearing loss and related risk factors remains underexplored.

This study aims to address these gaps by investigating the neighborhood-level prevalence of pediatric hearing loss in Bohol, Philippines, and its association with key characteristics such as local OM prevalence, distance to healthcare facilities, household socioeconomic status, and exposure to household smoke. Given the proximity of residential areas to Tagbilaran Airport, this study also examines the impact of residential distance to the airport as an exposure of interest. Airports are known sources of environmental noise and air pollution, both of which can have adverse health effects, including potential impacts on hearing (144-147). The close vicinity of the airport to residential areas in Bohol underscores the importance of evaluating this factor in the context of pediatric hearing loss.

Using spatial analytical techniques, the current analysis seeks to elucidate the spatial heterogeneity in these associations and identify areas with higher vulnerability. This analysis provides a comprehensive understanding of the spatial dynamics of pediatric hearing loss in Bohol, informing localized public health strategies to mitigate this issue.

5.2 Methods

5.2.1 Data Collection Methods

This study used secondary data from a follow-up study of a double-blinded randomized controlled trial (RCT) registered under the International Standard Randomized Controlled Trial Number [ISRCTN] 62323832, examining the effectiveness of an 11-valent pneumococcal conjugate vaccine (PCV) among children under two years of age in Bohol, Philippines (50). The parent trial enrolled 12,191 infants born between July 2000 and December 2004, with 8,926 (73.2%) children participating in the follow-up study conducted from September 2016 to February 2020. The study area spans seven districts in Southwestern Bohol: Tagbilaran City, Corella, Cortes, Dauis, Baclayon, Balilihan, and Panglao, covering a predominantly rural agricultural area of 397 km^2 with a population of 175,000 in 2000 (81). The parent trial involved randomizing participants at 48 government primary health care centers to receive either PCV or a placebo (saline) injection. Sanofi Pasteur prepared the PCV, and the trial performed allocation using individual-level block randomization, with treatment assignments blinded to administer of allocated vaccine or placebo, participants, and clinical staff who evaluated the participant data.

For the follow-up study, field personnel conducted home visits to locate participants, obtaining verbal parental consent and child assent or consent as appropriate. Parents or primary caregivers then completed a questionnaire covering demographics, behavioral factors, socioeconomic status, and health conditions. After that, children underwent various ear examinations and hearing assessments at the study office in Tagbilaran city. Geographic data, including shapefiles of healthcare facilities, the Tagbilaran Airport, political boundaries, and roads were obtained from the Philippine

Geoportal (https://www.geoportal.gov.ph) and the Bohol Provincial Planning and Development Office (https://ppdo.bohol.gov.ph/).

5.2.2 Variable Definitions

5.2.2.1 Hearing Loss

As part of the follow-up, children underwent audiology screening using noise-attenuating earphones in a quiet environment to detect potential hearing loss. Children meeting any of the following criteria were referred to the Bohol Hearing Center for a formal audiology evaluation:

a. Indications of possible or probable hearing loss in the audiology screening;

b. A history of eardrum perforation, ear discharge, or hearing issues;

c. An abnormal tympanogram in the ear disease screening; or

d. Failure of the distortion product otoacoustic emissions (DPOAEs) test in the ear disease screening.

The formal evaluation assessed the child's ability to hear the softest sounds for each ear at octave frequencies from 500 to 8,000 Hz. For each ear, the average of decibel (dB) levels heard at frequencies of 1000, 2000, and 4000 Hz for air conductance (AC) was calculated to be pure tone average (PTA) (91). I created a dichotomous variable indicating whether participants had hearing loss (>16 db PTA) in at least one ear.

5.2.2.2 Ear Disease (OM)

Ear disease was classified based on physician examination and tympanometry during follow-up. Ear disease included any form of OM, from AOM to CSOM.

5.2.2.3 Vaccine Coverage in the Neighborhood

Vaccine coverage (VC) in each neighborhood was defined as the ratio of children who received PCV in the parent trial to the total number of children enrolled in that neighborhood (81, 96).

5.2.2.4 Distance to Healthcare

I measured distance to healthcare for each neighborhood with the mean Euclidean distance in kilometers (km) from each participant's residence to the nearest hospital.

5.2.2.5 Traffic-related Noise Pollution

The primary source of traffic-related noise pollution was Tagbilaran Airport (IATA: TAG; Coordinates: 09°39′50.69″N, 123°51′11.69″E), located in the city center and surrounded by residential areas. The airport operated from the 1960s until November 2018, when it was replaced by Bohol-Panglao International Airport. During the 2000s and 2010s, it was congested, having reached its capacity. To assess noise pollution from the airport, I calculated the Euclidean distance in km from Tagbilaran Airport to each participant’s residence and then computed the mean distance.

5.2.2.6 Other Sociodemographic Characteristics

The follow-up study collected various sociodemographic characteristics with a parental questionnaire during the household visit, including child's age and sex, birthweight, household crowding index (number of people per room), child's birth order, breastfeeding history, household wealth index created using the Demographic and Health Surveys Program (DHS) methodology, smoking exposure in the household, parental education/employment, and history of malnutrition diagnoses (110). The household wealth index, a composite measure incorporating various indicators of household assets, assesses aspects such as consumer goods ownership and housing characteristics. Principal component analysis (PCA) is utilized to calculate a wealth score for each household, where higher scores denote greater wealth. In the context of the Philippines, the index encompasses specific indicators like roofing and flooring materials, access to electricity, ownership of appliances such as refrigerators and televisions. It also includes access to improved water sources and sanitation facilities. This localized methodology ensures that the index accurately represents the variations in socioeconomic status within the country.

5.2.3 Location Information

5.2.3.1 Waypoints

Waypoints are sets of coordinates that identify an exact location. During the follow-up study, field personnel collected waypoints of the residential location of each participant using Garmin eTrex devices. The Geographic Information System (GIS) officer processed the global positioning system (GPS) data and consolidated daily files into monthly and yearly files. I then linked all geographic data to the follow-up survey data for each participant.

5.2.3.2 Defining Neighborhoods

I created a square polygon grid overlaying the study area, designating each grid cell as a neighborhood and it is solely defined by geography. To find the optimal neighborhood size for analysis, I constructed grids with varying grid cell sides from 800 to 2,500 meters, which increased in 100-meter intervals. The main study hospital, Gov. Celestino Gallares Memorial Hospital, served the centroid of a grid cell. For the neighborhoods covering both sides of the strait, I divided them into two parts, one on each side. I then used spatial join to assign participants to the neighborhoods created and excluded neighborhoods with less than four participants to ensure robustness. I further restricted to neighborhoods connected to the main landmass for the analysis. I selected the final neighborhood size based on the lowest combined rankings of neighborhood and participant counts to maximize both numbers and considered the highest variability in hearing loss prevalence.

5.2.3.3 Neighborhood-level Characteristics

I aggregated all characteristics of interest for each neighborhood and calculated the prevalence of hearing loss. Percentages were computed for categorical characteristics, and means were calculated for continuous characteristics.

5.2.4 Inclusion and Exclusion Criteria

5.2.4.1 Inclusion Criteria

a. The child participated in the parent RCT conducted between 2000 and 2004.

b. Verbal consent was provided for both the parent trial and the follow-up study.

5.2.4.2 Exclusion Criteria

a. Parents or the child were unwilling to participate in the surveys and assessments.

b. The child died before the completion of the follow-up study.

c. The child was lost to follow-up.

d. No ear or hearing examination results were available for the child.

5.2.5 Analysis

After identifying the optimal neighborhood size, I compared individual characteristics between the entire sample and those within the final neighborhoods using t-test for continuous variables and chi-squared tests for categorical variables. Next, I created neighborhood level characteristics.

To visualize the spatial distribution of hearing loss and other characteristics, I created neighborhood level maps. I used Moran's I index with the queen's case contiguity weight matrix to assess the global spatial autocorrelation of local prevalence of hearing loss, vaccine coverage, the mean distance to the nearest hospital, and the mean distance to Tagbilaran Airport, and employed local indicators of spatial autocorrelation (LISA) maps to identify local clusters and/or outliers (106, 107).

I used a Poisson regression model to statistically analyze the data. The dependent variable was the number of participants with hearing loss in each neighborhood, with an offset term for the total number of participants that resided in the neighborhood. I began with bivariate regression analyses and included covariates with p-values less than 0.20 in the multivariable models. The final multivariable Poisson regression model was built using backward stepwise selection, minimizing the Akaike Information Criterion (AIC) value. I tested goodness-of-fit using residual deviance and assessed potential multicollinearity using the variance inflation factor (VIF) with a threshold of 5. I also checked Moran's I of the residuals to determine if spatial pattern distorted the Poisson regression model results.

To investigate spatial non-stationarity of associations between key characteristics and hearing loss, I utilized geographically weighted regression (GWR) modeling. I obtained a fixed bandwidth (caliper) and performed a Poisson generalized GWR model using the R package spgwr (109). The coefficients in each neighborhood from GWR modeling were mapped to present the results.

All statistical analyses were conducted using ArcGIS Pro and R v4.3.2, with statistical significance set at the p level of 0.05 unless otherwise specified.

5.3 Results

Of the 12,191 participants in the parent PCV trial, 8,926 (73.2%) were included in the follow-up study, and their parents or primary caregivers completed a questionnaire (Figure 25). Among these, 564 participants did not return for an ear exam, one child could not understand the instructions, and ear disease and hearing status could not be classified for 189 children. After excluding these individuals, 112 children lacked documented waypoints of their residential location, yielding 8,060 (66.1% of those in the parent trial) participants with valid ear exam data and recorded residential locations.

5.3.1 Neighborhood Definition

To determine the optimal neighborhood size for analysis, I assessed grid sizes ranging from 800 meters to 2,500 meters per side. For each grid size, I recorded the number of neighborhoods, the number of participants covered, the mean percentage of participants with hearing loss and its variance, and the number of neighborhoods without participants with hearing loss (Table 8). Table 8 also lists the total number of neighborhoods required to cover all participants and the reasons for excluding some of them from the analysis. As grid size increased, the number of neighborhoods analyzed decreased while the number of participants included increased. Figure 26 illustrates the changes in the number of neighborhoods and participants with increasing grid size. The study area is divided into 119 barangays by existing political boundaries. To ensure spatial granularity, I did not consider grid sizes that resulted in fewer than 119 neighborhoods, which excluded grid sizes of 1,800 meters or larger. Balancing data comprehensiveness and neighborhood sample size, I selected a grid size of 1,600 meters for analysis. This grid size included data from 98.2% of participants with complete parental questionnaires, ear and hearing exams, and residential location records (7,913 out of 8,060) and encompassed nearly 59% of the neighborhoods created (137 out of 234).

To understand the difference between the available sample and those included in the final neighborhoods, I conducted t-tests for continuous variables and chi-square tests for categorical variables. There were no statistically significant differences at the 0.05 level between the two groups for any study characteristics, except for the Euclidean distance from Tagbilaran Airport (Table 9). Participants within the final neighborhoods lived significantly closer to Tagbilaran Airport (6.87 km) compared to the full sample (7.21 km, $t=-3.54$, $p < 0.01$). This difference is attributed to the fact that those excluded due to small neighborhood sample sizes were mostly located farther from the city center (Figure 27).

5.3.2 Neighborhood-Level Characteristics and Maps

I aggregated characteristics to neighborhood level using the size of 1,600 meters on the sides (Table 10). The mean percentage of participants with hearing loss per neighborhood was 8.5%, and the mean percentage of participants vaccinated in the parent trial was 50%. The Euclidean distance from the nearest hospital ranged from 0.36 to 15.00 km, with an average of 7.16 km. The distance from each participant's residence to Tagbilaran Airport ranged from 0.77 to 27.33 km, with an average of 11.15 km.

I created neighborhood level maps to visualize the spatial distribution of participants and their characteristics. In the final sample of neighborhoods, the number of participants per neighborhood ranged from 4 to 540 (Figure 27). Higher participant densities clustered around the main study hospital in Tagbilaran City and along the north shore of the island of Dauis and Panglao. Neighborhoods on that island also tended to have higher percentage of participants with hearing loss, as well as some neighborhoods in inland area in the northeast (Figure 28a). The percentage of participants vaccinated during the parent trial did not show clear clustering patterns across the study area (Figure 28b). Hospitals in or near the study area were primarily located along the coastline of the larger island, resulting in shorter distances to hospitals for neighborhoods closer to the central region (Figure 29). Neighborhoods in the southern part of the island of Dauis and Panglao, along with some neighborhoods in the northern region, showed clear clustering of longer distances to the nearest hospital.

5.3.3 Spatial Autocorrelation

I evaluated the spatial autocorrelation of neighborhood level hearing loss prevalence, vaccine coverage, mean Euclidean distance to the closest hospital, and mean Euclidean distance to Tagbilaran Airport both globally and locally. The global Moran's I for hearing loss prevalence was 0.048, with a z-score of 1.12 ($p=0.26$), indicating no significant clustering at the $\alpha=0.05$ level (Table 11). Similarly, vaccine coverage had a global Moran's I close to zero at -0.049, with a z-score of -0.84 ($p=0.40$), suggesting random distribution without significant spatial autocorrelation. As expected, both the mean distance to the nearest hospital (Moran's I=0.46) and to Tagbilaran Airport (Moran's I=0.23) showed significant spatial clustering (both $p<0.001$).

I used LISA maps to assess local spatial heterogeneity in them (Figure 30). LISA maps identified local clusters and outliers and present them in different colors. Taking local hearing loss prevalence as an example, pink areas indicated clusters where neighborhoods with high prevalence of hearing loss surrounded by other neighborhoods with high prevalence; light blue areas indicated clusters where neighborhoods with low prevalence surrounded by other neighborhoods with low prevalence; red areas indicated outliers where neighborhoods with high prevalence surrounded by neighborhoods with low prevalence; and dark blue areas indicated outliers where neighborhoods with low prevalence surrounded by neighborhoods with high prevalence (Figure 30). The LISA analysis for prevalence of hearing loss and vaccine coverage revealed few neighborhoods with significant local spatial heterogeneity (Figure 30a-b). For mean distance to the nearest hospital, the central area around the main study hospital showed local clusters of low values, indicating good geographical access to healthcare facilities (Figure 30c).

5.3.4 Regression Analysis

In the bivariate Poisson regression models, several characteristics were selected for multivariable analysis: local ear disease prevalence, distance to healthcare measured by mean Euclidean distance to the nearest hospital, traffic-related noise pollution measured by mean Euclidean distance to Tagbilaran Airport, mean crowding index, mean household wealth index, mean age of the child participant, percentage of participants with household members who regularly smoke, percentage of participants with parent(s) employed at a manager/professional/technical level, and percentage of participants with at least one parent whose highest education level was high school or above, some college or above, and college or above (Table 12).

I initially included all these characteristics in the model. Due to high VIF for multiple parental education level predictors, I retained only the percentage of participants whose parents' highest education level was high school or above for the multivariable modeling. After applying backward selection to minimize the model AIC value, four characteristics were significantly associated with a higher expected count of hearing loss cases in the neighborhood: higher percentage of participants with ear disease, longer mean distance from the nearest hospital, lower percentage of participants with household members who smoke regularly, and lower mean household wealth index (Table 13).

The final model had a lower AIC (532.99) compared to the full multivariable model (543.17), indicating a better fit. The goodness-of-fit test using residual deviance was not statistically significant (test statistic=155.40, df=132, p=0.08), suggesting a well-fitted model. No multicollinearity was found within the final model using a VIF threshold of 5. The model residuals showed no global spatial autocorrelation (Figure 31, Moran's I=-0.030, p=0.68), indicating that spatial autocorrelation did not distort the Poisson regression results.

Exponentiation of the final model coefficients provided incidence rate ratios (IRRs). After adjusting for the population size of each neighborhood and holding all other variables constant, a one percent increase in the percentage of participants with ear disease was associated with an increased rate of hearing loss by 3.06 times (95% CI: 1.56, 6.05). Each additional kilometer farther from the nearest hospital increased the rate of hearing loss by 1.03 times (95% CI: 1.00, 1.05). A one-unit increase in the mean household wealth index was associated with a reduced hearing loss rate (IRR=0.72, 95%

CI: 0.52, 0.99), while a one percent increase in the percentage of participants with household members who smoke regularly increased the hearing loss rate by 2.05 times (95% CI: 0.79, 5.35).

To explore the spatial variability in the relationships between hearing loss and key characteristics, I conducted GWR using the generalized GWR function in the R package spgwr (109). The median coefficients for all key characteristics from GWR were close to those from the Poisson regression model (Table 13). A higher percentage of participants with ear disease was consistently associated with a higher incidence rate across the study area, especially in the inland area northeast of Tagbilaran City (Figure 32a). Higher socioeconomic status, indicated by a higher household wealth index, was associated with lower incidence rates of hearing loss (Figure 32c). Higher percentages of participants exposed to household smoke were associated with higher incidence rates of hearing loss, particularly in the northeast part of Dauis, Panglao, and Tagbilaran City (Figure 32d).The effect of distance from the nearest hospital varied, with longer distances associated with lower incidence rates of hearing loss in the middle of the study area in Tagbilaran City and higher incidence rates in the rest of the study area (Figure 32b).

5.4 Discussion

This study identified several key characteristics associated with an increased hearing loss rate on a neighborhood level among a cohort of children in Bohol, Philippines, including higher local ear disease prevalence, longer mean distance from the nearest hospital, lower household socioeconomic, and more household smoke exposure. The results also highlighted spatial variations in these associations.

This analysis found that a higher percentage of participants with ear disease (OM) in a neighborhood was associated with a significantly increased incidence rate of pediatric hearing loss. This association was consistent across the study area, with particularly high IRRs in the inland region northeast of Tagbilaran City (Figure 32a). This finding aligns with studies conducted on individual levels that emphasize the strong link between hearing impairment and OM, particularly CSOM (7, 8, 31, 55, 142, 148). CSOM often occurs following poor management of AOM, especially in LMICs where access to healthcare is limited (17, 55).

Neighborhoods exhibiting the strongest association between higher OM prevalence and increased incidence ratios of hearing loss tended to be farther from the nearest hospital, indicating poor access to healthcare (Figure 29 and Figure 32a). Additionally, healthcare access, as measured by the mean Euclidean distance to the nearest hospital, was a significant factor itself after adjusting for other key factors. Neighborhoods farther from hospitals had a higher incidence rate of hearing loss. However, this association displayed spatial heterogeneity; while longer distances were associated with increased incidence rate in most areas, central regions of Tagbilaran City, where most hospitals are concentrated, exhibited an inverse or negligible association (Figure 32b). This spatial inconsistency suggests that other contextual factors beyond mere proximity to healthcare facilities may play a role, such as the availability and quality of transportation infrastructure, socioeconomic disparities, and localized healthcare resources. Studies have shown that transportation barriers can significantly affect access to healthcare services, especially in regions where public transportation is limited or of poor quality (149-151). Additionally, localized variations in healthcare quality and resource allocation can lead to differential health outcomes, even in areas with similar proximity to healthcare facilities (152). It is also important to note that the R package to perform GWR model for Poisson regression in this study is still under development, and no p-value for the local estimates are available (109). While the central Tagbilaran City area shows inverse or negligible associations, the significance of these negative associations remains uncertain. Future research should integrate advancements in methodological approaches to provide more precise public health recommendations.

The identification of both mean distance to the nearest hospital and local OM prevalence as key factors underscores the need for improved healthcare access and effective, timely management of AOM to prevent progression to CSOM and subsequent hearing loss.

Household wealth index was inversely related to the incidence rate of hearing loss at the neighborhood level. The index, constructed using DHS Program methodology, combines various indicators of household assets and services through PCA (110). For the Philippines, this includes context-specific factors like housing materials and access to basic amenities. This comprehensive measure effectively captures socioeconomic disparities. Children from neighborhoods with a higher cumulative living standard were less likely to experience hearing impairment, highlighting the protective effect of higher socioeconomic status. Moreover, since the participants who did not return for ear examination and excluded from the current analysis are from families of lower socioeconomic status, the missing data pattern could have introduced a selection bias that may affect the overall findings. The exclusion of these participants could lead to an underestimation of the true burden of hearing loss in lower socioeconomic status groups. If individuals from these backgrounds with hearing loss were systematically excluded, the observed association between household wealth and hearing loss might be weaker than the actual relationship. This bias could partially mask the true extent of health disparities driven by socioeconomic factors. To mitigate this limitation in future studies, it would be valuable to employ methods such as multiple imputation or sensitivity analyses to better estimate the potential impact on the observed associations.

The identified link between household wealth and hearing loss aligns with existing individual-level literature, which links lower socioeconomic status to a higher prevalence of hearing loss among children in both LMICs and high-income countries (29, 31, 153). Lower socioeconomic status may not directly cause hearing loss but is associated with various risk factors such as low birth weight, limited access to healthcare services and immunization, and undernutrition (29, 154). Additionally, families with one or more hearing-impaired members are more susceptible to lower family income because of employment limitations (29). This study examined low birthweight, distance to healthcare, history of malnutrition diagnosis, and parental employment as potential key characteristics associated with hearing loss on a neighborhood level. Among these factors, parental employment was associated with hearing loss in bivariate analysis but not multivariable analysis. In contrast, distance to healthcare was significantly associated with hearing loss on the neighborhood level both in bivariate and multivariable analyses. This suggests that other elements within household socioeconomic status contribute to hearing loss, which are not yet fully understood. The consistent association between household wealth index and hearing loss on neighborhood level across the study area reinforces the need for targeted interventions in economically disadvantaged neighborhoods (Figure 32c).

Exposure to regular smokers in the household was also a key risk factor, with higher percentages of participants exposed to smoke on the neighborhood level correlating with increased incidence rate of hearing loss. This association was particularly strong in Dauis, Panglao, and Tagbilaran City (Figure 32d). The detrimental effects of smoke exposure on children's health, including hearing loss, are well-documented (142, 155-157). The current analysis adds a valuable neighborhood-level perspective to this body of evidence and emphasize the need for public health initiatives aimed at reducing smoking within households, particularly in vulnerable neighborhoods.

The application of GWR in this analysis provided further insights into the spatial variability of these associations. The consistency of median coefficients with those from the Poisson regression model confirmed the robustness of our findings. The spatial analysis highlighted areas with higher vulnerability, guiding targeted interventions to regions with the greatest need. The observed spatial heterogeneity in the associations between hearing loss and the key characteristics associated with it suggests that localized public health strategies are essential. For instance, interventions aimed at improving healthcare access should consider the unique geographic and infrastructural challenges of each area, while efforts to reduce household smoke exposure should be tailored to specific communities, such as those in Dauis and Panglao (Figure 32d).

Distance to the airport has been recognized as a significant factor associated with pediatric hearing loss due to the high levels of environmental noise and air pollution generated by airport activities (145-147). In this study, the shortest distance from a residential location to Tagbilaran Airport in Bohol was 0.096 km (0.06 miles). Out of the 7,913 participants, 545 lived less than 1 km from the airport, 2,133 within 2 km, and 3,152 within 4 km. Previous literature often categorizes children living within 2 to 4 kilometers of an airport as being in an exposure group, reflecting the significant impact of environmental noise and pollutants within this range (145, 147, 158, 159). In the current analysis, mean Euclidean distance to Tagbilaran Airport was statistically significant in bivariate analysis, suggesting an initial association with pediatric hearing loss. However, this significance did not persist in the multivariable analysis and including this characteristic did not improve the multivariable model per AIC. Interestingly, the bivariate analysis revealed a counterintuitive finding that the longer the distance from the airport, the more hearing loss cases were observed. This unexpected result could be attributed to the spatial distribution of healthcare facilities in the study area. Tagbilaran Airport is situated close to numerous hospitals and the correlation between individual level Euclidean distance to Tagbilaran Airport and Euclidean distance to the nearest hospital was 0.82 (Figure 29). This high correlation suggests that the observed association may be overshadowed by the proximity to healthcare facilities. Essentially, what was initially perceived as an association with distance to the airport may actually reflect the impact of distance to care. These findings may indicate that other characteristics, such as socioeconomic status, healthcare access, and household smoke exposure, play more dominant roles when it comes to pediatric hearing loss when considered alongside distance to the airport. Additionally, the variation in individual susceptibility to environmental noise and pollutants might dilute the apparent impact of proximity to the airport. Lastly, the community's adaptation and mitigation measures, such as improved housing insulation and noise reduction strategies, might also reduce the overall exposure effect.

The findings of this study hold substantial implications for public health strategies aimed at reducing pediatric hearing loss in LMICs. Enhancing healthcare access requires establishing more healthcare facilities in underserved areas, reducing travel distances for children. Strengthening transportation infrastructure is crucial for better access to existing services, while mobile health clinics and telemedicine can effectively reach remote populations. Targeted interventions in economically disadvantaged neighborhoods are necessary, including community-based health education on early detection and treatment of ear infections, financial assistance for healthcare services, and promoting economic development initiatives to improve overall socioeconomic status. In addition, stricter regulations on smoking within homes, especially in households within children, are important. Public health campaigns should educate parents about the risk of secondhand smoke and provide resources to help quit smoking, and policy initiatives and community programs should support the creation of smoke-free environments.

While this analysis offers valuable insights, it has limitations. The cross-sectional design limits causal inferences, and the reliance on self-reported data may introduce biases. Specifically, the direction of causality between the distance to the nearest hospital and hearing loss is uncertain; it is possible that families with more susceptible children may have moved closer to healthcare facilities. Similarly, while a higher household wealth index might be associated with better cognitive outcomes, it is also plausible that families facing increased financial burdens due to a child's hearing impairment may experience reduced income. For smoking, the temporal relationship is also unclear whether smoking occurred before or after the child's hearing impairment remains uncertain. Furthermore, the exclusion of participants due to incomplete data might affect the generalizability of the findings. Future research should employ longitudinal designs to address these limitations and provide a clearer understanding of the causal relationships, incorporating more comprehensive data to validate and extend these results.

By integrating spatial epidemiological methods with traditional regression analyses, this analysis contributes to the growing body of literature on the social determinants of health and emphasizes the importance of geographic context in public health research. These findings have significant implications for public health planning and resource allocation, particularly in LMICs, where targeted interventions can substantially improve health outcomes for vulnerable populations.

In conclusion, this analysis identified critical factors associated with pediatric hearing loss in Bohol, Philippines, and highlighted spatial variations in these associations. Addressing local ear disease prevalence, improving healthcare access, enhancing household socioeconomic conditions, and reducing household smoke exposure are essential strategies to mitigate hearing loss. Ther spatial insights from this analysis can guide targeted public health interventions to improve hearing health outcomes for children in this region.

Figure 25. CONSORT diagram.

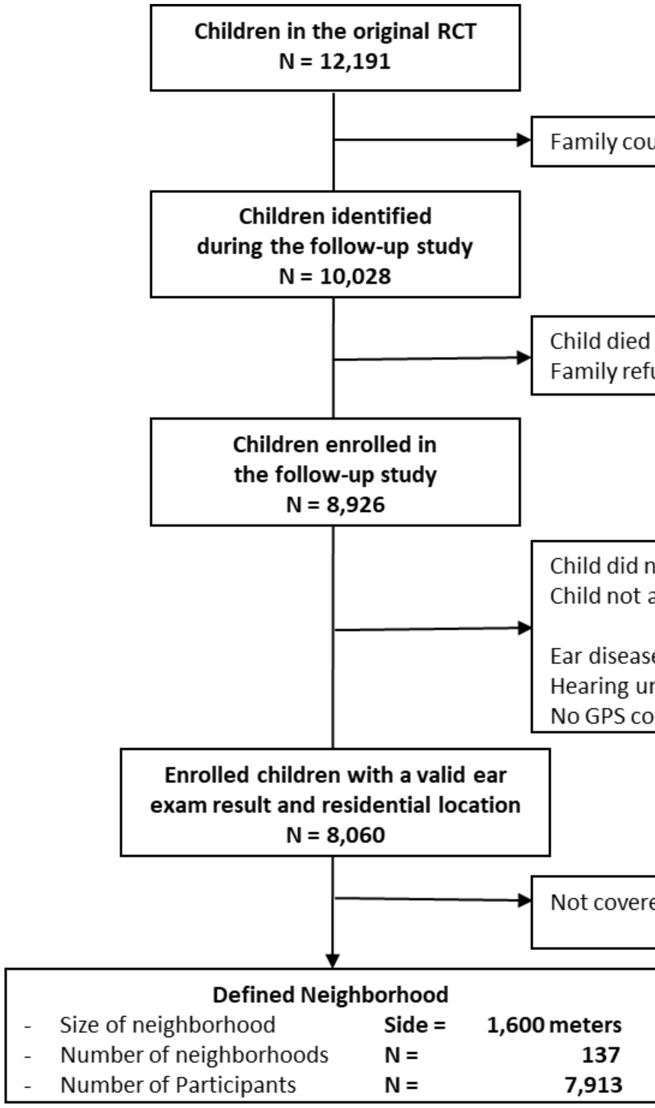


Figure 26. Variations in neighborhood count and participant coverage across different grid sizes from 800 to 2,500 meters per side.

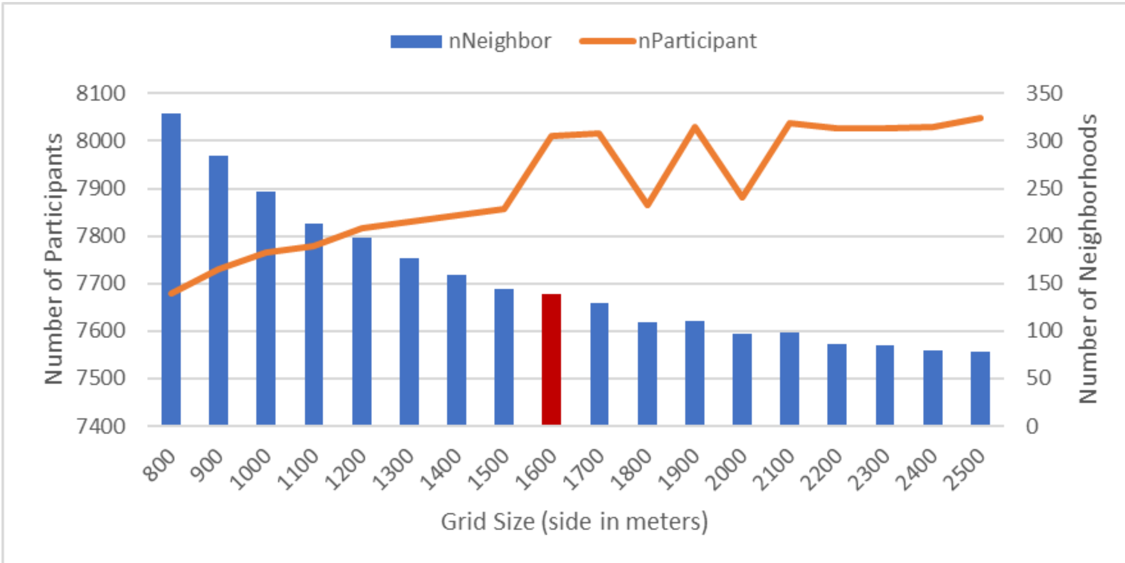
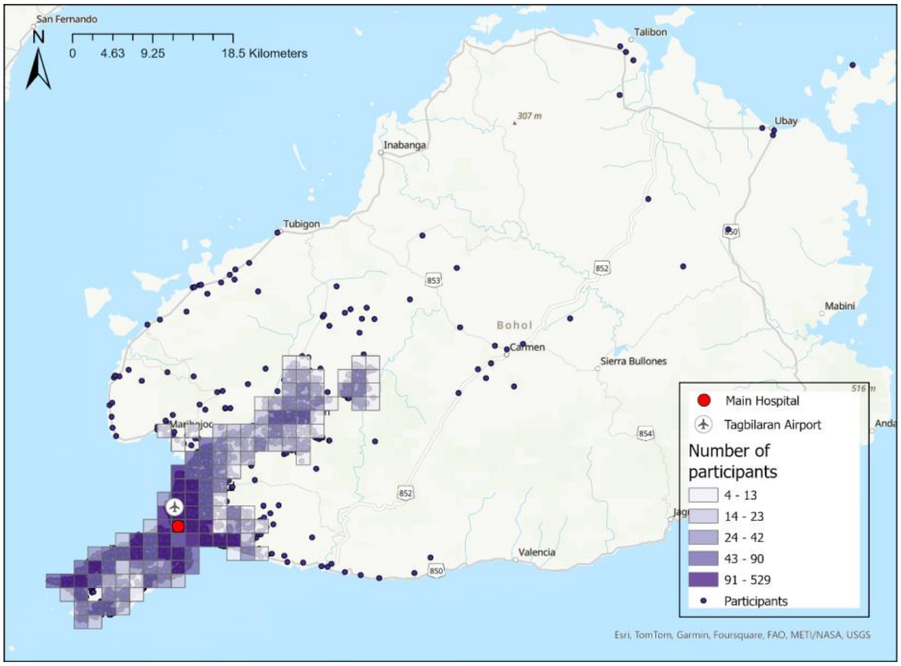
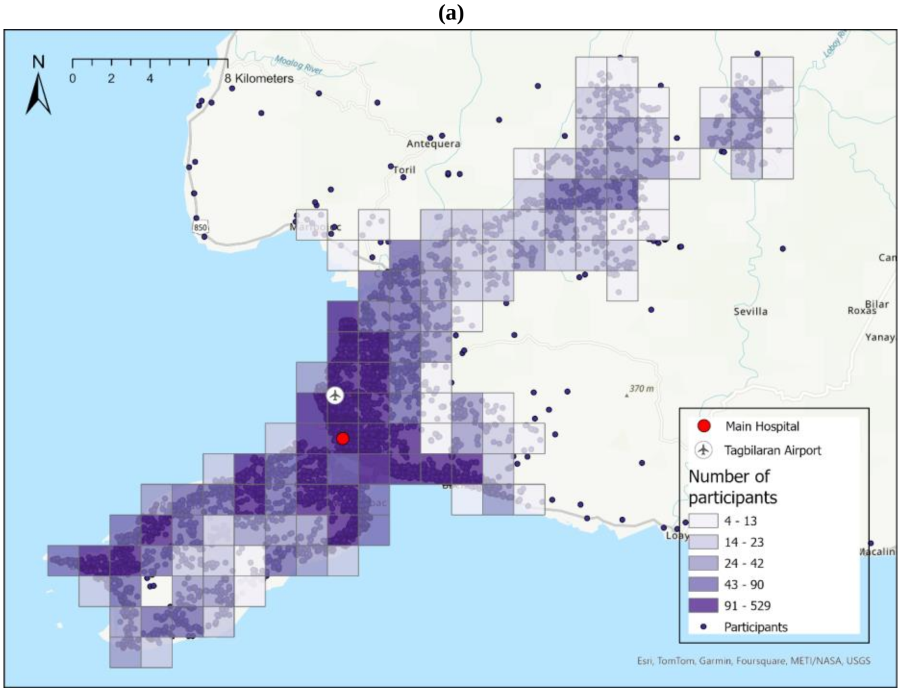


Figure 27. Number of participants per neighborhood.

(a) Bohol, Philippines, and (b) Zoomed in to the analyzed sample with 1,600-meter neighborhoods.

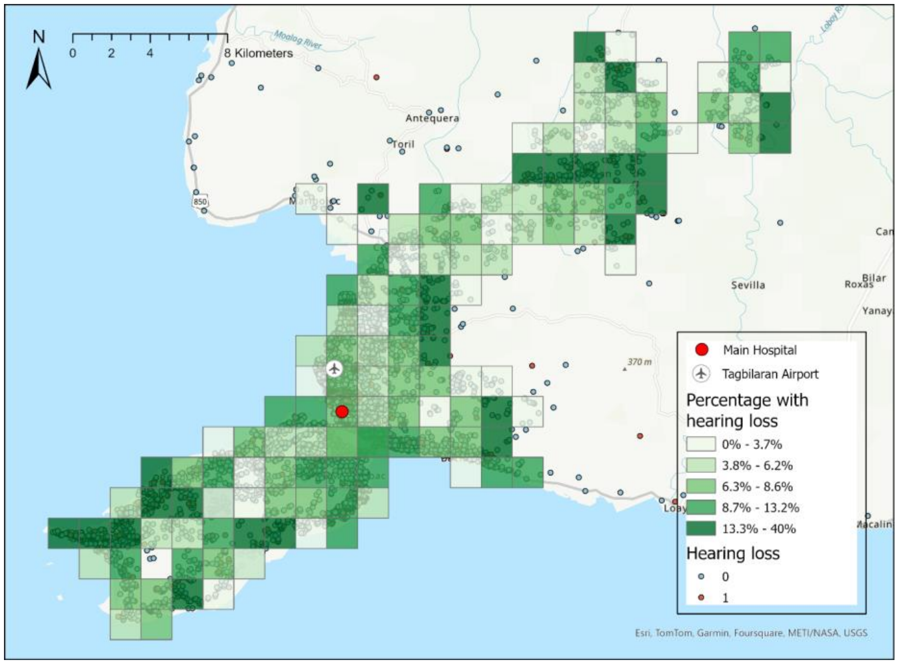


(a)

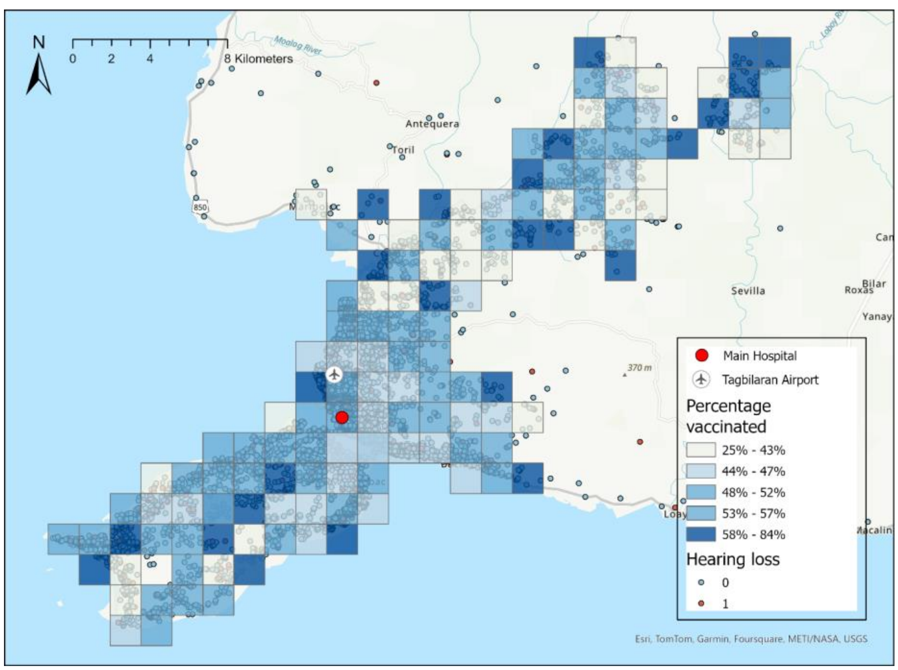


(b)

Figure 28. Neighborhood level percentage of participants (a) with hearing loss and (b) vaccinated during the parent trial (ISRCTN: 62323832) in Southwestern Bohol, Philippines (neighborhood size: 1,600 meters).



(a)



(b)

Figure 29. Neighborhood level mean distance to the closest hospital (neighborhood size: 1,600 meters).

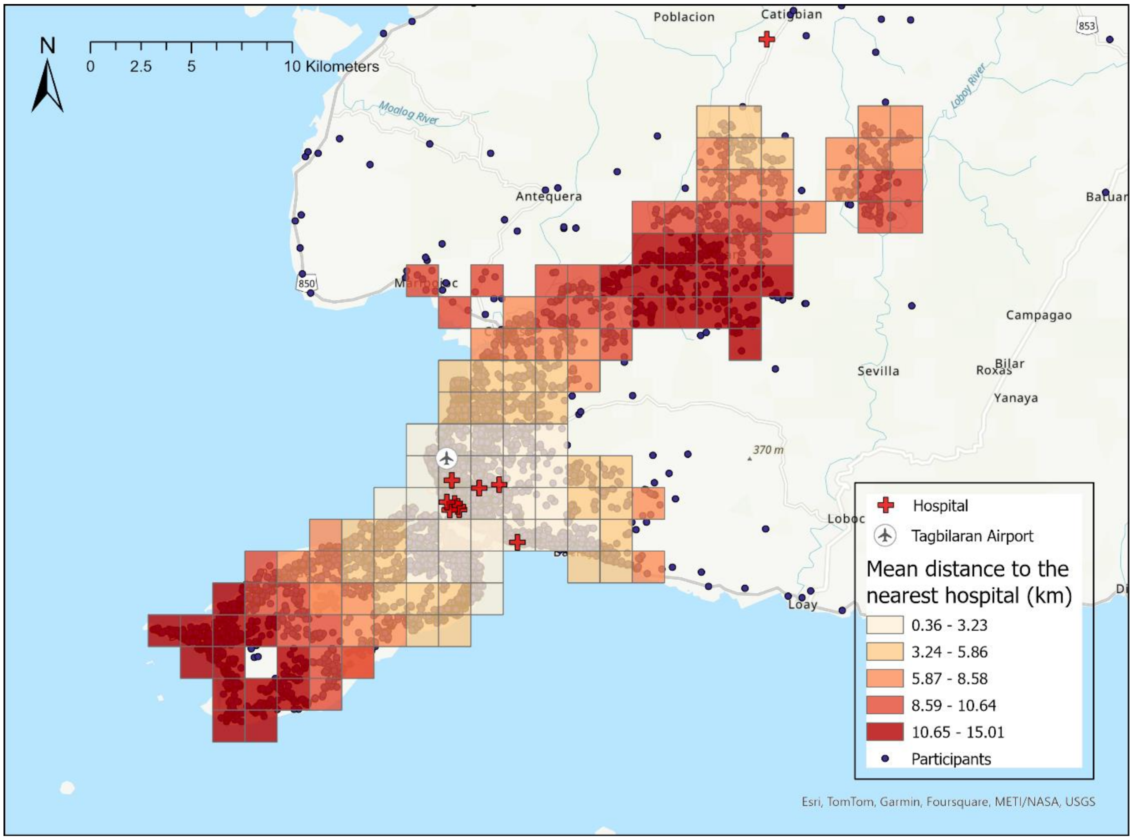
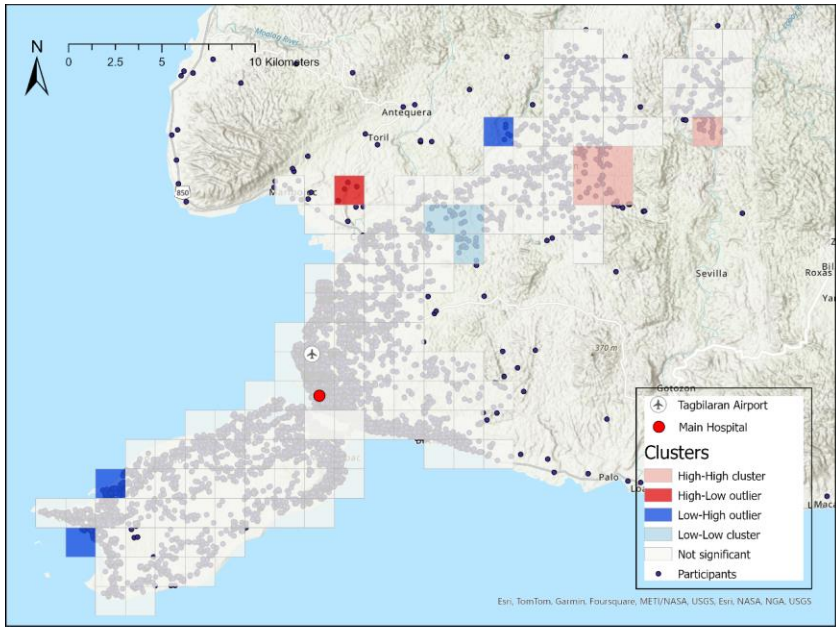
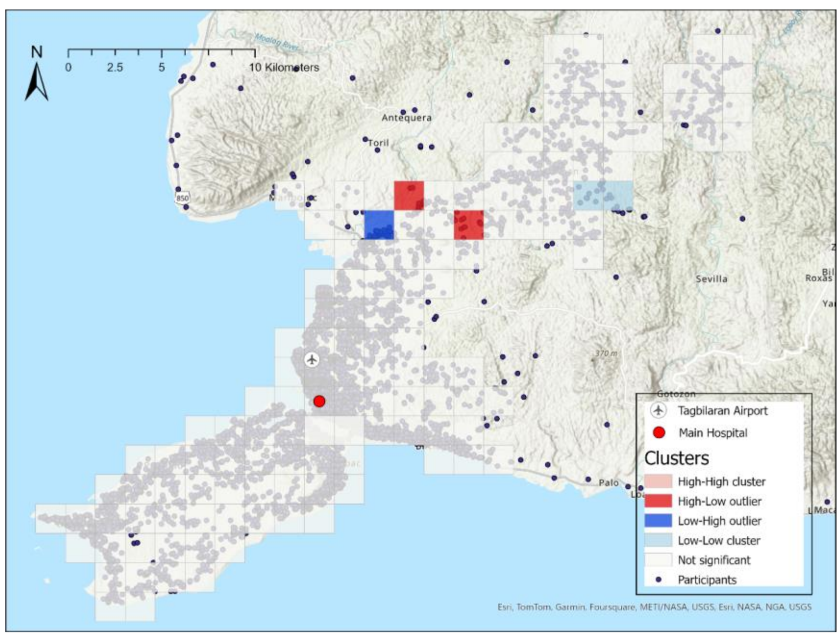


Figure 30. Local indicator of spatial association (LISA) maps on neighborhood level of (a) prevalence of hearing loss, (b) vaccine coverage, (c) mean distance to the nearest hospital, and (d) mean distance to Tagbilaran Airport in Bohol, Philippines (neighborhood size: 1,600 meters).



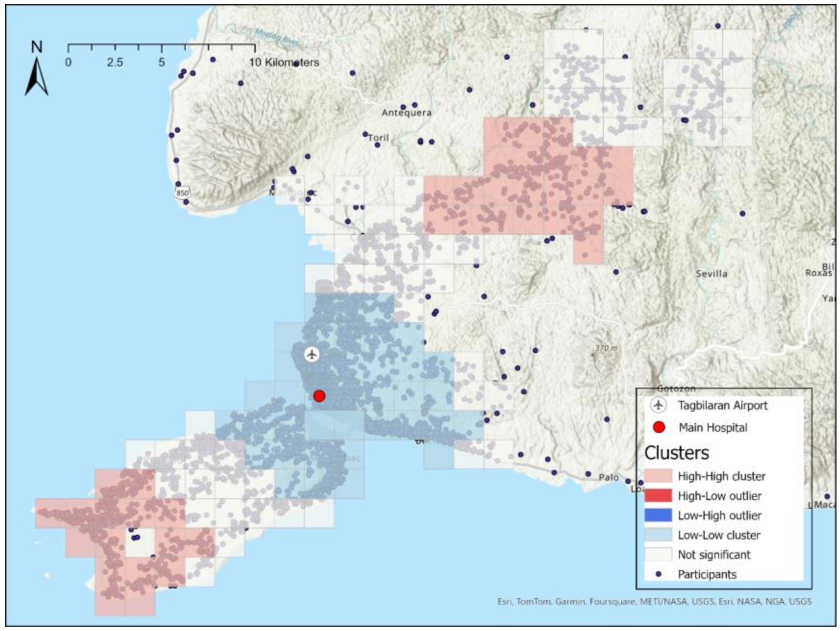
(a)



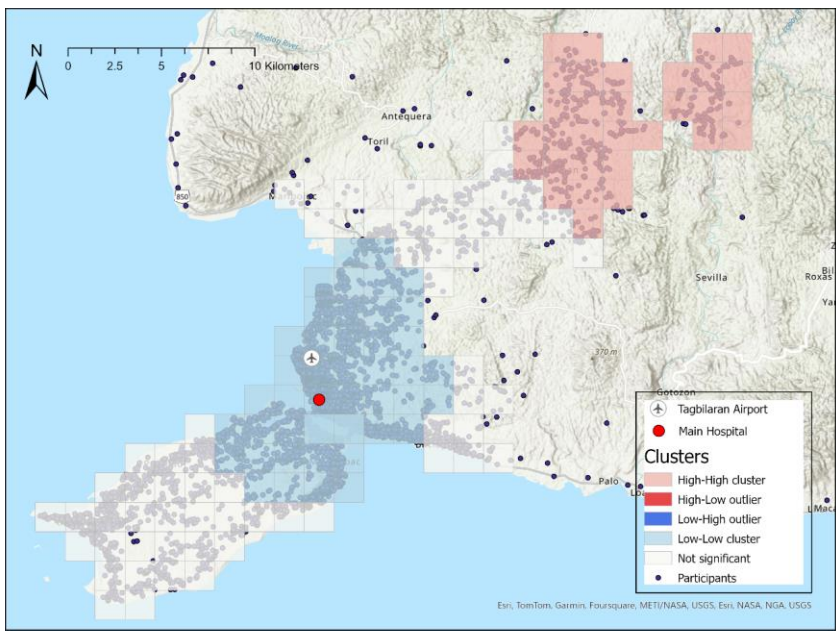
(b)

Continued

Figure 30. Continued



(c)



(d)

Figure 31. Residual plot of the final Poisson regression model.

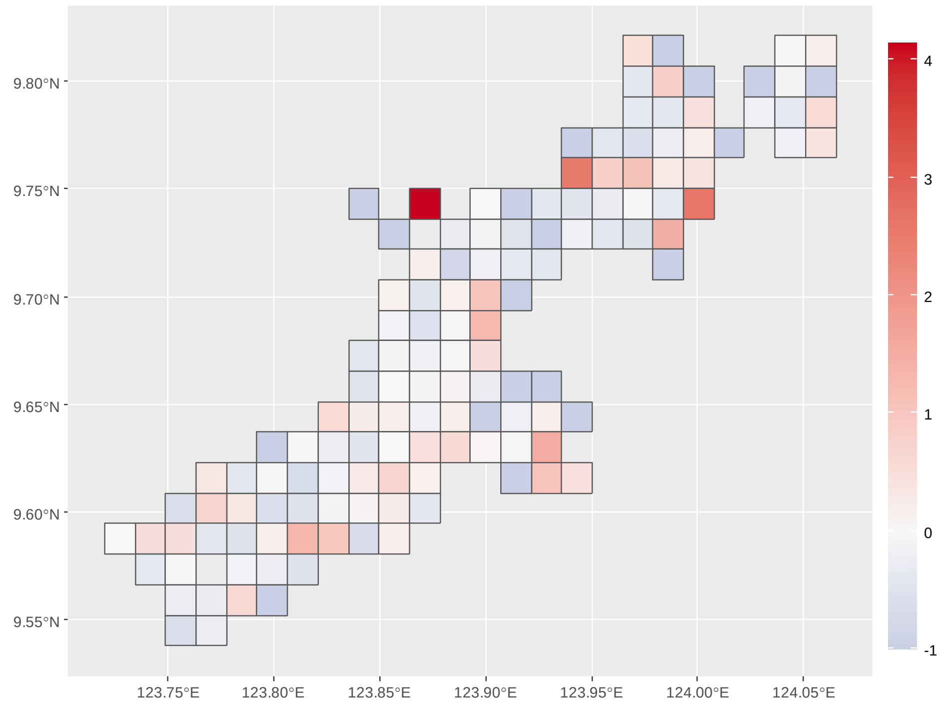
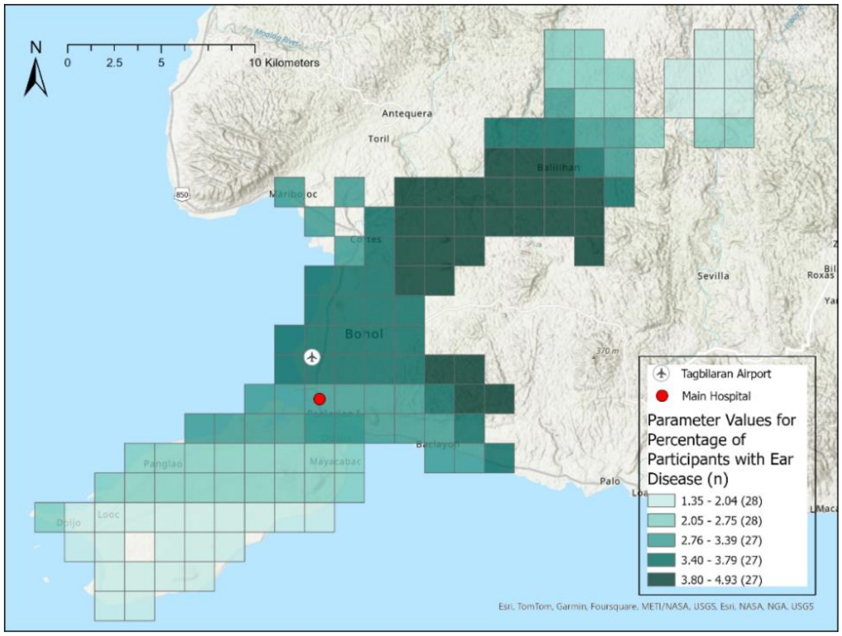
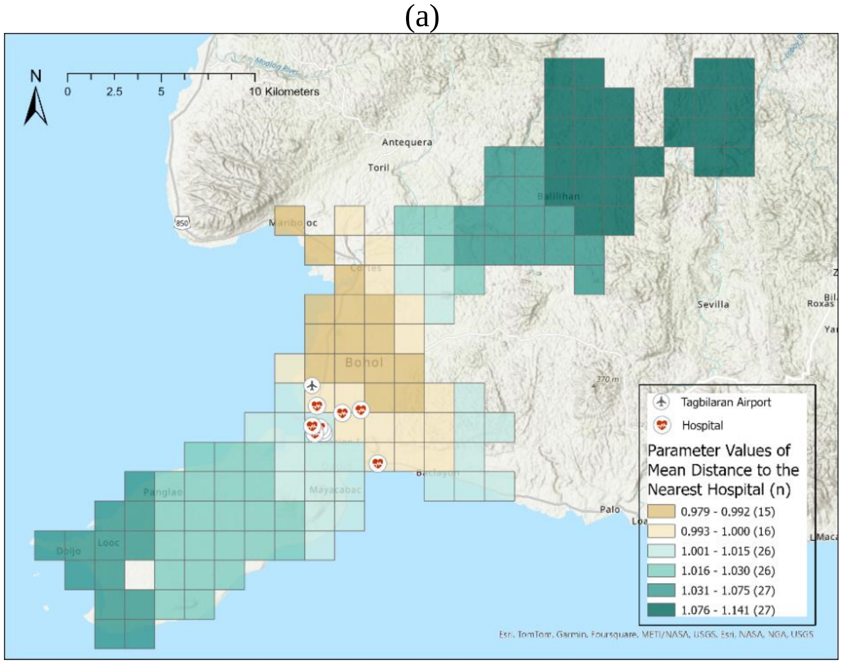


Figure 32. Parameter values from geographically weighted regression (GWR) for each key characteristic.

(a) Percentage participants with ear disease, (b) Mean distance to the nearest hospital in km, (c) Mean household wealth index, and (d) Percentage of participants with household member(s) regularly smoke.



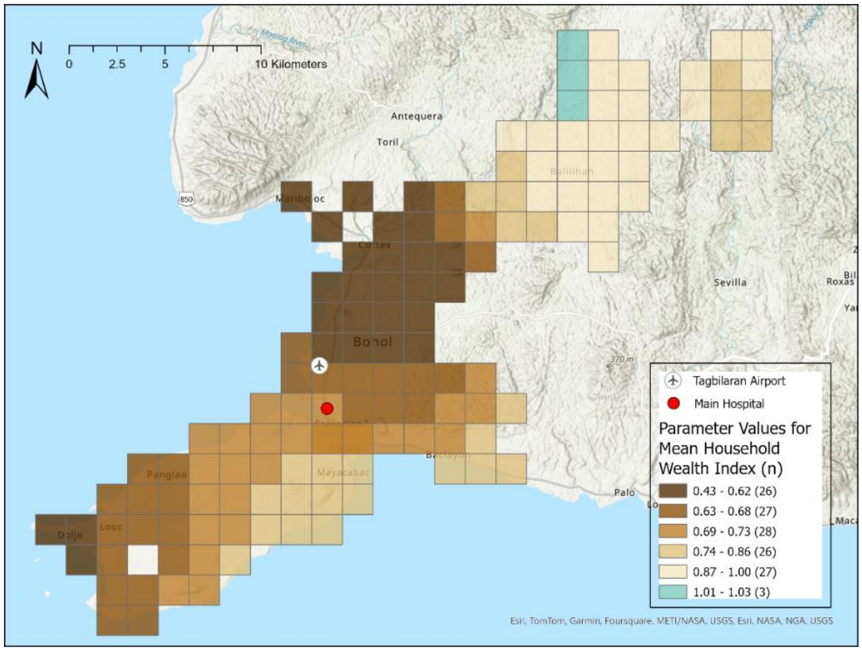
(a)



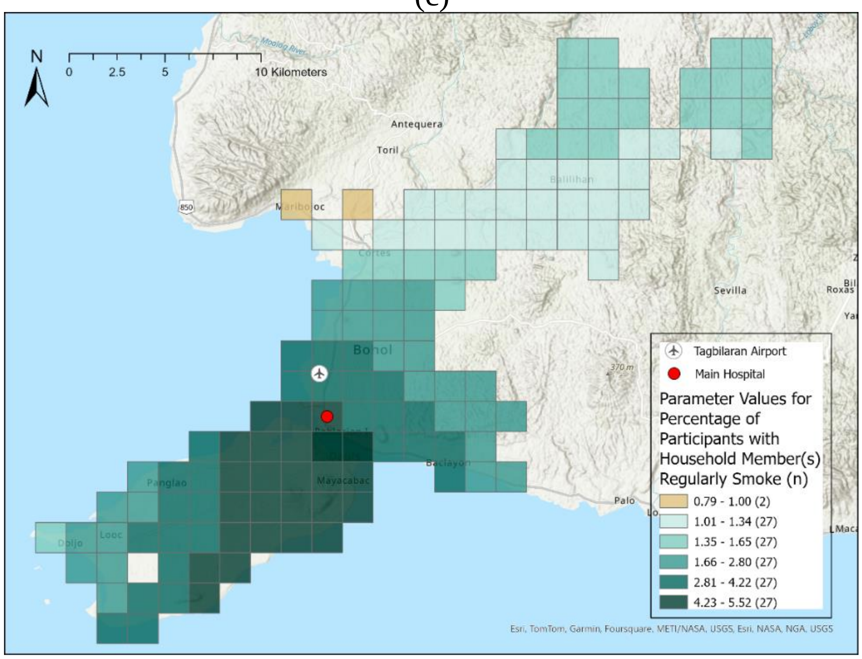
(b)

Continued

Figure 32. Continued



(c)



(d)

Table 8. Metrics for determining optimal neighborhood size to identify key characteristics associated with hearing loss.

Using the main study hospital as the centroid for the initial grid cell, grids of varying sizes were created overlaying the study area. For grid sizes from 800 to 2,500 meters per side, the table presents the number of neighborhoods (NB) in the final sample, the number of participants included, the mean percentage of participants with hearing loss with its variance, the number of neighborhoods without hearing loss cases, the total number of neighborhoods created, and the reasons for excluding certain neighborhoods. This data was used to guide the selection of the optimal neighborhood size.

Grid size (m)	Number of NB[1]	Number of Participants	Mean % with HL[2]	Variance	Number of NB with no participants with HL	Original sample size (NB)	Removed due to	
							Small sample size	Not connected to main mass
800	329	7581	0.088	0.0087	109	562	216	17
900	284	7631	0.084	0.0065	89	476	174	18
1000	246	7663	0.086	0.0074	63	420	155	18
1100	213	7680	0.086	0.0070	48	374	149	12
1200	198	7715	0.086	0.0076	44	336	122	16
1300	177	7728	0.083	0.0048	36	306	119	10
1400	159	7743	0.083	0.0042	28	281	113	8
1500	143	7754	0.084	0.0040	21	251	100	8
1600	**137**	**7913**	**0.085**	**0.0045**	**19**	**234**	**97**	**0**
1700	129	7913	0.086	0.0044	18	223	93	1
1800	109	7763	0.086	0.0040	13	206	88	9
1900	111	7927	0.083	0.0036	16	200	86	2
2000	97	7779	0.076	0.0035	19	185	50	37
2100	98	7936	0.078	0.0032	17	180	81	1
2200	86	7924	0.087	0.0001	10	170	80	4
2300	85	7924	0.085	0.0046	11	165	76	3
2400	80	7928	0.079	0.0026	11	159	76	3
2500	78	7945	0.091	0.0041	9	145	64	3

[1] NB: neighborhoods
[2] HL: hearing loss

Table 9. Descriptive statistics of parent trial participants in Bohol, Philippines (ISRCTN: 62323832): Comparison between follow-up assessment completers (n=8,060) and those reside in final neighborhoods with 1,600-meter grid size (n=7,913).

	Participants completed the follow-up study N=8,060			Participants covered by the final neighborhoods (Grid size: 1,600m) N=7,913				
Characteristics	**N**	**n**	**%**	**N**	**n**	**%**	**$\chi 2$**	**p[1]**
Child has hearing loss	8,060			7,913			<0.01	0.98
Yes		649	8.1		639	8.1		
No		7,411	91.9		7,274	91.9		
Child has ear disease	8,060			7, 913			0.05	0.82
Yes		3,525	43.7		3,476	43.9		
No		4,535	56.3		4,437	56.1		
Vaccinated in the parent trial	8,060			7, 913			0.04	0.83
Yes		4,052	50.3		3,964	50.1		
No		4,008	49.7		3,949	49.9		
Child sex	8,060			7, 913			<0.01	0.97
Male		4,091	50.8		4,012	50.7		
Female		3,969	49.2		3,901	49.3		
Parental education (highest)	8,048			7,902			0.04	1.00
College or post grad		2,576	32.0		2,517	31.9		
Some college		1,332	16.6		1,309	16.5		
HS or Vocational school grad		3,141	39.0		3,092	39.1		
Elementary school or less		999	12.4		984	12.5		
Parental employment (highest)	7,408			7,274			0.05	1.00
Manager/Professional/Technical		1,262	17.0		1,230	16.9		
Clerical/Service/Armed Forces		3,417	46.1		3,358	46.2		
Agriculture/Crafts/Skilled labor/Plant or machine operator or assembler		1,514	20.4		1,487	20.4		
Unskilled labor/Farmer		1,215	16.4		1,199	16.5		
Member(s) in the household regularly smoke	8,054			7,907			0.07	0.78
Yes		2,975	36.9		2,938	37.2		
No		5,079	63.1		4,969	62.8		
Low birth weight (<1,500 grams)	8,040			7,893			<0.01	1.00
Yes		144	1.8		142	1.8		
No		7,896	98.2		7,751	98.2		
Child ever diagnosed with malnutrition	8,045			7,898			<0.01	0.96
Yes		470	5.8		464	5.9		
No		7,575	94.2		7,434	94.1		

Continued

Table 9. Continued

	Participants completed the follow-up study N=8,060			Participants covered by the final neighborhoods (Grid size: 1,600m) N=7,913				
Characteristics	**N**	**Mean**	**SD[2]**	**N**	**Mean**	**SD[2]**	**t**	**p**
Child's age at follow-up assessment	8,060	16.05	1.30	7,913	16.02	1.29	-1.10	0.27
Euclidean distance from the closest hospital (km)	8,060	4.82	4.13	7,913	4.75	4.08	-1.15	0.25
Euclidean distance from Tagbilaran Airport (km)	8,060	7.21	6.57	7,913	6.87	5.58	-3.54	<0.001
Crowding	8,036	2.79	1.68	7,889	2.79	1.68	0.15	0.88
Household Wealth Index	8,060	0.02	0.96	7,913	0.02	0.96	0.02	0.98

[1] p-value is for the difference between all enrolled participants with valid ear exam and residential location records and participants covered by the final neighborhoods from t-tests (continuous variables) or chi-squared tests (categorical variables)
[2] SD: standard deviation.

Table 10. Neighborhood level descriptive statistics among a cohort of children participated in the follow-up assessment of a randomized controlled trial (RCT) on pneumococcal conjugate vaccine (PCV) in Bohol, Philippines (137 neighborhoods with sides of 1,600m).

Characteristics	**Mean (SD[1])**	**Median (IQR[2])**
Mean age of the child participants	16.56 (0.64)	16.62 (0.84)
Mean crowding index	2.79 (0.50)	2.76 (0.65)
Mean wealth index	-0.18 (0.38)	-0.20 (0.48)
Mean Euclidean distance from the closest hospital (km)	7.15 (3.87)	7.17 (6.17)
Mean Euclidean distance from Tagbilaran Airport (km)	11.16 (6.66)	9.69 (9.68)
	Mean %	**95% CI[3]**
Percent of participants with hearing loss	8.53	7.41, 9.65
Percent of participants with ear disease	40.70	38.09, 43.31
Percent of participants vaccinated in the parent trial	50.14	48.49, 51.79
Percent of participants with birth weight less than 1500 grams	2.63	1.79, 3.47
Percent of participants with members in the house regularly smoke	41.22	38.89, 43.55
Percent of female participants	48.87	46.93, 50.81
Percent of participants whose parents' highest education level was		
High school or vocational school grad or above	81.86	79.72, 84.00
Some college or above	38.02	34.85, 41.19
College or post grad	23.40	20.63, 26.17
Percent of participants whose parents' highest employment level was		
Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler or *above*	73.58	71.09, 76.07
Clerical/Service/Armed Forces or *above*	52.90	50.14, 55.66
Manager/Professional/Technical	11.95	10.13, 13.77
Percent of participants ever diagnosed with malnutrition	5.00	4.12, 5.88

[1]SD: standard deviation
[2]IQR: Inter-quartile range
[3]CI: confidence interval

Table 11. Global Moran's I statistics for neighborhood level characteristics.

	Global Moran's I Index	**Variance**	**z-score**	**p-value**
Prevalence of hearing loss	0.0482	0.0025	1.1222	0.26
Vaccine coverage	-0.0494	0.0025	-0.8422	0.40
Mean distance to the nearest hospital	0.4571	0.0024	9.4537	<0.001
Mean distance to Tagbilaran Airport	0.2334	0.0025	4.8371	<0.001

Table 12. Bivariate analysis of characteristics potentially associated with neighborhood level prevalence of hearing loss in Bohol, Philippines, using Poisson regression models (n=137 neighborhoods).

	Bivariate Analysis		
Characteristics	**Estimate**	**Standard error**	**p value**
Percentage of participants vaccinated in the parent trial	0.604	0.683	0.38
Percentage of participants had ear disease	1.231	0.372	<0.001*
Mean Euclidean distance from the closest hospital (km)	0.044	0.009	<0.001*
Mean Euclidean distance from Tagbilaran Airport (km)	0.030	0.006	<0.001*
Percentage of participants with birth weight less than 1500 grams	1.247	1.210	0.30
Mean crowding index	0.288	0.117	0.01*
Mean household wealth index	-0.616	0.122	<0.001*
Mean age of the child participants	0.187	0.053	<0.001*
Percentage of participants with members in the house regularly smoke	1.751	0.399	<0.001*
Percentage of female participants	-0.867	0.623	0.16
Percentage of participants whose parents' highest education level is			
high school or vocational school grad or above	-1.750	0.376	<0.001*
some college or above	-1.075	0.239	<0.001*
college or post grad	-1.276	0.275	<0.001*
Percentage of participants whose parents' highest employment level is			
Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler or *Clerical/Service/Armed Forces* or *Manager/Professional/Technical*	0.030	0.348	0.93
Clerical/Service/Armed Forces or *Manager/Professional/Technical*	-0.353	0.337	0.30
Manager/Professional/Technical	-2.147	0.495	<0.001*
Percentage of participants ever diagnosed with malnutrition	0.972	0.459	0.972

* Significant at 0.20 level. Included in the multivariable analysis.

Table 13. Results from the Poisson regression model and geographically weighted regression (GWR) model.

	Poisson Regression		GWR		
Characteristics	**IRR**	**95% CI**	**Min**	**Median**	**Max**
Percentage of participants with ear disease	3.06***	1.56, 6.05	1.353	3.043	4.935
Percentage of participants with household member(s) regularly smoke	2.05	0.79, 5.35	0.788	2.268	5.520
Mean distance to the nearest hospital	1.03*	1.00, 1.05	0.979	1.024	1.141
Mean household wealth index	0.72*	0.52, 0.99	0.430	0.713	1.367
Intercept	0.03***	0.02, 0.06	0.018	0.029	0.052

* p<0.05 ** p<0.01 *** p<0.001

Chapter 6. Key Characteristics Associated with Cognitive Development

6.1 Introduction

Cognitive development during childhood and adolescence is a crucial aspect of overall health and well-being, exerting profound influences on future educational attainment, occupational achievements, and overall quality of life (160). In low- and middle-income countries (LMICs), children often face challenges that can hinder their cognitive development, including poverty, undernutrition, limited access to healthcare, and exposure to diseases such as otitis media (OM) (2, 21, 75, 161-167). OM is a common childhood condition that has been linked to hearing loss and subsequent delays in language acquisition, both of which can negatively impact cognitive development (3, 168). Despite the global burden of OM and its potential impact on cognitive outcomes, research on neighborhood-level factors associated with child cognition, particularly in LMICs, remains limited.

The existing literature primarily focuses on individual-level determinants of cognitive development, such as parental education and household wealth (153, 165, 169). Previous studies have shown that children living in impoverished neighborhoods are at greater risk of cognitive delays, likely due to a combination of limited access to healthcare, lower parental education levels, and fewer educational resources (161, 166). Other factors explored on individual level include low birth weight, secondhand smoke exposure, traffic-related noise pollution, malnutrition, and OM (12, 14, 75, 76, 164, 167, 169-175). However, neighborhood level characteristics associated with cognitive outcomes has been less explored, especially in LMICs. Neighborhoods are not only physical spaces, but also social environments where children interact with others, access resources, and receive healthcare services. Understanding these associations on neighborhood level, including those between cognitive development and prevalence of diseases like OM or hearing loss and socioeconomic conditions can inform targeted public health policies and interventions aimed at fostering optimal cognitive development across diverse geographic and socioeconomic contexts.

This study aims to address this research gap by investigating key neighborhood-level characteristics associated with cognitive development among a cohort of children in Bohol, Philippines. Specifically, the study explores factors including the local prevalence of OM, traffic-related noise pollution level, household socioeconomic status, preschool attendance rates, and parental education at the neighborhood level in shaping cognitive outcomes. By focusing on neighborhood-level analysis, the research seeks to provide nuanced insights into the spatial dynamics of cognitive development in Bohol. The findings from this study are expected to contribute to the growing body of evidence on the social determinants of health and inform future public health interventions aimed at reducing disparities in cognitive development in LMICs.

6.2 Methods

6.2.1 Data Source

I utilized secondary data from a follow-up investigation of a double blinded randomized controlled trail (RCT) of a pneumococcal conjugate vaccine (PCV) among children born into Bohol, Philippines in July 2000 to December 2004 (ISRCTN: 62323832) (50). Approximately three quarters (73.2%) of the 12,191 infants enrolled in the parent study participated in the follow-up conducted from September 2016 to February 2020. The study area was a predominantly rural and agricultural area (397 km^2) covering seven districts: Tagbilaran City, Panglao, Dauis, Corella, Cortes, Balilihan, and Baclayon (81). Participants in the original trial were randomized at 48 government primary health care centers to receive either the PCV or a placebo (saline) injection, with the PCV provided by Sanofi Pasteur. The randomization was conducted at the individual level using block randomization, ensuring blinding for both administer of the allocated vaccine or placebo, participants, and the clinical review team who evaluated participant data.

In the follow-up study, field staff performed home visits to locate participants, securing verbal parental consent and child consent or assent, if applicable. Parents or primary caregivers then filled out a questionnaire that included demographic information, behavioral factors, socioeconomic status, and health conditions. Afterward, the children took ear examinations and hearing tests at the study office in Tagbilaran City. Geographic information, including shapefiles of healthcare facilities, political boundaries, and roads, was obtained from the Bohol Provincial Planning and Development Office (https://ppdo.bohol.gov.ph/) and the Philippine Geoportal (https://www.geoportal.gov.ph).

6.2.2 Variable Definitions

6.2.2.1 Cognitive Development (Full-Scale Intelligence Quotient [FSIQ])

Cognitive development was assessed using the Wechsler Intelligence Scale for Children® Fifth Edition (WISC-V) during follow-up evaluations. The WISC-V is a comprehensive intelligence test widely used to measure cognitive abilities in children aged 6 to 16 years and 11 months, encompassing intellectual ability across five cognitive domains critical to performance (23). Despite its standard age range, our study extended the applicability of the WISC-V to participants aged 14.9 to 19 years old, justified by developmental continuity. The previous age restriction was partially due to the need for reference data to calculate individual score. However, for this analysis, we used the raw scores and calculated z-scores based on our own sample, thus mitigating concerns about extending beyond the standard age range. This approach allowed for a thorough evaluation during a pivotal developmental period extending into late adolescence. FSIQ derived from the WISC-V served as the primary measure of cognitive development, reflecting overall intellectual functioning (95). Raw FSIQ scores were normalized into age-specific z-scores to facilitate standardized comparisons across different age groups, ensuring robust analysis of cognitive outcomes. The z-scores were calculated as: ((individual FSIQ score – population mean FSIQ score)/population FSIQ standard deviation), with the mean and SD calculated within each 4-month age group. All analyses were conducted in standard deviation units, providing a uniform metric for evaluating cognitive development within our study population.

6.2.2.2 Hearing Loss

Children underwent audiology screening with noise-attenuating earphones in a quiet environment during follow-up. Those showing signs of possible hearing loss, having a history of ear issues, an abnormal tympanogram, or failing the distortion product otoacoustic emissions (DPOAEs) test were referred to the Bohol Hearing Center for a formal evaluation. This evaluation measured the ability to hear the softest sounds at frequencies from 500 to 8,000 Hz for each ear. A dichotomous variable was created to indicate the presence of hearing loss in at least one ear.

6.2.2.3 Ear Disease (Otitis media [OM])

During follow-up, ear disease was identified through physician examinations and tympanometry. This analysis classified ear disease into two groups, normal and having OM, ranging from acute otitis media (AOM) to chronic suppurative otitis media (CSOM).

6.2.2.4 Vaccine Coverage in the Neighborhood

Vaccine coverage (VC) in each neighborhood was calculated as the proportion of children who received the PCV in the parent trial compared to the total number of children enrolled in that neighborhood.

6.2.2.5 Traffic-related Noise Pollution

Tagbilaran Airport (IATA: TAG; Coordinates: 09°39′50.69″N, 123°51′11.69″E) was the main source of traffic-related noise pollution. Situated in the city center and surrounded by residential areas, the airport operated from the 1960s until its closure in November 2018 when it was replaced by Bohol-Panglao International Airport. During the 2000s and 2010s, the airport was often congested due to reaching its capacity. To measure noise pollution from the airport for each neighborhood, I calculated the Euclidean distance from Tagbilaran Airport to each participant’s home and then calculated the mean distance.

6.2.2.6 Other Sociodemographic Characteristics

The follow-up assessment collected various sociodemographic factors during household visits through a parental questionnaire. These factors included the child’s age and sex, the maternal age of the child’s mother, birthweight, birth order, breastfeeding history, household wealth index (constructed using the Demographic and Health Surveys Program [DHS] methodology), smoking exposure in the household, preschool attendance, parental education attainment, parental employment status, and history of malnutrition diagnoses. The household wealth index is a composite measure of household assets, with higher scores indicating greater wealth. The index considered specific indicators relevant to the Philippines, such as roofing and flooring materials, ownership of appliances like refrigerators and televisions, and access to improved water sources and sanitation facilities, ensuring it accurately reflected socioeconomic status variations within the country.

6.2.3 Location Information

6.2.3.1 Waypoints

Waypoints denote precise coordinates identifying residential locations. Field personnel collected waypoints of each participant's residential location using Garmin eTrex devices. A Geographic Information System (GIS) officer processed global positioning system (GPS) data, consolidating daily records into monthly and yearly files. Subsequently, all geographic data were linked to respective participant follow-up survey records.

6.2.3.2 Defining Neighborhoods

I defined neighborhoods using a square polygon grid overlaying the study area, where each grid cell represented a neighborhood solely based on geographic boundaries. Grid cells varied in size from 800 to 2,500 meters per side, incremented by 100-meter intervals, with Gov. Celestino Gallares Memorial Hospital serving as the centroid for grid cell placement. Neighborhoods spanning both sides of the strait were bifurcated, assigning each side to distinct geographic entities. I then employed spatial join techniques to assign participants to neighborhoods, excluding those with fewer than four participants to ensure analytical robustness. Additionally, neighborhoods connected to the main landmass were prioritized for analysis. Final neighborhood size was determined based on optimizing participant and neighborhood counts while maximizing variability in cognitive development measurement.

6.2.3.3 Neighborhood-level Characteristics

I aggregated all relevant neighborhood characteristics and computed the mean z-score of FSIQ for each neighborhood. Categorical characteristics were expressed as percentages, while continuous characteristics were summarized using means.

6.2.4 Inclusion and Exclusion Criteria

6.2.4.1 Inclusion Criteria

a. Participants were enrolled in the parent trial conducted between 2000 and 2004.

b. Verbal consent was obtained for both the parent trial and the follow-up study.

6.2.4.2 Exclusion Criteria

a. Participants or their parents declined participation in surveys or assessments.

b. Participants passed away before completion of the follow-up study.

c. Participants were lost to follow-up.

d. Ear, hearing examination, or cognitive test results were unavailable for participants.

6.2.5 Analysis

After determining the optimal neighborhood size, I compared individual characteristics of the entire sample with those included in the final neighborhoods using t-tests for continuous variables and chi-squared tests for categorical variables. These characteristics were then aggregated at the neighborhood level, and spatial distribution maps of cognitive development and vaccine coverage were created. Global spatial autocorrelation was assessed using the global Moran's I index with a queen's case contiguity weight matrix, and local clusters were identified using location indicators of spatial association (LISA) maps (106, 107).

For statistical modeling, I conducted bivariate analyses to identify covariates with p-values less than 0.20. Starting with a full multivariable ordinary least squares (OLS) model, I employed backward selection to optimize the Akaike Information Criterion (AIC) and develop the final model. The overall significance of the final model was evaluated using the F-test and R-squared values. Potential multicollinearity was examined using the variance inflation factor (VIF), with a threshold of 5, and variables were selected based on the correlation matrix when multicollinearity was present. Residual plots were used to detect heteroskedasticity, outliers, and curvature. To assess spatial distortions in the OLS model, Moran's I was calculated on the residuals and compared to the Moran's I of the areal mean z-score of FSIQ.

To examine spatial homogeneity of the association between key characteristics and cognitive development across the study area, I used geographically weighted regression (GWR) modeling. The bandwidth that minimized the corrected Akaike Information Criterion (AICc) was chosen to balance bias and variance. Monte Carlo significance tests assessed the statistical significance of estimated coefficients. Model evaluation included VIF, adjusted R-squared, and AICc values.

All statistical analyses were conducted using R version 4.3.2 and ArcGIS Pro. Statistical significance was set at the 0.05 level unless otherwise specified.

6.3 Results

Of the 12,191 participants in the parent trail, 8,926 (73.2%) were enrolled in the follow-up study with completed parental questionnaire (Figure 33). Excluding those without valid ear examination results, residential GPS coordinates, or cognitive assessment results, the final sample included 7,791 children.

6.3.1 Defining the Neighborhood

I listed the number of neighborhoods, participants covered, the mean z-score of FSIQ per neighborhood, and its variance across grid sizes from 800 to 2,500 meters to determine the optimal neighborhood size for analysis (Table 14). Table 14 also outlines the total number of neighborhoods required to encompass all participants and reasons for excluding certain neighborhoods from analysis. As grid size increased, fewer neighborhoods were included but more participants were covered, illustrated in Figure 34. The study area's 119 barangays influenced the decision not to consider grid sizes resulting in fewer than 119 neighborhoods, specifically those greater than or equal to 1,800 meters. Balancing data richness and neighborhood sample size, I selected a 1,700-meter grid size for analysis, encompassing 98.6% of participants with complete records (7,680/7,791) and over 63% of created neighborhoods (124/196). To compare characteristics between the included and total sample, chi-squared tests for categorical variables and t-tests for continuous variables were conducted, revealing no statistically significant differences (Table 15).

6.3.2 Neighborhood Level Characteristics and Maps

Using a neighborhood size of 1,700 meters, I aggregated each characteristic to neighborhood level for analysis (Table 16). The mean z-score of FSIQ was -0.098, and on average, 50% of the participants in each neighborhood were vaccinated during the parent trial. The mean Euclidean distance from the Tagbilaran Airport to participants' residential location ranged from 0.8 to 27.2 kilometers (km), averaging 11.1 km. One neighborhood had no participants with OM and the average percentage of participants with OM was 40%. Approximately 9% of the participants had hearing loss across all neighborhoods, and 15 of the neighborhoods had no hearing loss cases.

To visualize participant distribution and characteristics across the study area, neighborhood-level maps were created, depicting each characteristic in quintiles. Neighborhood sizes ranged from 4 to 560 participants, with clustering observed around Gov. Celestino Gallares Memorial Hospital in Tagbilaran city and along the northeast shore of Panglao and Dauis (Figure 35). The area around Gov. Celestino Gallares Memorial Hospital and Tagbilaran Airport in Tagbilaran city showed higher mean z-scores of FSIQ, along with some neighborhoods in the northeast (Figure 36). Vaccination coverage did not exhibit spatial clustering (Figure 37a), reflecting random distribution across the study area.

6.3.3 Spatial Autocorrelation

To assess the spatial clustering of neighborhood-level mean z-score of FSIQ and vaccine coverage, I conducted both global and local spatial autocorrelation analyses.

Using the queen's case contiguity weight matrix, the global Moran's I for mean z-score of FSIQ was 0.17 (z=3.37, p<0.001), indicating significant clustering of neighborhoods with similar cognitive development among children (Table 17). Vaccine coverage showed near-zero global Moran's I (-0.036, z=-0.54, p=0.70), suggesting a random distribution across the study area with no significant spatial autocorrelation detected. Local spatial heterogeneity was further analyzed using LISA maps (Figure 38) to identify clusters and outliers for each characteristic. High-high clusters of mean z-score of FSIQ were observed around the main study hospital and Tagbilaran Airport, while low-low clusters were in the northeast part of the study area (Figure 38a). Vaccine coverage did not exhibit significant local clustering despite some scatter outliers (Figure 38b).

6.3.4 Statistical Modeling

Based on the bivariate analysis, the following covariates were considered for the multivariable models: percentage of participants vaccinated in the parent trial, traffic-related noise pollution exposure, mean household wealth index, parental education and employment levels, and prevalences of ear disease, hearing loss, low birthweight (less than 2,500 grams), household smoke exposure, preschool attendance, being firstborn, and exclusively breastfed for the first six months of life (Table 18). These covariates were included in the full multivariable OLS model. After backward selection minimizing AIC, seven characteristics were associated with better cognitive development on neighborhood level: higher percentage of female participants, lower percentage of participants with ear disease, higher mean household wealth index, higher percentage of participants whose parents had high school education or more, lower percentage of participants exposed to smoking within household, lower percentage of participants exclusively breastfed for the first 6 months of life, and lower percentage of participants with parents employed as manual labor or above (Table 19). Among these characteristics, the first four were significantly associated with better cognitive development. The final model's overall significance was supported by a F-statistic of 12.27 on 7 independent variables and 116 degrees of freedom ($p<0.001$). The adjusted R-squared was 0.3908, indicating that the model explained 39.08% of the variance in neighborhood-level cognitive development. An analysis of variance (ANOVA) test comparing the full and final models showed no significant difference (F=0.23, DF=10, p=0.99), supporting the final model for its parsimony. No multicollinearity issues were detected with a VIF threshold of 5. The Moran's I for mean z-score of FSIQ decreased from 0.168 ($p<0.001$) to 0.027 (p=0.25) in the residuals, indicating that the OLS model explained some spatial autocorrelation (Figure 39). The residuals were not spatially autocorrelated, ensuring the OLS results were not biased by spatial patterns.

To address potential spatial non-stationarity in the association between cognitive development and key characteristics, I employed a GWR model (Table 19 and Figure 40). The GWR model outperformed the OLS model, with a higher adjusted R-squared (0.69 compared to 0.39 from the OLS model) and lower AICc (0.26 compared to 3.67 from the OLS model). The median effect of the seven characteristics remained consistent with those in the OLS model. A higher mean household wealth index was significantly associated with better cognitive development, particularly in neighborhoods within

Tagbilaran city (Figure 40b). Additionally, a higher percentage of female participants was linked to better cognitive development in neighborhoods located farther from the main study hospital, especially in the northeastern part of the study area (Figure 40d). This northeastern region also showed a significant association between higher parental education attainment and improved cognitive outcome among participants (Figure 40f). The Monte-Carlo significance test showed no significant spatial variation in local parameter estimates, indicating minimal spatial non-stationarity and favoring the OLS model for this analysis.

6.4 Discussion

This study aimed to identify key factors associated with cognitive development at neighborhood level among a cohort of children in Bohol, Philippines, and examined the consistency of these factors across the study area. The findings revealed significant association between cognitive development and several key characteristics, including ear disease, household wealth, parental education attainment, sex, household smoke exposure, breastfeeding, and parental employment status. These findings add on to existing literature conducted on individual level and highlight potential areas for intervention to support child development.

Our study identified local OM prevalence as a significant factor associated with cognitive development among children in the neighborhood. Specifically, higher OM prevalence in the neighborhood was associated with lower cognitive development scores compared to the neighborhoods with fewer OM cases. OM encompasses a range of inflammatory conditions affecting the middle ear, often associated with episodes of acute infection (acute otitis media [AOM]) or chronic inflammation (chronic suppurative otitis media [CSOM]) (2, 30). The presence of otitis media may lead to hearing impairment, which impacts language acquisition and cognitive abilities during critical developmental periods (10, 20, 55). Previous studies conducted on individual level have supported these associations. A longitudinal study found that, despite generally modest effects, middle ear disease significantly impacted behavior problems and language test performance at age 5, with effects persisting into age 10, when the follow-up ended (12). Additionally, children with a history of OM with effusion (OME) were found to exhibit persistent hyperactivity and inattentions, as well as lower IQ scores, into their early teens, with notable deficits in reading ability (13). Furthermore, the Avon Longitudinal Study of Parents and Children revealed that children with more exposure to OME and hearing loss had lower IQ scores at ages 4 and 8, particularly in homes with lower cognitive stimulation, emphasizing increased vulnerability in less stimulating environments (20).

Our study also examined the percentage of participants with hearing loss as a potential key factor associated with cognitive development. While this association was statistically significant in bivariate analysis (estimate=-0.059, p=0.16), it was no longer significant in multivariable analysis. Hearing loss can be caused by various factors other than OM, such as congenital conditions, noise exposure, and ototoxic medications, which may or may not impact hearing during critical developmental phases (153, 176). However, OM predominantly affects young children, making it more directly related to cognitive development outcomes (55, 112). Our study extends existing literature by confirming that higher OM prevalence within a neighborhood is associated with lower cognitive development scores, thereby highlighting the importance of early detection and treatment of ear diseases in promoting optimal cognitive development among children.

The household wealth index was constructed using DHS program methodology, combining various indicators of household assets and services (110). In the Philippines, the index encompasses context-specific elements such as the quality of housing materials and availability of essential amenities, providing a thorough gauge of socioeconomic disparities. A higher mean household wealth index in the neighborhood was associated with better cognitive performance among children in the neighborhood. Meanwhile, children from neighborhoods with higher parental education level were also more likely to score better in the cognitive test. These results echo previous studies highlighting the critical role of socioeconomic factors in child development. Studies across both high-income countries and LMICs consistently demonstrate that higher parental education levels and household wealth are associated with improved child cognitive outcomes (169). For instance, using the earlier version of our assessment tool (WISC-III), higher parental education was positively correlated with children achieving higher scores across multiple cognitive domains (177). Similarly, another study using the WISC-III showed that socioeconomic status, characterized by parental education and family income, significantly influenced cognitive scores, with parental education exerting a stronger influence than income (165). In the current neighborhood-level analysis, both parental education and household wealth exhibited significant association with cognitive development in the multivariable OLS model. These associations may be mediated through enhanced access to educational opportunities, different parent-child interactions, enriched environments, and resources aimed at improving family incomes.

The study area, initially segmented into 119 barangays based on political boundaries, posed limitations for detailed spatial analysis due to irregular shapes and varying sizes. To overcome these challenges and enable more precise spatial analysis, I implemented a 1,700-meter square grid to redefine neighborhoods across the study area. This grid-based approach ensured standardized and uniform spatial units, facilitating robust analysis of neighborhood-level characteristics and their associations with cognitive development outcomes. Covering 98.6% of participants with complete records, this methodological refinement upheld the study's representativeness, with no statistically significant differences observed between the included and total samples. By adopting this approach, our study not only enhanced the precision of spatial analyses but also uncovered local variations in cognitive development, underscoring the utility of our neighborhood-level approach for informing targeted public health interventions based on observed spatial patterns. We identified a spatial cluster of higher cognitive development scores around key locations such as the Tagbilaran city center and Tagbilaran Airport (Figure 36), suggesting potential advantage associated with proximity to urban amenities. This finding aligns with research indicating that access to urban resources positively influences child development outcomes (166, 178).

The use of GWR provided deeper insights into the spatial variability of associations between neighborhood characteristics and cognitive development among children. The consistency of median coefficients from the GWR with those from the OLS model confirmed the robustness of our findings. The GWR results highlighted areas of higher vulnerability, thereby guiding targeted interventions to regions with the greatest need. Notably, in neighborhoods in and around Tagbilaran city, higher household wealth index was significantly associated with better cognitive development outcomes (Figure 40b). Conversely, in the northeastern part of the study area, parental education level showed a significant association with cognitive development (Figure 40f). These patterns align with the distribution of the mean household wealth index (Figure 37b), indicating that household wealth was significant in areas with higher mean household wealth while parental education was significant in areas with lower mean household wealth. This suggests that the association between socioeconomic factors and child cognitive development differs in impoverished versus affluent areas. Household wealth shows a stronger association with child cognitive development in wealthier neighborhoods, whereas parental education shows a stronger association in less affluent areas. This nuanced understanding underscores the importance of tailoring interventions to specific community contexts to effectively address disparities in child development outcomes.

This analysis added a neighborhood-level perspective to the current literature on cognitive development of children in LMICs and provided detailed insights into the spatial distribution of cognitive development outcomes among children in Bohol, Philippines. The implementation of a 1,700-meter square grid ensured uniform spatial units, enhancing the precision of our spatial analyses. Moreover, the use of GWR allowed for the identification of local variations in the associations between neighborhood characteristics and cognitive development, offering valuable information for targeted interventions.

However, several limitations should be acknowledged. First, the cross-sectional nature of the study limits the ability to infer causality. Longitudinal studies are needed to establish temporal relationships between neighborhood characteristics and cognitive development outcomes. Second, the study relied on secondary data sources, which may be subject to reporting biases and inaccuracies. Future research could benefit from primary data collection to validate and enrich the findings. Lastly, while the study covered a large proportion of the target population, some participants were excluded due to incomplete records, which could introduce selection bias.

The findings of this study hold substantial implications for public health strategies aimed at enhancing child cognitive development in LMICs. The significant associations between local ear disease prevalence, socioeconomic factors, and cognitive development highlight the need for comprehensive interventions that address both health and socioeconomic determinants of child development. Early detection and treatment of ear diseases, coupled with efforts to improve household wealth and parental education, could substantially enhance cognitive outcomes among children. Moreover, the spatial analysis revealed areas of higher vulnerability, indicating regions where targeted interventions could be most effective. Policies aimed at improving access to urban amenities and resources in less affluent neighborhoods could help bridge the gap in cognitive development outcomes between different socioeconomic groups.

Future research should focus on longitudinal studies to explore the causal pathways between neighborhood characteristics and cognitive development. Additionally, investigating the potential mechanisms through which socioeconomic factors influence cognitive outcomes, such as parental behaviors and environmental conditions, would provide deeper insights into the underlying processes. Expanding the study to include other regions in the Philippines and different countries would also help to generalize the findings and understand the broader applicability of the results.

In conclusion, this study underscores the critical role of neighborhood-level socioeconomic factors and health conditions in shaping cognitive development outcomes among children in Bohol, Philippines. The findings highlight the importance of early intervention and comprehensive strategies that address both health and socioeconomic determinants to support optimal child development. By employing a robust spatial analysis approach, this study provides valuable insights for public health policies and targeted interventions aimed at reducing disparities and promoting cognitive development.

Figure 33. CONSORT diagram.

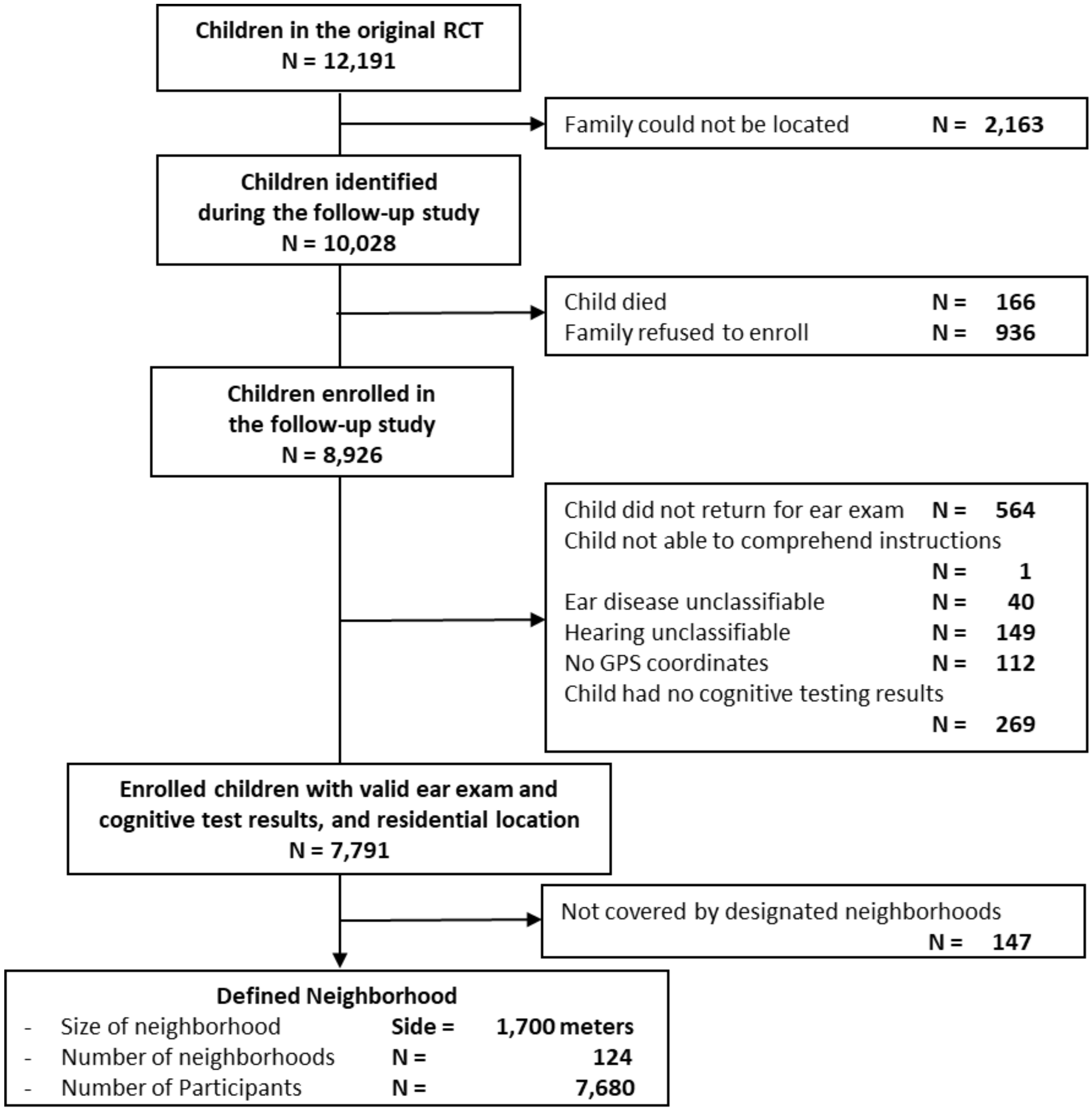


Figure 34. Changes in number of neighborhoods and number of participants covered across different grid sizes from 800 to 2,500 meters per side.

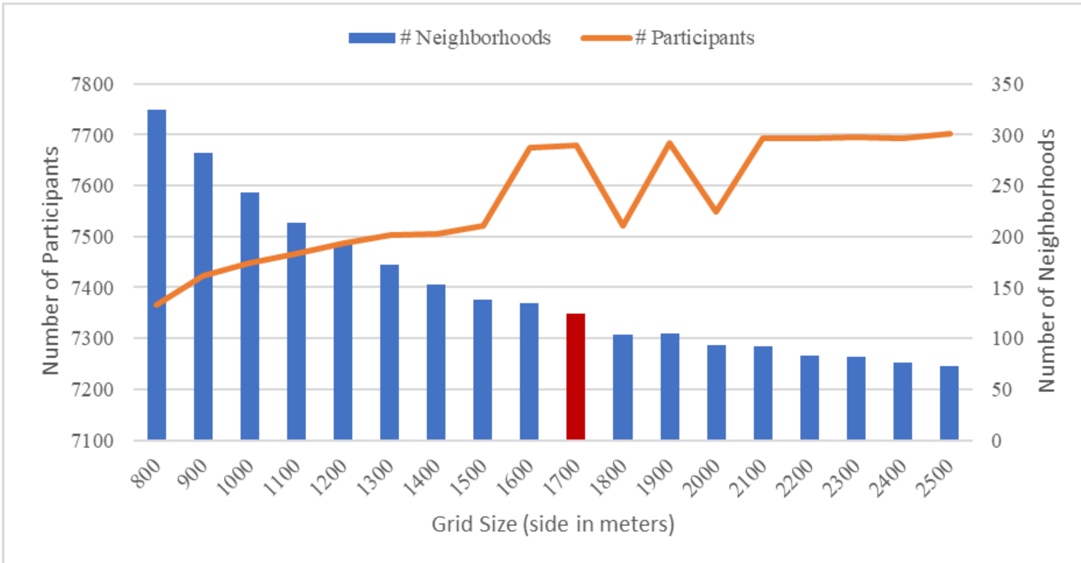


Figure 35. Number of participants per neighborhood with 1,700-meter neighborhoods in Southwestern Bohol, Philippines.

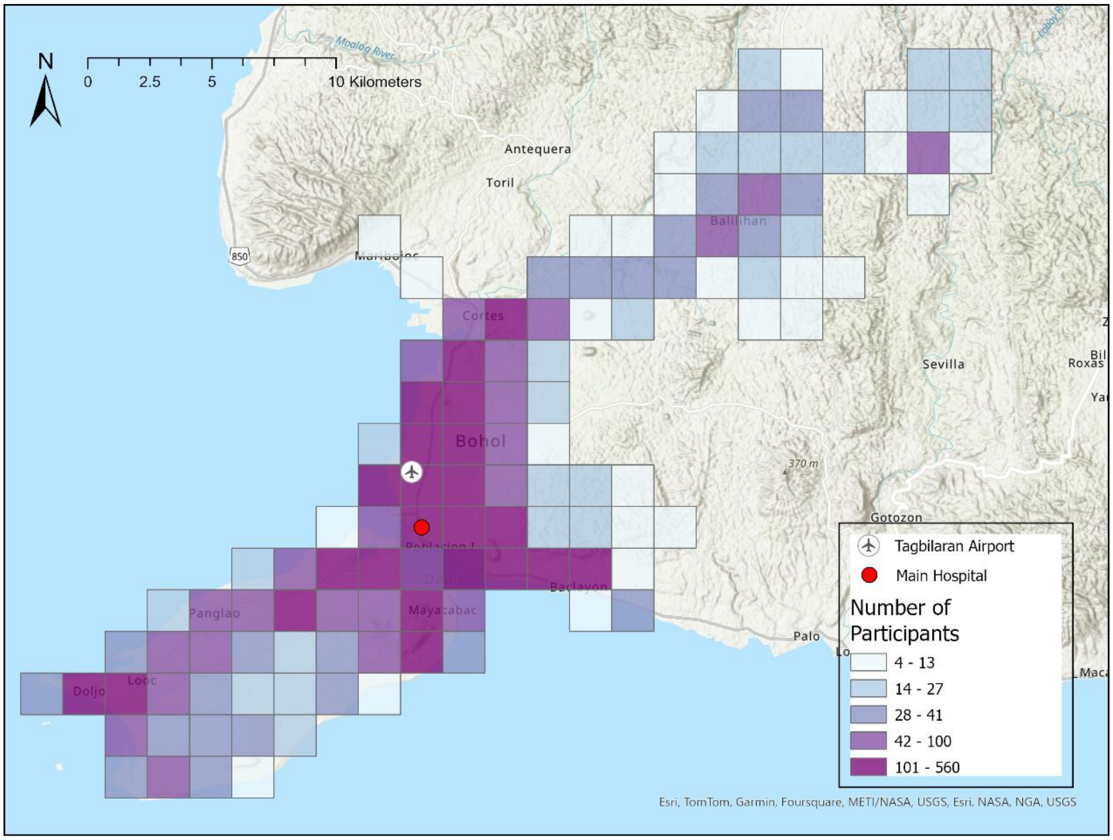


Figure 36. Neighborhood-level mean age-specific z-score of full-scale Intelligence Quotient (FSIQ) in Southwestern Bohol, Philippines (neighborhood size: 1,700 meters).

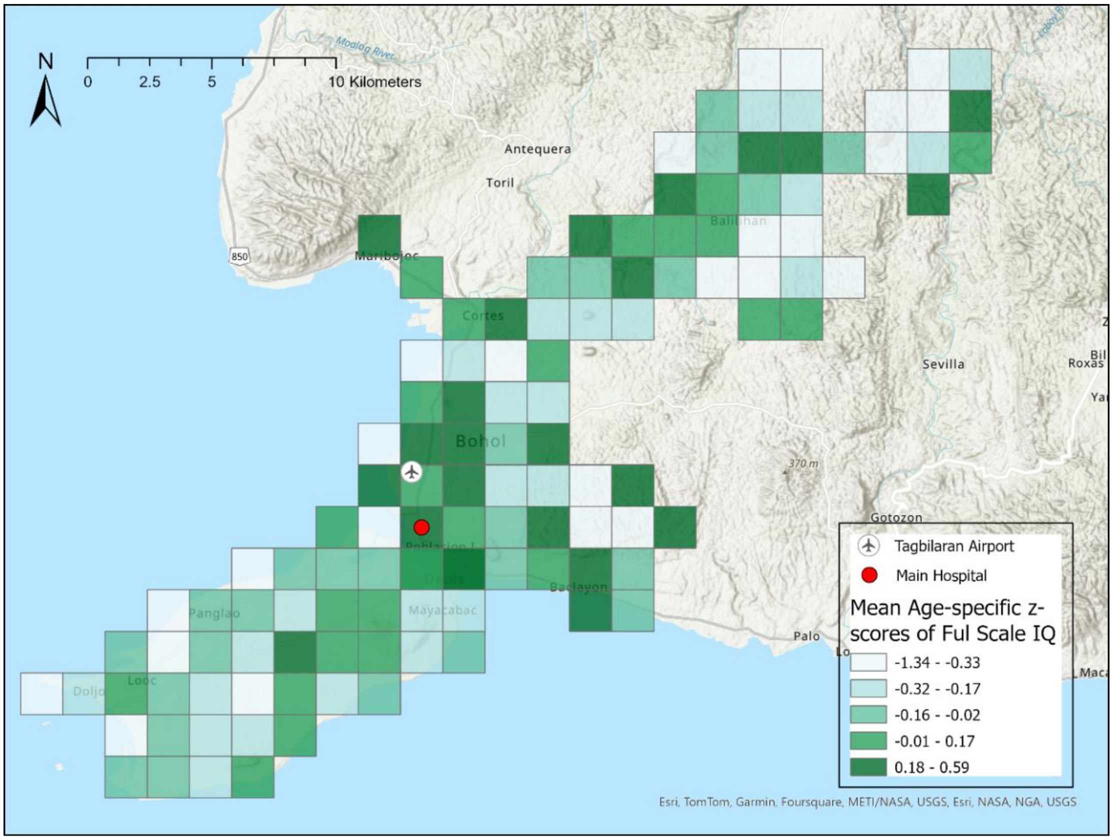
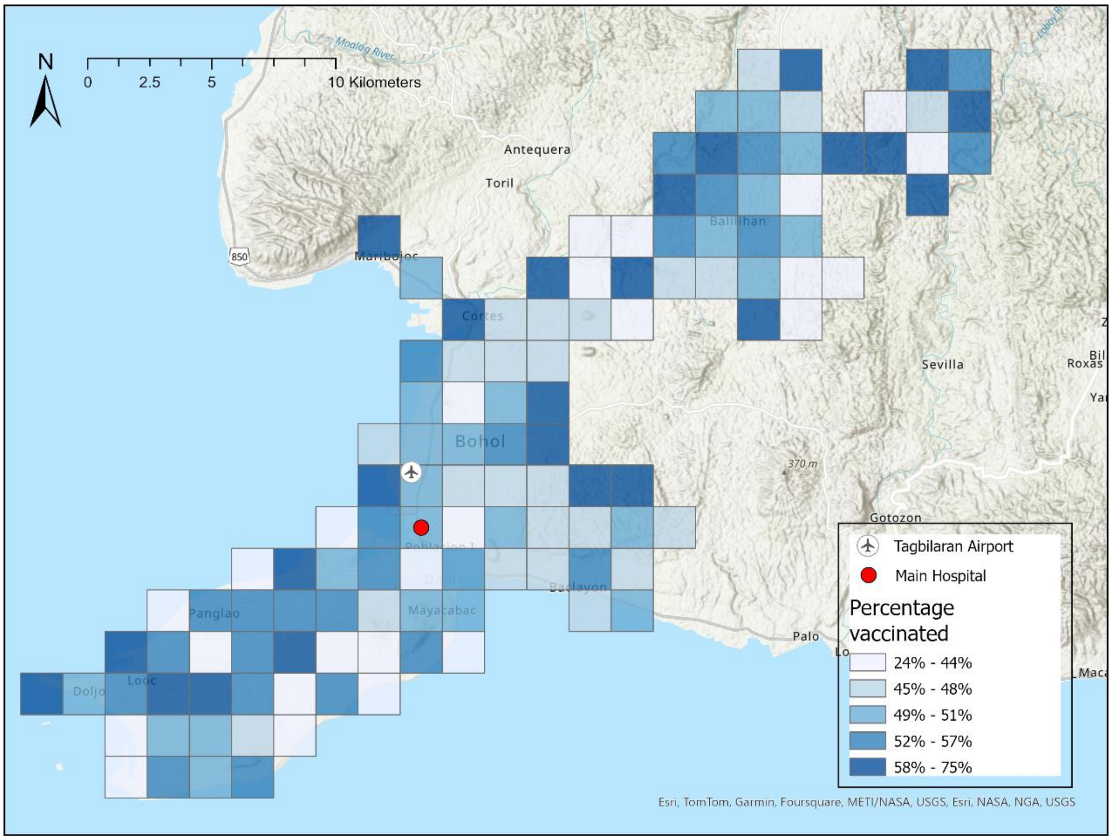


Figure 37. Neighborhood-level characteristics in Southwestern Bohol, Philippines (neighborhood size: 1,700 meters).

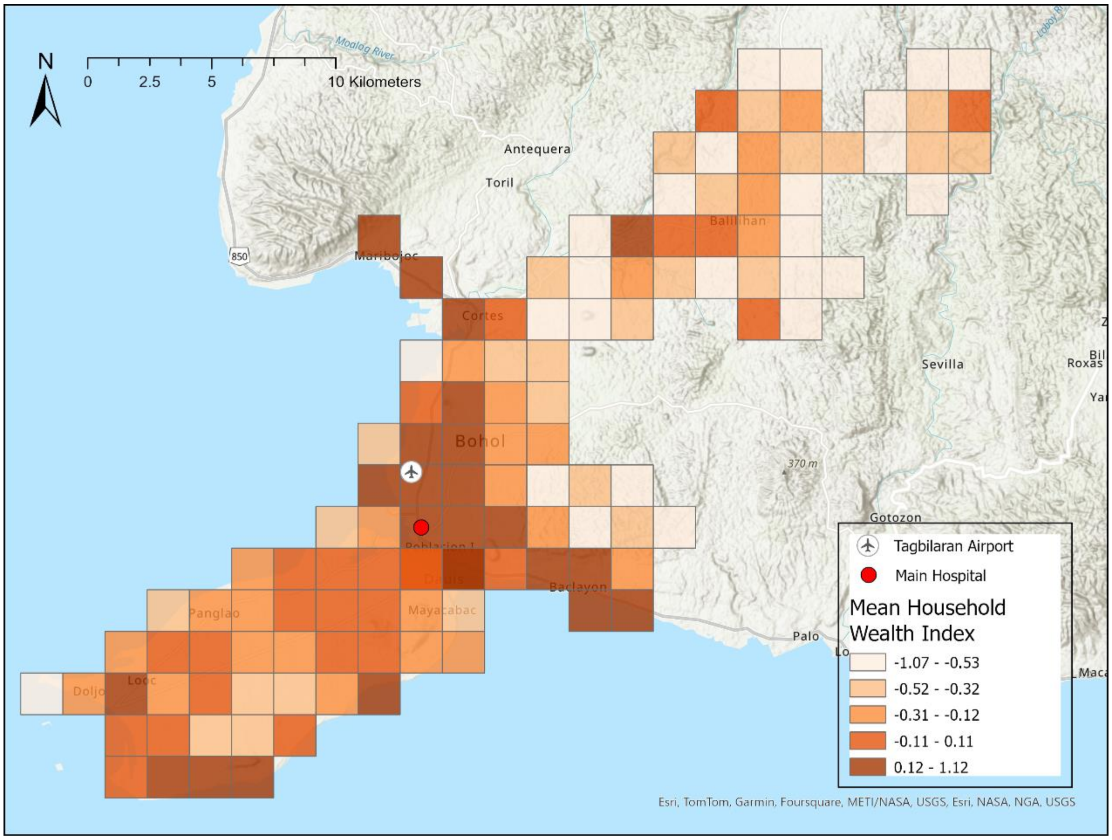
(a) percentage of participants vaccinated in the parent trial and (b) mean household wealth index.



(a)

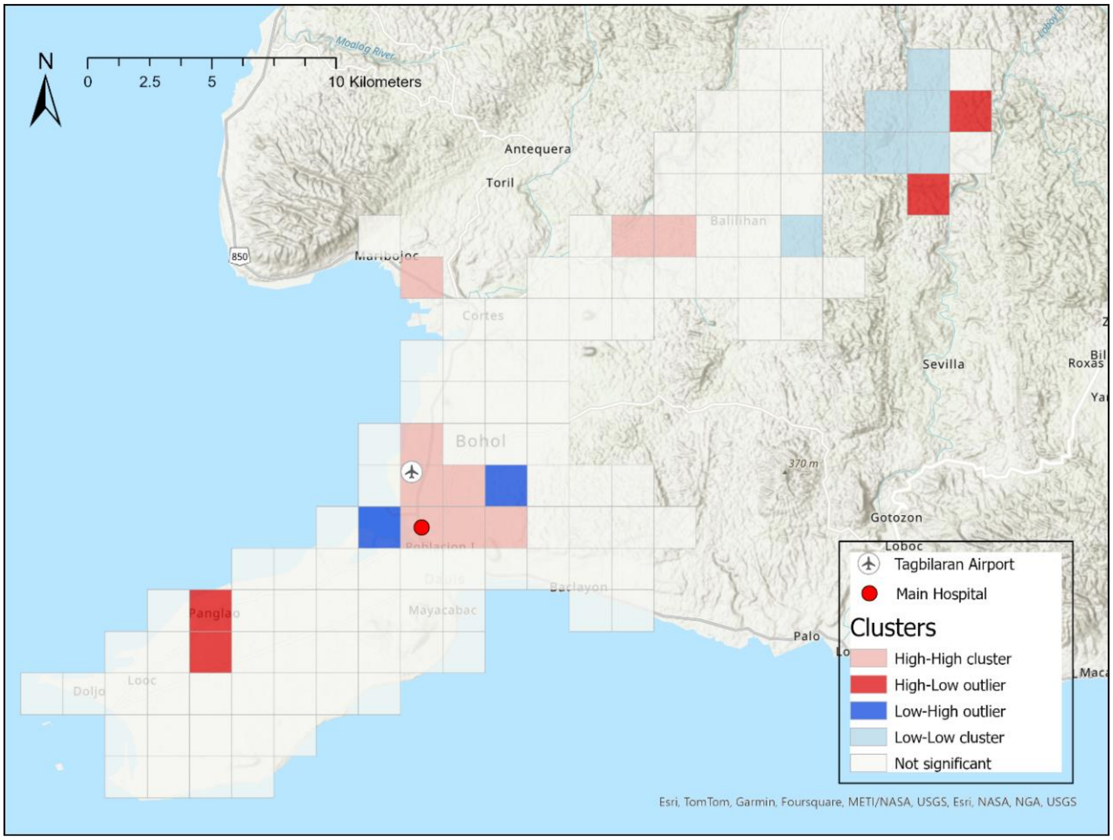
Continued

Figure 37. Continued



(b)

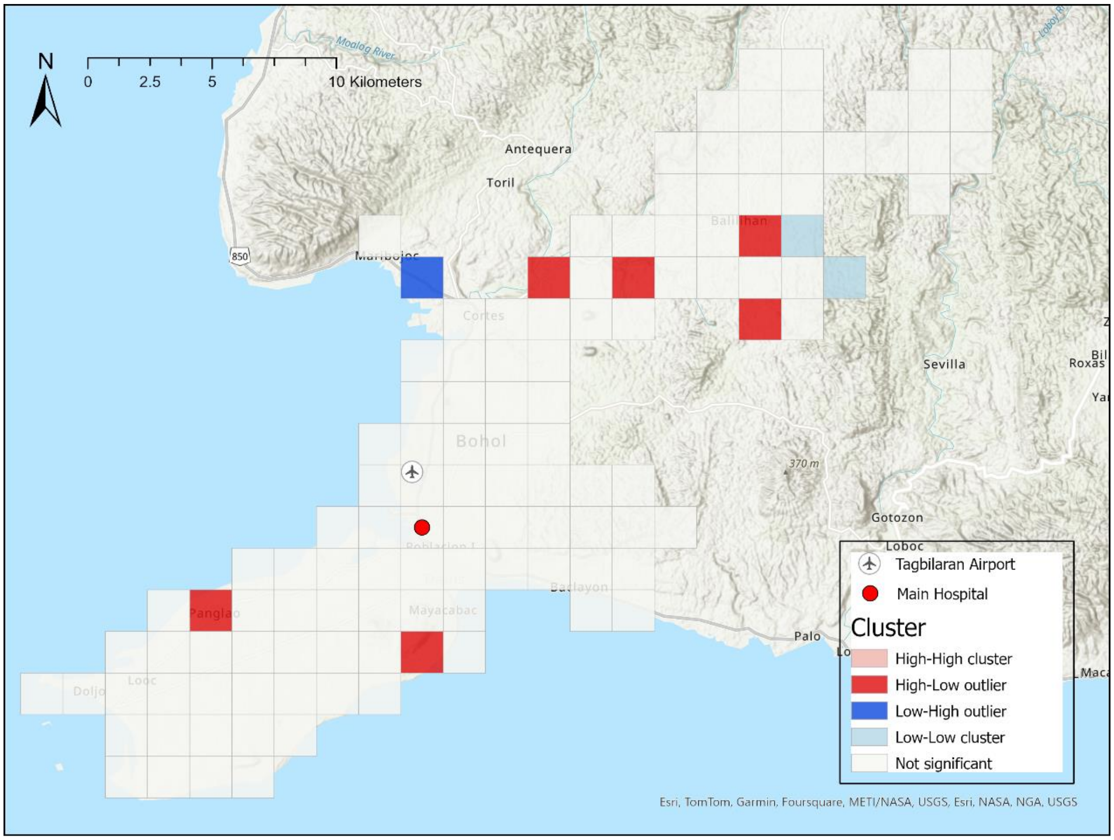
Figure 38. Local indicators of spatial association (LISA) maps on neighborhood level of (a) age-specific z-score of full-scale Intelligence Quotient (FSIQ) and (b) vaccine coverage.



(a)

Continued

Figure 38. Continued



(b)

Figure 39. Residual plot of the final ordinary least square (OLS) model.

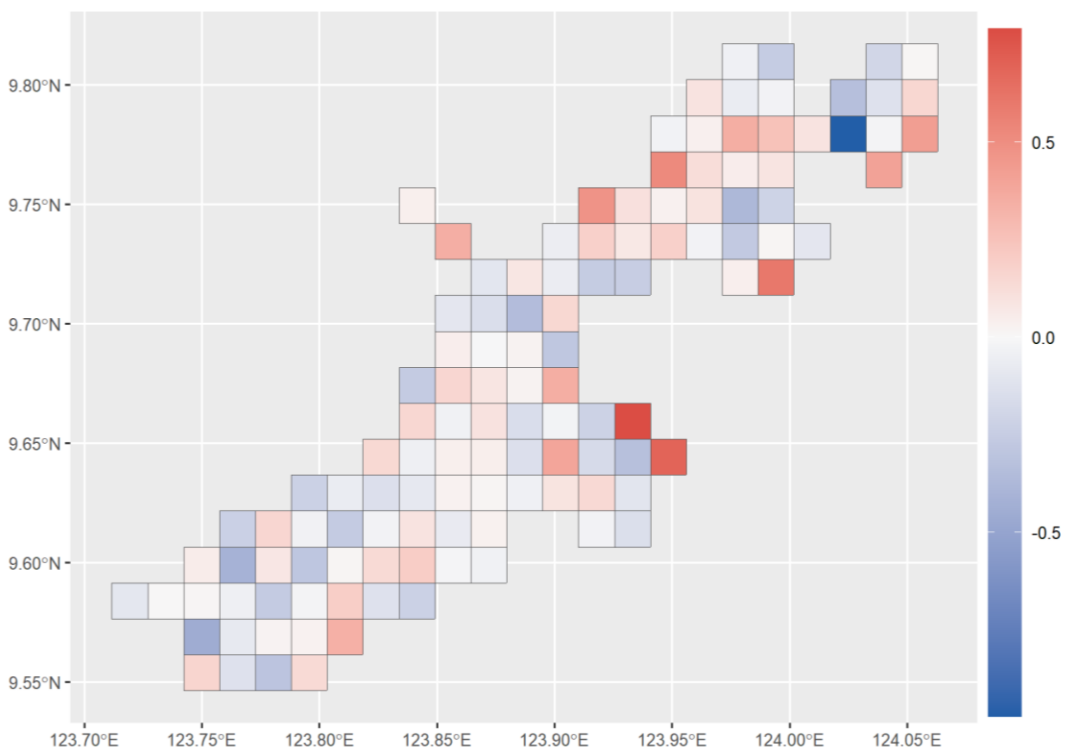
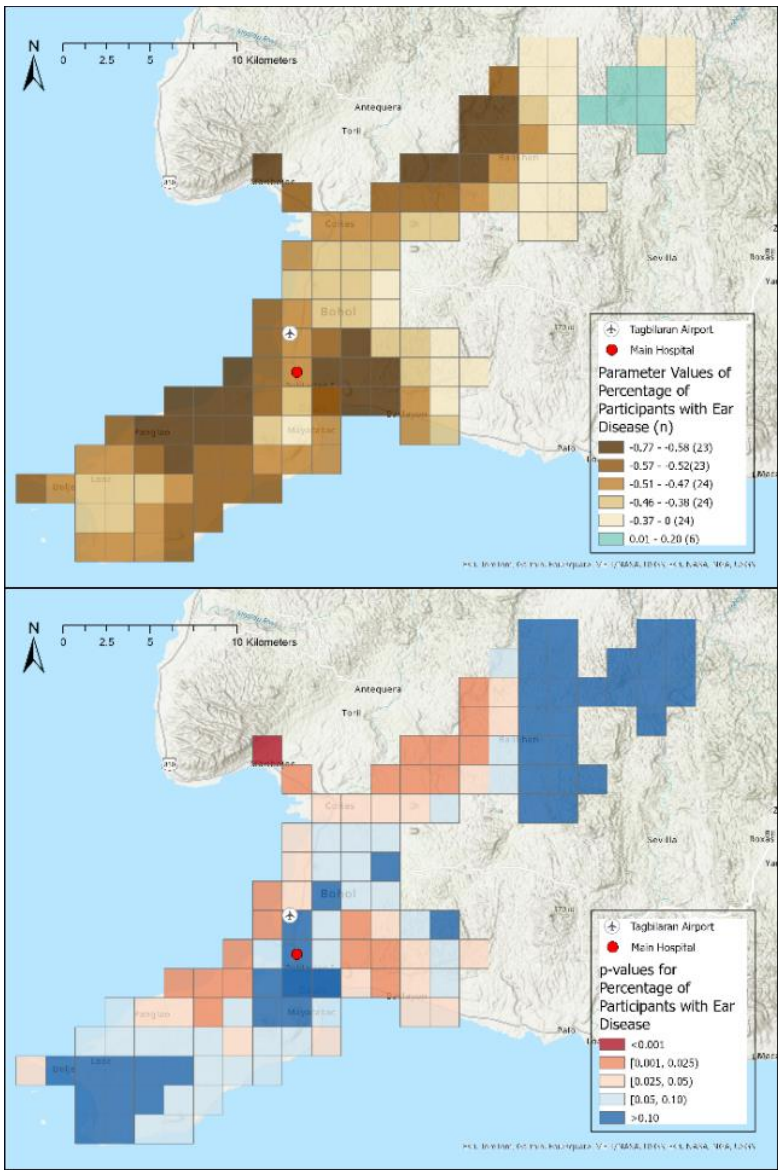


Figure 40. Parameter values and p-values from geographically weighted regression (GWR) for each key characteristic.

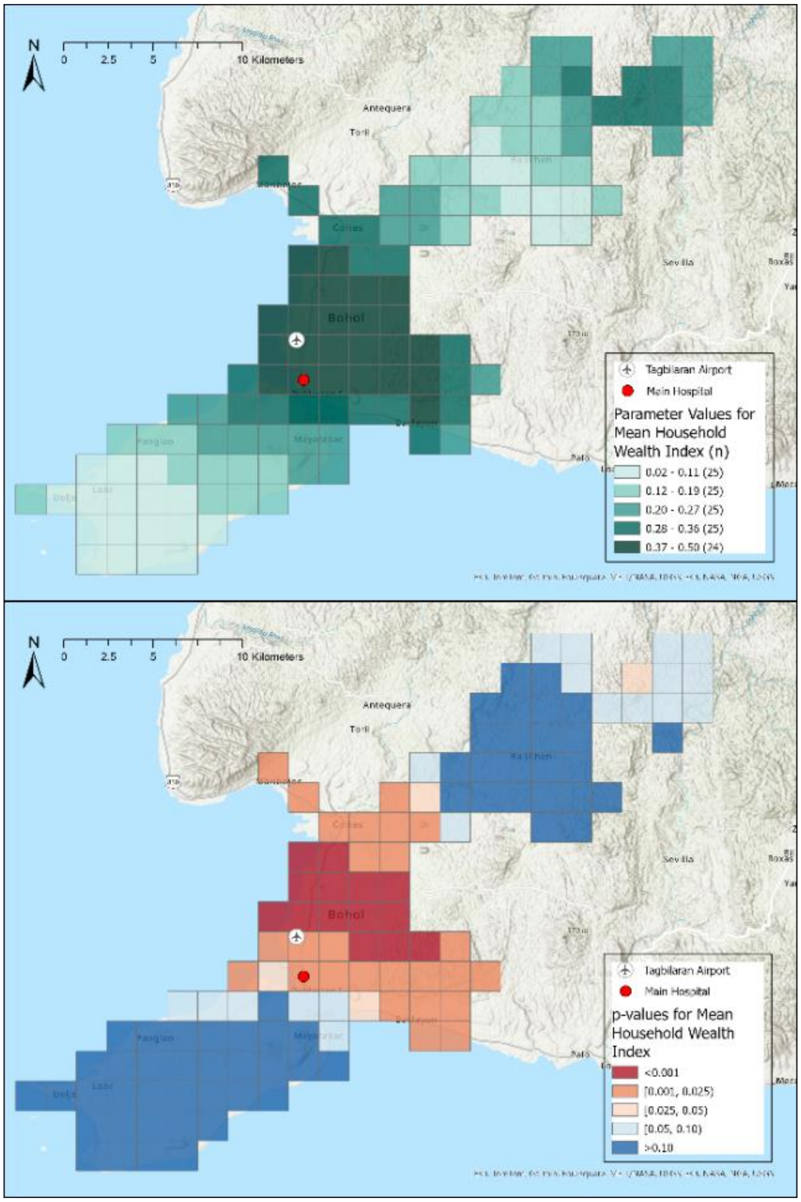
(a) Percentage of participants with ear disease, (b) Mean household wealth index, (c) Percentage of participants with household member(s) regularly smoke, (d) Percentage of female participants, (e) Percentage of participants who were exclusively breastfed in the first 6 months of life, (f) Percentage of participants whose parents' highest education level was high school or vocational school or above, (g) Percentage of participants whose parents' highest employment level was agricultural/crafts/skilled manual labor/plant or machine operator or above.



(a)

Continued

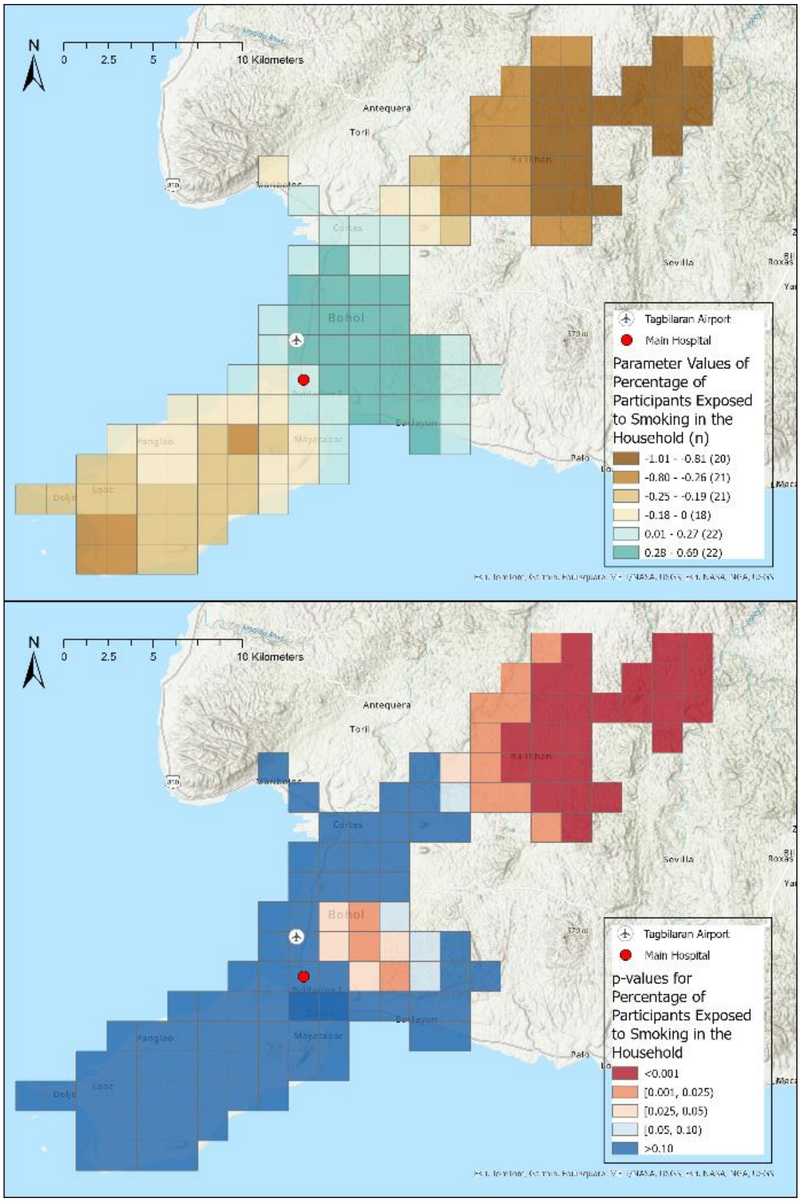
Figure 40. Continued



(b)

Continued

Figure 40. Continued



(c)

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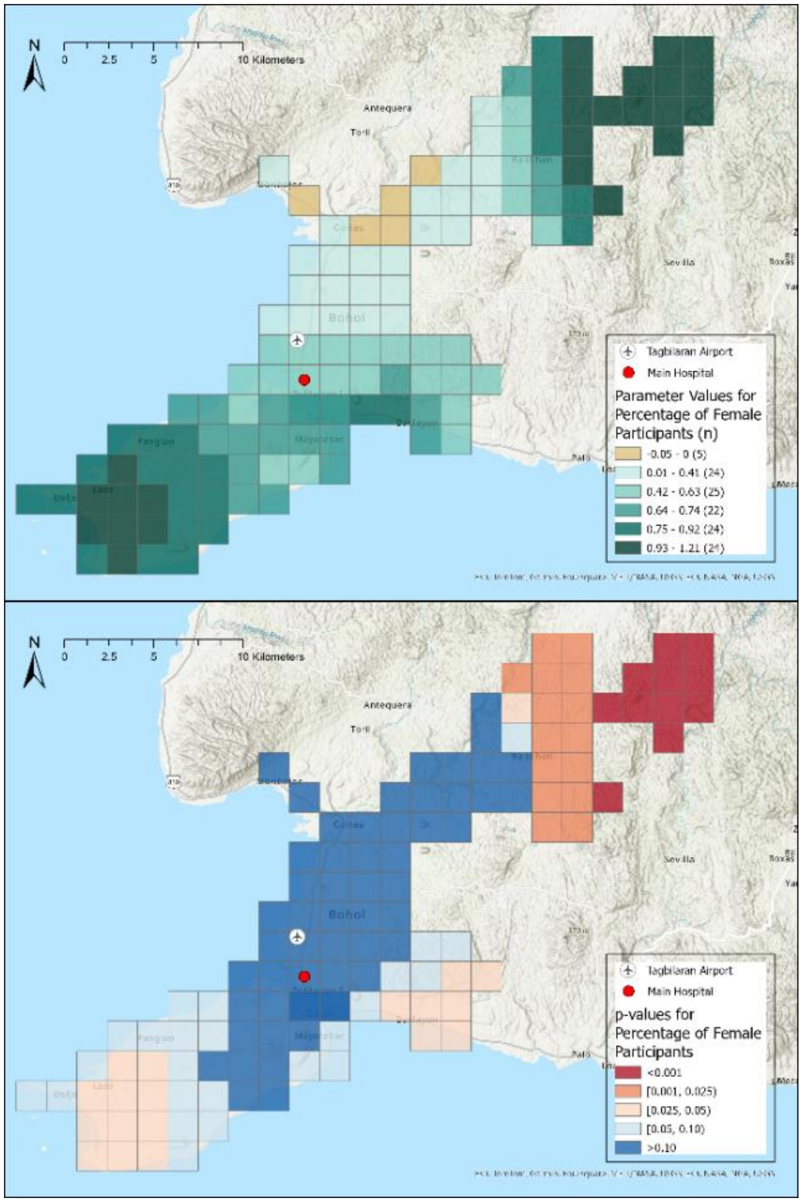
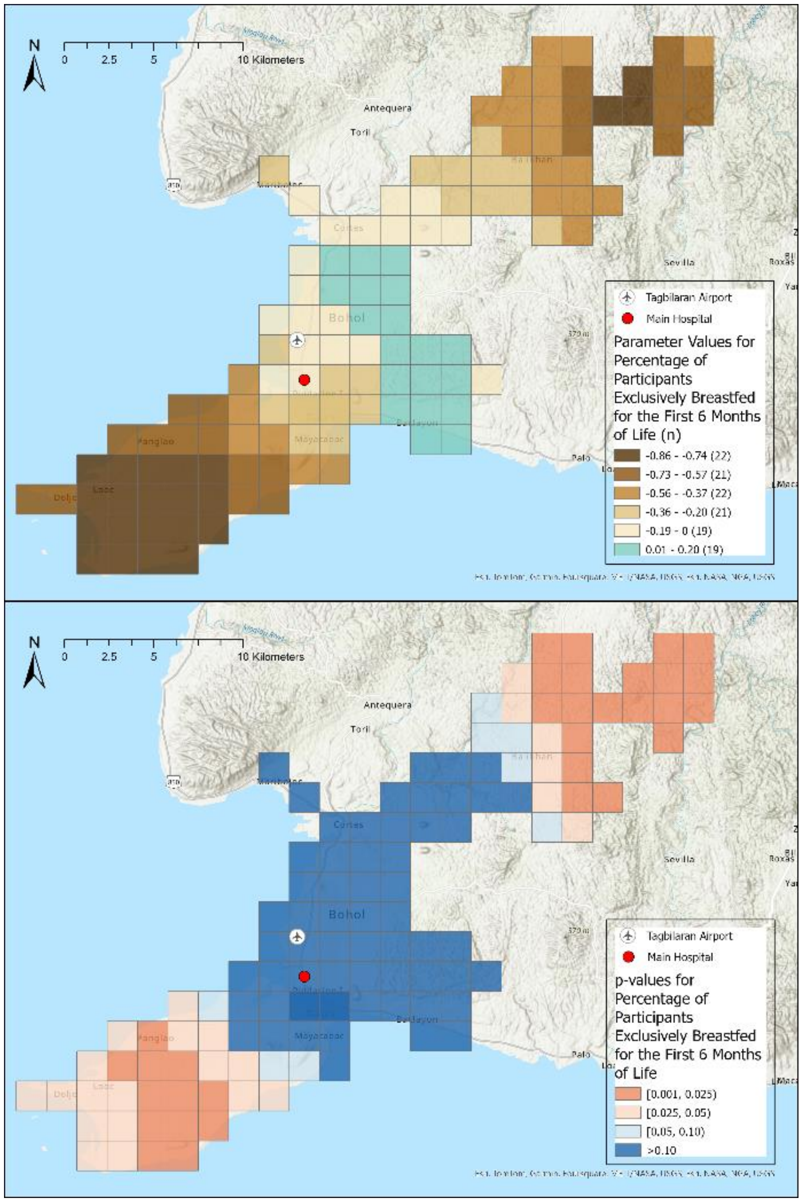
Figure 40. Continued



(d)

Continued

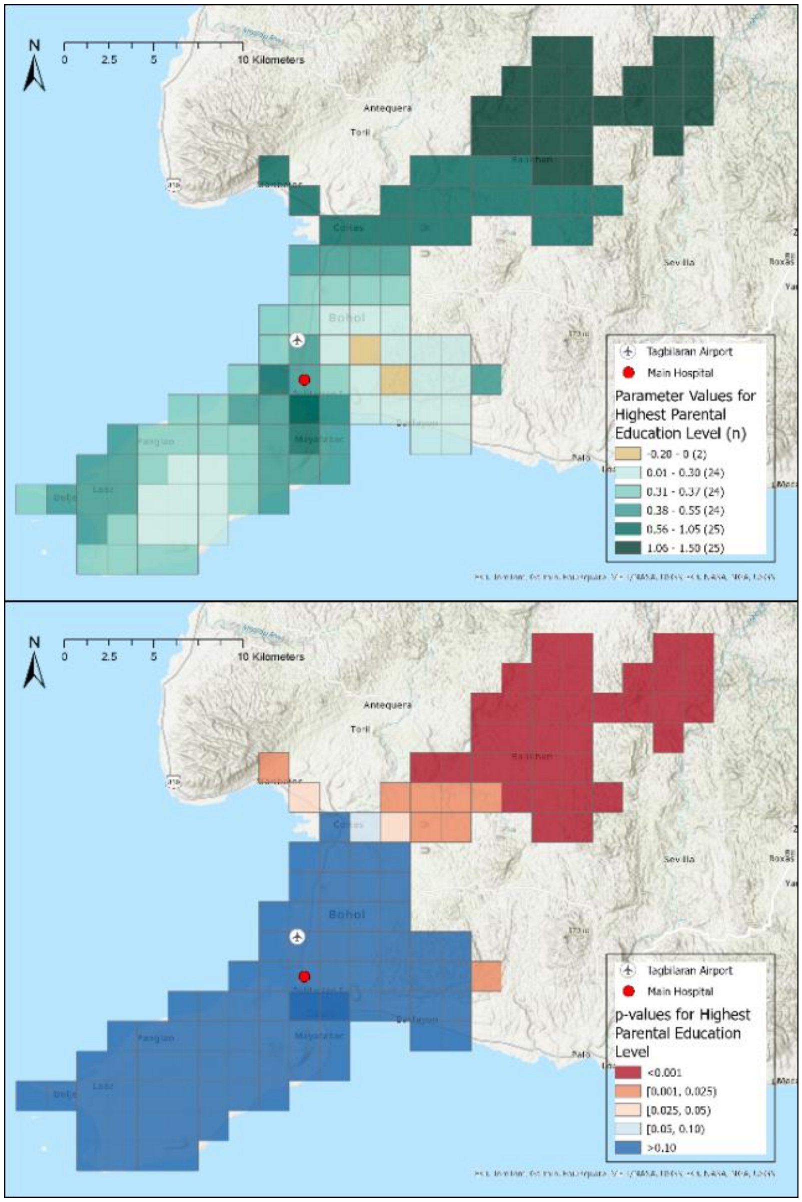
Figure 40. Continued



(e)

Continued

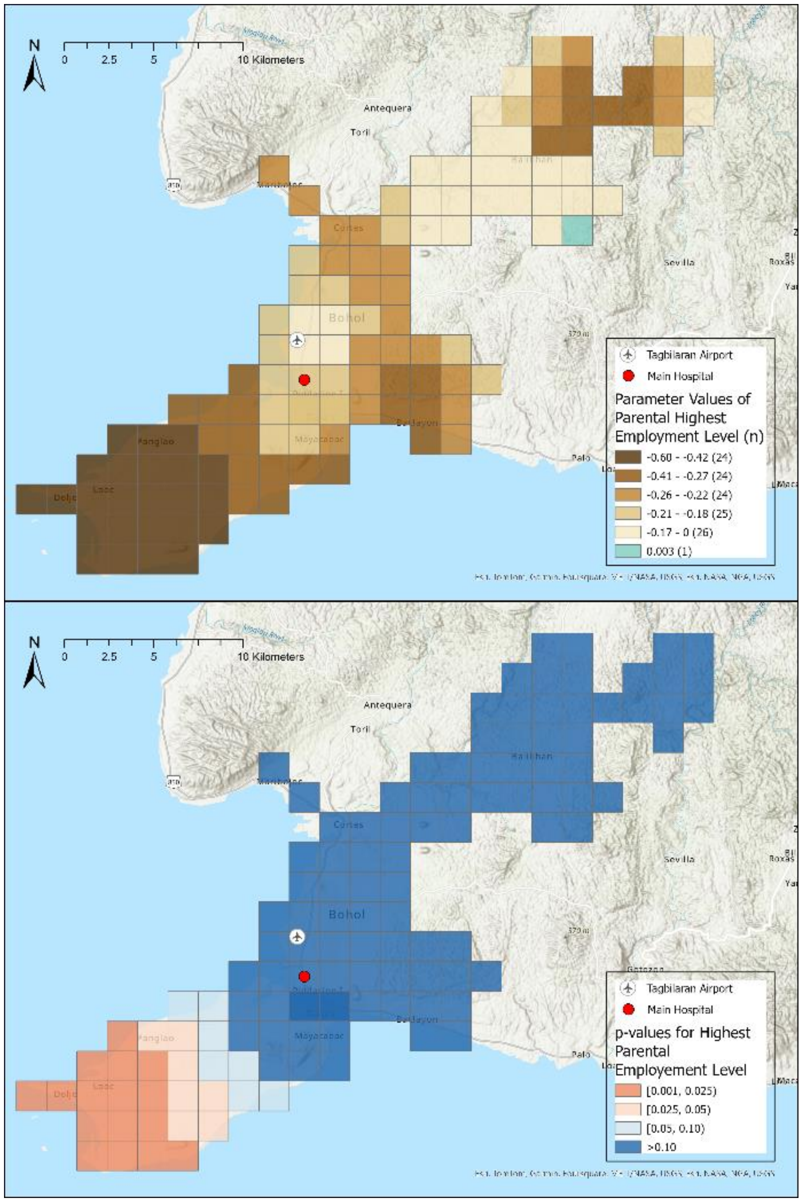
Figure 40. Continued



(f)

Continued

Figure 40. Continued



(g)

Table 14. Metrics used to choose optimal neighborhood size to identify key characteristics associated with cognitive development.

Using the main study hospital as the centroid for the initial grid cell, grids of varying sizes were created overlaying the study area. For grid sizes from 800 to 2,500 meters per side, the table presents the number of neighborhoods (NB) in the final sample, the number of participants included, the mean z-score of full-scale Intelligence Quotient (FSIQ) with its variance, the total number of neighborhoods created, and the reasons for excluding certain neighborhoods. This data was used to guide the selection of the optimal neighborhood size.

						Removed due to	
Grid size (m)	**Number of NB[1]**	**Number of Participants**	**Mean z-score of FSIQ[2]**	**Variance**	**Original sample size (NB)**	**Small sample size**	**Not connected to main mass**
800	325	7365	0.371	0.1375	524	182	17
900	282	7422	0.351	0.1233	439	139	18
1000	243	7448	0.335	0.1121	385	124	18
1100	213	7467	0.327	0.1071	342	117	12
1200	193	7488	0.318	0.1014	305	97	15
1300	172	7504	0.334	0.1113	273	91	10
1400	153	7505	0.314	0.0987	252	90	9
1500	138	7521	0.291	0.0845	222	76	8
1600	134	7674	0.286	0.0816	211	76	1
1700	**124**	**7680**	**0.303**	**0.0915**	**196**	**71**	**1**
1800	104	7522	0.265	0.0703	180	68	8
1900	105	7683	0.301	0.0905	173	67	1
2000	93	7548	0.285	0.0810	157	58	6
2100	92	7692	0.308	0.0951	155	62	1
2200	83	7692	0.272	0.0739	146	60	3
2300	82	7695	0.306	0.0938	144	62	0
2400	76	7694	0.249	0.0620	137	60	1
2500	73	7702	0.258	0.0664	127	54	0

[1] NB: neighborhoods
[2] FSIQ: full-scale Intelligence Quotient

Table 15. Descriptive statistics of parent trial participants in Bohol, Philippines (ISRCTN: 62323832): Comparison between follow-up assessment completers with cognitive test results (n=7,791) and those reside in final neighborhoods of 1,700-meter grid size (n=7,680).

	Participants completed the follow-up study with cognitive test results N=7,791			Participants covered by the final neighborhoods (Grid size: 1,700m) N=7,680				
Characteristics	**N**	**n**	**%**	**N**	**n**	**%**	**χ2**	**p[1]**
Child has hearing loss	7,791			7,680			<0.01	1
Yes		608	7.8		600	7.8		
No		7,183	92.2		7,080	92.2		
Child has ear disease	7,791			7,680			0.02	0.89
Yes		3,419	43.9		3,380	44.0		
No		4,372	56.1		4,300	56.0		
Vaccinated in the parent trial	7,791			7, 680			<0.01	0.96
Yes		3,912	50.2		3,852	50.2		
No		3,879	49.8		3,828	49.8		
Child sex	7,791			7, 680			<0.01	0.93
Male		3,926	50.4		3,864	50.3		
Female		3,865	49.6		3,816	49.7		
Firstborn in the family	7,789			7,678			0.04	0.85
Yes		2,124	27.3		2,082	27.1		
No		5,665	72.7		5,596	72.9		
Low birth weight (<2,500 grams)	8,040			7,893			<0.01	0.92
Yes		1,513	19.5		1,497	19.0		
No		6,258	80.5		6,163	78.1		
Breastfed exclusively in the first 6 months of life	7,775			7,664			<0.01	0.95
Yes		4,828	62.1		4,754	62.0		
No		2,947	37.9		2,910	38.0		
Preschool attendance	7,782			7,672			<0.01	0.96
Yes		3,102	39.9		3,054	39.8		
No		4,680	60.1		4,618	60.2		
Child ever diagnosed with malnutrition	7,776			7,674			<0.01	0.96
Yes		456	5.9		452	5.9		
No		7,320	94.1		7,213	94.0		
Member(s) in the household regularly smoke	7,785			7,674			<0.01	0.93
Yes		2,882	37.0		2,847	37.1		
No		4,903	63.0		4,827	62.9		

Continued

Table 15. Continued

	Participants completed the follow-up study with cognitive test results N=7,791			Participants covered by the final neighborhoods (Grid size: 1,700m) N=7,680				
Characteristics	**N**	**n**	**%**	**N**	**n**	**%**	**χ2**	**p**[1]
Parental education (highest)	7,779			7,668			0.04	1
College or post grad		2,490	32.0		2,443	31.9		
Some college		1,282	16.5		1,265	16.5		
HS or Vocational school grad		3,047	39.2		3,010	39.3		
Elementary school or less		960	12.3		950	12.4		
Parental employment (highest)	7,161			7,060			0.03	1
Manager/Professional/Technical		1,224	17.1		1,200	17.0		
Clerical/Service/Armed Forces		3,299	46.1		3,254	46.1		
Agriculture/Crafts/Skilled labor/Plant or machine operator or assembler		1,472	20.6		1,453	20.6		
Unskilled labor/Farmer		1,166	16.3		1,153	16.3		
Characteristics	**N**	**Mean**	**SD**[2]	**N**	**Mean**	**SD**[2]	**t**	**p**
Maternal age of the child's mother	7,644	29.24	6.40	7,537	29.24	6.40	0.01	0.99
Euclidean distance from Tagbilaran Airport (km)	7,791	7.12	6.21	7,680	6.88	5.59	-2.50	0.01
Household Wealth Index	7,791	0.02	0.96	7,680	0.02	0.96	0.07	0.95

Table 16. Neighborhood level descriptive statistics among a cohort of children participated in the follow-up study of a randomized controlled trial (RCT) on pneumococcal conjugate vaccine (PCV) in Bohol, Philippines (124 neighborhoods with sides of 1,700m).

Characteristics	**Mean (SD[2])**	**Median (IQR[3])**
Mean z-score of FSIQ[1]	-0.10 (0.30)	-0.08 (0.37)
Mean maternal age of the participant's mother	29.27 (1.76)	29.11 (1.69)
Mean household wealth index	-0.20 (0.36)	-0.20 (0.50)
Mean Euclidean distance from Tagbilaran Airport (km)	11.11 (6.54)	9.80 (9.70)
	Mean %	**95% CI[4]**
Percent of participants with hearing loss	8.57	7.44, 9.70
Percent of participants with ear disease	39.87	37.28, 42.46
Percent of participants vaccinated in the parent trial	50.46	48.83, 52.09
Percent of participants with birth weight less than 2500 grams	22.74	20.34, 25.14
Percent of participants with members in the house regularly smoke	40.07	37.61, 42.53
Percent of female participants	49.33	47.50, 51.16
Percentage of participants attended preschool	33.56	30.20, 36.92
Percentage of participants that were firstborn in the family	27.48	25.86, 29.10
Percentage of participants exclusively breastfed for the first 6 months of life	69.92	67.21, 72.63
Percent of participants whose parents' highest education level was		
High school or vocational school grad or above	82.01	79.75, 84.27
Some college or above	37.47	34.26, 40.68
College or post grad	23.09	20.38, 25.80
Percent of participants whose parents' highest employment level was		
Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler or *above*	79.88	77.23, 82.53
Clerical/Service/Armed Forces or *above*	57.01	53.97, 60.05
Manager/Professional/Technical	12.41	10.55, 14.27
Percent of participants ever diagnosed with malnutrition	5.57	4.61, 6.53

[1] FSIQ: full-scale Intelligence Quotient
[2] SD: standard deviation
[3] IQR: Inter-quartile range
[4] CI: confidence interval

Table 17. Global Moran's I statistics for neighborhood level characteristics.

	Global Moran's I Index	Variance	z-score	p-value
Mean z-score of FSIQ[1]	0.1683	0.0027	3.3674	<0.001
Vaccine coverage	-0.0364	0.0028	-0.5363	0.70

[1] FSIQ: full-scale Intelligence Quotient

Table 18. Bivariate analysis of characteristics potentially associated with cognitive development at neighborhood level in Bohol, Philippines, using linear regression models (n=124 neighborhoods).

	Bivariate Analysis		
Characteristics	**Estimate**	**Standard error**	**p value**
Percentage of participants vaccinated in the parent trial	0.557	0.291	0.06*
Percentage of participants had ear disease	-0.313	0.184	0.09*
Percentage of participants with hearing loss	-0.594	0.422	0.162*
Mean Euclidean distance from Tagbilaran Airport (km)	-0.014	0.004	<0.001*
Percentage of participants with birth weight less than 2500 grams	-0.412	0.198	0.04*
Mean household wealth index	0.378	0.067	<0.001*
Mean maternal age of the participant's mother	0.006	0.016	0.70
Percentage of participants with members in the house regularly smoke	-0.634	0.188	<0.001*
Percentage of female participants	0.503	0.260	0.06*
Percentage of participants attended preschool	0.269	0.141	0.06*
Percentage of participants that were firstborn in the family	0.544	0.293	0.07*
Percentage of participants exclusively breastfed for the first 6 months of life	-0.646	0.168	<0.001*
Percentage of participants whose parents' highest education level was			
high school or vocational school grad or above	1.240	0.181	<0.001*
some college or above	0.677	0.137	<0.001*
college or post grad	0.761	0.164	<0.001*
Percentage of participants whose parents' highest employment level was			
Agricultural/Crafts/Skilled manual labor/Plant or machine operator or assembler or *Clerical/Service/Armed Forces* or *Manager/Professional/Technical*	0.298	0.180	0.10*
Clerical/Service/Armed Forces or *Manager/Professional/Technical*	0.522	0.151	<0.001*
Manager/Professional/Technical	0.625	0.253	0.02*
Percentage of participants ever diagnosed with malnutrition	-0.228	0.504	0.65

* Significant at 0.20 level. Included in the multivariable analysis.

Table 19. Results from the ordinary least squares (OLS) regression model and geographically weighted regression (GWR) model.

	OLS		GWR			
Characteristics	$\boldsymbol{\beta}$	**Std. Err.**	**Min**	**Median**	**Max**	**MC Sig. Test**[1]
Percentage of female participants	0.471*	0.21	-0.050	0.673	1.210	0.531
Percentage of participants with ear disease	-0.577***	0.16	-0.768	-0.485	0.193	0.681
Mean household wealth index	0.206*	0.09	0.030	0.232	0.494	0.582
Percentage of participants with household member(s) regularly smoke	-0.222	0.16	-1.005	-0.187	0.686	0.055
Percentage of participants exclusively breastfed for the first 6 months of life	-0.333	0.18	-0.585	-0.402	0.191	0.247
Percentage of participants whose highest parental education level was high school or above	0.774***	0.23	-0.196	0.439	1.499	0.512
Percentage of participants whose parents' highest employment level was agricultural/crafts/skilled manual labor/plant or machine operator or above	-0.226	0.16	-0.597	-0.237	0.003	0.523
Intercept	-0.192	0.28	-0.588	-0.168	0.563	0.669
Diagnostics						
Adjusted R^2		0.39				0.69
AICc		3.67				0.26

* p<0.05 ** p<0.01 *** p<0.001

[1] Monte-Carlo significance test

Chapter 7. Conclusions

Otitis media (OM) and its sequelae, including hearing loss and cognitive development delays, impose substantial burdens on children worldwide, particularly in low- and middle-income countries (LMICs) (1-3). Despite the availability of preventive measures such as pneumococcal conjugate vaccines (PCVs), there remains a critical gap in understanding the spatial dynamics and environmental determinants associated with these conditions, especially in LMIC settings like Bohol, Philippines. This dissertation aimed to address these gaps by investigating the spatial variations of OM, hearing loss, and cognitive development among children in Bohol, while also examining the potential secondary impact of PCV coverage on these outcomes.

The study found significant spatial autocorrelation in OM prevalence across the study area, with local clusters of high OM prevalence in the island of Dauis and Panglao and clusters of low prevalence in the northern part of the study area. OM prevalence was found to be associated with a complex interplay of demographic, environmental, and socioeconomic factors. Previous studies have stated that OM occurs less frequently among females, and the current analysis expanded the understanding to neighborhood level (116-121). While OM is not contagious itself, reduced exposure to respiratory pathogens, through factors like being firstborn and smaller family size, is associated with lower OM prevalence (3, 30, 124). Key findings also highlighted the protective role of exclusive breastfeeding and maternal health insurance coverage associated with areal OM prevalence. The associations between these factors and OM have been established within individual-level studies and the current analysis provides an additional neighborhood-level perspective (2, 3, 17, 30, 68, 126). In the current analysis, higher maternal health insurance coverage, primarily through PhilHealth, was associated with lower OM prevalence at the neighborhood level, likely due to improved access to healthcare and preventive care. However, proximity to healthcare facilities, measured by the Euclidean distance to the closest hospital, did not show a significant association with neighborhood-level OM prevalence. A hotspot analysis revealed that areas with longer distances to hospitals coincided with higher OM prevalence, suggesting some impact of healthcare accessibility on health outcomes. The findings underscore the importance of expanding insurance coverage, especially in areas with lower rates, such as Tagbilaran city center, Panglao, and Dauis. Surprisingly, this analysis identified an unexpected inverse association between traffic-related air pollution, as proxied by road length, and neighborhood-level OM prevalence. This finding raises important questions about the validity of the proxy. In urban settings, previous studies used direct measurements of certain pollutants (e.g., fine particulate matter, sulfur dioxide, nitrogen dioxide) or data from local agencies to quantify air pollution (25, 113). We relied on the proxy of total length of national and provincial roads within the neighborhood due to the unavailability of direct pollutant data. It doesn’t directly quantify air pollution, and its lack of specificity may lead to measurement error or misclassification. For example, in our study area, by 2019, less than half of the provincial roads were paved, and fine particles on these roads are one of the major exposure we measured, potentially underestimating exposure on unpaved local roads (135). The inverse association observed might be due to this underestimation or could reflect that road length measures access to healthcare rather than pollution exposure. Notably, the neighborhoods showing this association were located northeast of a forest/watershed area, where no hospitals were present. This highlights the need for future research to incorporate direct measurements of air pollution to help clarify whether the observed association is a true reflection of traffic-related air pollution's impact or a consequence of the limitations of this proxy measure. PCV vaccination does not seem to be associated with OM prevalence on neighborhood level.

Similarly, disparities in pediatric hearing loss on neighborhood level were linked to local OM prevalence, geographical proximity to healthcare facilities and socioeconomic status. Our analysis revealed a significant link between higher neighborhood OM prevalence and increased rates of pediatric hearing loss, particularly in the inland region northeast of Tagbilaran City. This association was the strongest in areas farther from hospitals, highlighting the role of limited healthcare access. Interestingly, central Tagbilaran City, with better healthcare access, showed weaker or even inverse associations. The overall results emphasize the need for improved healthcare access and effective management of acute otitis media (AOM) to prevent progression to chronic suppurative otitis media (CSOM) and subsequent hearing loss. Addressing these factors is crucial for reducing the burden of hearing loss in affected communities. Our study also found that children from economically disadvantaged neighborhoods experienced higher rates of hearing impairment. This result aligns with previous individual level studies linking lower socioeconomic status to higher hearing loss rates due to factors like low birth weight, limited healthcare access, and undernutrition (31, 153, 154). Families with one or more hearing-impaired members are also more likely to experience reduced family income due to employment restrictions (29). This association is consistent across most of the study area. The strong and widespread link features the critical need for targeted public health interventions in economically disadvantaged neighborhoods.

In terms of cognitive development, this study revealed that neighborhoods with higher OM prevalence had notably lower cognitive development scores. OM, which includes a spectrum of disease from AOM to CSOM, can lead to hearing impairment, affecting language acquisition and cognitive abilities during critical developmental periods (2, 10, 30, 55). Previous research has shown that children with a history of OM are at risk of behavioral issues, lower Intelligence Quotient (IQ), and deficits in reading ability, with these effects persisting into later childhood, especially in children from less cognitively stimulating environments (20). Our study confirms these associations at the neighborhood level, reinforcing the importance of early detection and treatment of OM to support optimal cognitive development in children. The study also revealed that neighborhood-level socioeconomic factors, particularly household wealth and parental education levels, were associated with cognitive outcomes among children in Bohol. Higher household wealth and parental education correlated with better cognitive test scores, emphasizing the role of socioeconomic disparities in shaping developmental trajectories. These findings are consistent with global research on individual level and provided an additional neighborhood level confirmation (165, 169, 177). Spatial analyses further identified localized variations in cognitive development outcomes, highlighting disparities between areas with higher mean household wealth and those with lower household wealth. Meanwhile, household wealth was more influential in Tagbilaran city and parental education was more significant in northeastern areas. These findings underscore the importance of tailored interventions to support cognitive development in disadvantaged communities, focusing on addressing socioeconomic inequities across different area.

The findings from this dissertation carry significant implications for public health practice and policy, particularly within LMIC contexts. This study explored the spatial variations of OM, hearing loss, and cognitive development and key characteristics associated with them in a LMIC setting. This is significant because these countries face an excessively high burden of OM and pediatric hearing loss, with children having limited access to specialized support needed for equal progress in cognitive development (3, 5, 55, 179). This analysis used a square grid methodology to define neighborhoods for analysis, ensuring standardized and geometrically uniform spatial units across the study area, which allowed for consistent and comparable neighborhood definitions in the analysis. This dissertation also demonstrates the utility of spatial methods in public health research to identify target areas for interventions. For LMICs where public health resource is limited, pinpointing target area can increase the cost-effectiveness of interventions.

Based on the revealed associations, this analysis had a couple of suggested interventions. Areas with higher OM prevalence could benefit from expanded PhilHealth coverage and breastfeeding promotion programs. Tagbilaran city, Dauis, and Panglao could benefit significantly from initiatives to expand PhilHealth coverage, given the lower coverage in these areas compared to the rest of the study area and the significant association between maternal insurance coverage and OM prevalence there. Addressing healthcare access disparities is crucial for reducing pediatric hearing loss and improving children's cognitive development, requiring the expansion of healthcare infrastructure in underserved areas and community-based initiatives for early OM detection and management. Promoting socioeconomic equity through policies that enhance household wealth and parental education can positively impact child cognitive development. Investments in education, social welfare programs, and community support systems are essential for narrowing socioeconomic disparities and ensuring equitable access to developmental resources. These integrated approaches are pivotal for fostering holistic child health and well-being in LMIC settings.

The data used in the current study comes from a large sample with comprehensive residential location data recorded for most participants, enhancing the robustness of the analysis. Additionally, the study benefits from data derived from physical exams conducted by medical professionals, providing an accurate assessment of OM prevalence and associated hearing loss. However, several limitations should be noted. The cross-sectional design inherently limits our ability to infer causality. The reliance on secondary data sources, particularly survey data, introduces potential self-report biases and inaccuracies. To mitigate these issues, I cross-referenced findings with insights from researchers familiar with the study area and supplementary data from local government sources. Additionally, the exclusion of some participants due to incomplete data may introduce potential selection bias. Finally, while the findings are significant, caution is needed when extrapolating results, as there is a risk of ecological fallacy.

For future research, longitudinal studies are needed to establish temporal relationships between neighborhood characteristics and each outcome to support causal inference. Studies using direct measurements of air pollution can be used to validate the proxy used in this analysis. The study can be replicated in other LMIC regions to test the generalizability of findings. And researchers can develop and test public health interventions targeting economically disadvantaged neighborhoods and improving healthcare access, including accessibility of healthcare facilities and health insurance coverage.

In conclusion, this dissertation contributes to our understanding of the complex interplay between environmental, socioeconomic, and health factors associated with OM and its sequelae in LMICs. By elucidating spatial patterns and identifying key characteristics associated with OM, hearing loss, and cognitive development, this research informs evidence-based interventions and policy decisions aimed at improving child health outcomes and promoting health equity globally. Continued interdisciplinary research and collaboration are essential for effectively addressing these challenges and fostering healthy childhood development worldwide.

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