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Geographic Clustering of Maternal Characteristics, Birth Outcomes, Healthy Infant Growth, and Development Outcomes in Rural Malawi

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Contents

Abbreviations and Acronyms

ANOVA	analysis of variance
AOI	area of interest
CSR	complete spatial randomness
GA	gestational age
GPS	global positioning system
HCZ	head circumference-for-age z-score
LAIS	Lungwena Antenatal Intervention Study
LAZ	length-for-age z-score
MUAC	mid-upper arm circumference
SD	standard deviation
SES	socioeconomic status
UTM	Universal Transverse Mercator
VPS	visual processing speed
WAZ	weight-for-age z-score
WLZ	weight-for-length z-score
WHO	World Health Organization

Executive Summary

Background. Various nutrition and behavioral interventions to promote healthy child growth have been designed and implemented in different locations, with mixed results. Some of this heterogeneity could be explained by differences in study design or data collection. Alternatively, it may be caused by "true" heterogeneity due to differences in the spatial distribution of risk factors and related outcomes.

Objective. The objective of this research was to analyze the geographical distribution of various variables describing fetal and child growth and cognitive development and selected maternal background characteristics in a seemingly homogeneous population in rural Malawi.

Design. This research involved a secondary analysis of data collected in Malawi for a recent study into the possible links between known risk factors for adverse child development in a low-resource setting and measurable variations in eye-tracking measures of visual and cognitive function at 7 and 9 months of age. We segmented the original study area into five residential areas and tested for the association of these areas with selected outcomes. In addition, we conducted spatial clustering analyses using the Getis-Ord Gi* statistic in ArcGis software and tested whether areas of "good" and "bad" outcomes could be identified.

Results. In general, our results showed that maternal background characteristics and child health outcomes clustered geographically, both by residential area and household cluster. The clustering by residential area was most consistent for maternal background characteristics and somewhat consistent for child growth at 9 months and eye-tracking outcomes.

Overall, six of the 21 considered outcomes showed a statistically significant difference between the residential areas; for five of these outcomes, the northern part of the study area scored "worse" and the southern part of the study area scored "best." The results were somewhat less clear for the infant cognition outcomes, although the southern part of the study area scored "best" on five of the nine eye-tracking variables.

Conclusions. At least some of the heterogeneity found in results from various nutrition and behavioral interventions aiming to promote healthy growth implemented in different locations could be due to "true" spatial variance in background risk factors and related outcomes. The spatial variance for outcomes within one trial dataset are likely not due to differences in study design or data collection, but reflect "true" spatial differentiation in the selected child health and maternal outcomes.

1 Introduction

Healthy growth and development of infants and young children are key to enabling individuals to reach their full physical and mental potential. The consequences of poor growth are severe and far reaching in terms of mortality, morbidity, and impaired cognitive development, with their impact extending into adulthood. With the global prevalence of stunting decreasing very slowly and at least 165 million children younger than 5 years old who are currently stunted (Black et al. 2013; de Onis 2017; WHO 2017b), supporting healthy growth and development—especially during the critical 1,000 days between pregnancy and a child's second birthday—is high on the global agenda (WHO 2017a). Several international documents, like the World Health Assembly global targets for 2025, include growth-related goals for stunting and wasting among children under 5 years (Prendercast 2014; de Onis 2017).

The etiology of stunting is not very well known, but it is plausible that the biological, environmental, and socioeconomic mechanisms that cause stunting vary by child's age. Suggested risk factors include poor maternal nutritional status during pregnancy, poor complementary feeding practices at infancy, and infections in later childhood (Prendergast 2014). To promote healthy growth and development, various nutrition and behavioral interventions have been designed and implemented in different locations around the world, some with positive growth results and some showing no impact on growth. The heterogeneity of the results could be explained partly by differences in study design or data collection. In addition, they may be "true" heterogeneity in apparently homogenous populations, suggesting spatial differences in the distribution of risk factors and related outcomes.

With recent advances in spatial analysis techniques, there has been a trend in research to assess the contribution of geographic factors to a number of health-related outcomes (Yao 2014; MacQuillan 2017). This study is a secondary analysis of a study we recently conducted in Malawi, a country with especially high stunting prevalence of approximately 50% among children under 5 (National Statistical Office 2015). Our aim was to analyze the geographical distribution of various indicators of child growth and cognitive development, as well as some selected maternal factors, among a group of children who had participated in an observational study on early infant development (Pyykkö et al. 2017). The study was conducted jointly by the University of Malawi and the University of Tampere. Participants were enrolled from a seemingly homogenous population residing in predominantly rural area. We also recorded the coordinates of the participants' homes. Using this dataset, we tested a hypothesis that the study area would include areas where several "good" and "bad" child growth, eye-tracking, and maternal factors cluster together.

2 Methods

2.1 Study Objectives and Hypotheses Tested

The main aim of this study was to investigate whether the trial participants' residential location was associated with selected maternal characteristics and newborn, child growth, and eye-tracking outcomes.

To test this idea, we formulated the following study objective:

> **Objective**—To determine whether the location of a participant's home is associated with maternal background characteristics and well-being outcomes, birth outcomes, child growth at 9 months, and child eye-tracking outcomes in the MiTrack trial[1].

The objective was investigated in two ways: First, by checking whether an a priori designed residential area yields differences in trial outcomes, and secondly by investigating statistically significant household-level clustering of outcome values within the trial area.

The objective led us to formulate the following hypotheses:

> **Hypothesis 1**—A predetermined areal segmentation of the study area shows statistically significant differences for selected maternal background characteristics and well-being outcomes, birth outcomes, and outcomes related to child growth at 9 months and child eye-tracking.

> **Hypothesis 2**—Selected newborn, child growth, background, and eye-tracking variables in the study area show household-level clusters of selected maternal background characteristics and well-being outcomes, birth outcomes, and outcomes related to child growth at 9 months and child eye-tracking.

2.2 Study Design and Participants

In the first phase of the study, we established the technical feasibility of implementing eye-tracking tests in a low-resource setting in rural Malawi (Forssman et al. 2015). The main study assessed the validity of eye-tracking tests of cognitive and social development among young infants in rural Africa, showing that there was little difference between preterm and full-term infants in eye-tracking assessment of cognitive function at 9 months of age and that infant nutritional status and rearing environment were not consistently associated with eye-tracking outcomes (Pyykkö et al. 2017).

The analyses in this report are secondary analyses of data collected for the MiTrack trial, a prospective cohort study conducted in rural Malawi. The target population included newborn infants without a congenital malformation, severe illness, or known visual impairment who lived in the Lungwena and Malindi areas in Malawi's Mangochi District. For the study sample, we enrolled healthy babies under 4 weeks of age who were born 32.0–41.9 gestation weeks and whose parents gave consent for the child's participation. The study included five visits: three at the clinic (the enrollment after birth and visits at 7 and 9 months) and two home visits. The enrollment was done either at the Lungwena Health Center or the St. Martin's Hospital in Malindi. Post-enrollment clinic visits were conducted at the Lungwena Health Center.

Before enrollment, a study nurse performed an obstetric ultrasound assessment of all women who started antenatal care at either of the two health facilities. The nurse measured fetal biparietal diameter, femur

[1] The MiTrack trial assessed the validity of eye-tracking tests of cognitive and social development among young infants in rural Africa. For more information, see https://www.fantaproject.org/research/eye-tracking-method-assess-infant-cognition.

length, and abdominal circumference and determined the duration of pregnancy based on these measurements and Hadlock tables. The results and the estimated date of delivery were recorded in a log book and the woman's health passport so that the information could later be retrieved to calculate gestational age (GA) at birth for those individuals who were later enrolled in the study.

The recruitment was stratified based on infants' GA. The target was to enroll 425 infants who were born 32.0–36.9 completed gestation weeks (preterm), 37.0–38.9 gestation weeks (early term), and 39.0–41.9 gestation weeks (full term) at a ratio of 1:2:2. These categories were selected based on a recent redefinition of a term pregnancy that reflects new information about different outcome expectations for the offspring after early-term and full-term births (American College of Obstetricians and Gynecologists Committee on Obstetric Practice, Society for Maternal-Fetal Medicine 2013). To achieve the desired number of participants in each stratum, we offered enrollment to every mother whose child was born preterm but to only some of the mothers whose infant was born early or full term. In practice, after the enrollment of a new preterm participant, we recruited the next two eligible infants from the same recruitment site to the 37.0–38.9 gestation weeks stratum and another two infants to the 39.0–41.9 stratum. The ratio of enrollment was changed to 1:5:5 after we had enrolled 251 participants. The change was due to a slower-than-expected recruitment pace for preterm infants.

The target sample size provided the study with 80% power and 95% confidence to document a statistically significant difference in the eye-tracking scores between the preterm and the full-term infants, for an effect size in the target population of 0.45 standard deviation (SD) or larger. For the comparison between early-term and full-term infants, the study had 80% power (and 95% confidence) to detect an effect size of 0.35 or larger. For the description of single proportions, the sample size provided a precision of approximately ±3 percentage points.

We conducted the study in accordance with the ethical standards of the Helsinki declaration. The study protocol was approved by the College of Medicine Research and Ethics Committee, Malawi; the Ethical Committee of Pirkanmaa Hospital District, Finland; and the Ethics Committee of the Tampere Region, Finland. Written informed consent was obtained from the participating infants' mothers before the start of the study. Mothers signed (48%) or thumb-printed (52%) the consent form on behalf of themselves and their infants and received both compensation for their travel costs and incentives on every visit (first visit, reusable napkins; second visit, soap; third visit, 1 kg of rice; fourth visit, 1 kg of sugar; and fifth visit, a piece of fabric).

2.3 General Procedure

Data for the study were collected in Malawi between November 2014 and July 2016. The enrollment visit at the clinic was done after the child's birth, before the child was 28 days of age. During enrollment, we took anthropometric measures (weight, length, mid-upper arm circumference [MUAC], and head circumference for the child; weight and height for the mother) and asked questions related to the delivery of the child and the child's living environment. The home location for the mother and child was recorded soon after consent for participation in the study was given.

Participants were visited at their home 15 weeks after the birth to collect information on possible home location changes and to conduct a maternal cognition assessment. Another home visit took place 29 weeks after birth to collect information on possible home location changes and on the social and demographic environment, food security, and maternal social support and to make a home observation.

During the clinic visits at 7 and 9 months (30 and 39 weeks after birth, ±14 days, respectively), we assessed each infant's cognitive functioning (via eye tracking) and social communication skills (via structured observation), took anthropometric measures of the child, and measured the mother's weight.

We also made a medical examination of the child and observed the child's motor milestones. The eye-tracking test battery administered consisted of two separate sessions (approximately 15–20 minutes in total). In between the two eye-tracking sessions, a structured observation was administered to assess social communication skills (approximately 10 minutes). At 7 months, we also interviewed the mother to assess maternal depression and the strength of the mother's bond with her infant. At 9 months, we interviewed the mother again to assess maternal stress and the impact of life events. The eye-tracking outcomes analyzed in this report are from the 9-month visits.

2.4 Eye-Tracking Assessment

During the eye-tracking assessment, the infants were positioned in a baby carrier, sitting on their mother's lap (or directly on the mother's lap if they refused to be placed in the baby carrier) at an approximately 60 cm viewing distance in front of a 22-inch monitor connected to a corneal-reflection eye tracker with a sampling rate of 60 hertz (Tobii X2-60, Tobii Technology, Stockholm, Sweden).

For the eye-tracking assessment, three different tasks were presented in rotation: (1) a visual search task (modeled on Kaldy et al. 2011), (2) a switch-task (modeled on Kovács and Mehler 2009), and (3) an attention disengagement task (modeled on Forssman et al. 2014). As a composite measure of the infants' visual processing speed (VPS), a combined reaction time score was created based on average reaction times from these three eye-tracking tasks.

The visual search task assessed the infant's ability to search for a target (a red apple) presented by itself (referred to as a single-search, one-object condition), among distractors of one kind (e.g., "same shape, but different color," referred to as a single-search, multiple-objects condition), or among distractors of two kinds ("same shape, but different color" and "different shape, but same color," referred to as a conjunction condition) (total number of trials = 24: 8 single-search, one-object conditions; 8 single-search, multiple-objects conditions; and 8 conjunction conditions). For this task, the proportion of successful searches for each condition was calculated.

The switch-task assessed the infant's ability to learn to anticipate the side (left or right) where a target would appear (pre-switch phase) and then be able to inhibit this initial rule in favor of a new rule when the appearance of the target switched sides (post-switch phase). For this task, the target appeared on one side for the first 8 trials and then appeared on the other side for the last 8 trials (two sets; total number of trials = 32: 16 pre-switch and 16 post-switch). The outcome measure for this task was the proportion of correct anticipatory looks on the pre- and post-switch trials.

The attention disengagement task assessed the ability of the infant to disengage from a centrally presented stimulus (e.g., an emotional face, happy or fearful, or a control stimulus [randomized pixels]) to a lateral stimulus (an animated movie) (total number of trials = 32: 8 happy, 8 fearful, and 16 control). The outcome measure for this task was the proportion of missed attention shifts toward the lateral stimulus in each of the three conditions (happy, fearful, control). The difference in the proportion of occurred attention shifts for the control stimulus (a non-face pattern) and facial expressions (happy and fearful) in this task gives an indication of the infant's attentional bias for emotional faces.

Briefly, the eye-tracking data was analyzed in following ways:

- VPS: The mean of the three variables defined below (at least two required[2]), which were also analyzed separately:

[2] In order to have enough data spread, VPS was only calculated if data were available for at least two of these three variables.

  - Visual search—single-search condition without distractors, reaction time: Time point when gaze enters the area of interest (AOI). Mean of reaction times observed between 150 and 1,000 milliseconds (ms).
  - Switch-task—all anticipatory saccades to the correct location, reaction time: Time point the gaze enters the AOI when the child anticipates the correct side of the stimulus. Mean of reaction times observed between 150 and 1,000 ms.
  - Attention disengagement—control stimulus, reaction time: Time point the gaze enters the lateral AOI after leaving the central AOI. Mean of reaction times observed between 150 and 1,000 ms.
- Visual search—proportion of followed searches by condition: Successful search is registered if the gaze hits the AOI within the predefined time limit (150–2,000 ms). Proportions were calculated as the number of successful searches for each condition divided by the total number of valid trials for that condition.
- Switch-task—correct anticipations, by pre- and post-switch: Proportions were calculated as the number of successful anticipations divided by the total number of valid trials for pre-switch and for post-switch, excluding first trials (pre- and post-switch) as they do not represent anticipation.
- Attention disengagement—occurred shifts and dwell times on faces: An occurred shift was defined as a shift of gaze from the central to the lateral stimulus occurring within the predefined time limit (150–4,000 ms after the appearance of the lateral stimulus). Proportions of occurred shifts were calculated by dividing the number of occurred shifts by the total number of valid trials. Dwell time on faces was calculated as the average millisecond value for occurred shifts for trials with a non-control (i.e., emotional face) centrally presented stimulus.

The eye-tracking data were stored on a laptop computer, pre-processed, and analyzed offline using *gazeAnalysisLib* (Leppänen et al. 2014). The pre-processing of the data was automated and included median filtering of the data with a moving window of 7 samples (equaling 117 ms in time), removal of abrupt spikes (technical artifacts), and interpolation of data gaps (maximum of 200 ms). In each task, trials that failed to meet predetermined data quality criteria (e.g., violated upper limit of interpolation) or specific task criteria (e.g., violation of lower-limit fixation time on central stimulus in the attention disengagement task) were excluded. For a participant to be included in the statistical analyses of a particular task, the infant needed to provide at least 3 valid trials for each condition (e.g., for visual search: at least 3 valid trials out of 8 in the single-search, one-object condition; 3 out of 8 in the single-search, multiple-objects condition; and 3 out of 8 in the conjunction condition). Thus, the final sample size varies between different eye-tracking outcome measures according to specific inclusion criteria for the eye-tracking tasks. More details on the eye-tracking procedures used in this study are provided in the main study report (Appendix 1 of Pyykkö et al. 2017,).

2.5 Anthropometric Assessment

Infant length was assessed using a length board (Harpenden Infantometer, Holtain Limited, Crosswell, Crymych, UK) and recorded to the nearest 1 mm. Infant weight was assessed using an electronic infant scale (SECA 735, Seca GmbH & Co., Hamburg, Germany) with reading increments of 10 g. MUAC and head circumference were measured with non-stretchable plastic insertion tapes (ShorrTape, Weigh and Measure, LLC, Olney, MD, USA), with the results recorded to the nearest 1 mm. All anthropometric measurements were done in triplicate by trained personnel. We used the mean of the first two readings if they did not differ by more than a prespecified tolerance limit (5 mm or 100 g). If the difference was above the limit, the third measurement was compared with the first and second measurements, and the pair of measurements that had the smallest difference was used to calculate the mean. If there were only one or two measurements, the mean of those was used for the analyses.

Age- and sex-standardized anthropometric indices (length-for-age [LAZ], weight-for-age [WAZ], and weight-for-length [WLZ], head circumference-for-age [HCZ] z-scores) were calculated using World Health Organization (WHO) Child Growth Standards (WHO 2006).

To estimate infant measurements (length, weight, and head circumference) at birth (0 days of age), we back-calculated birth measurements using enrollment measurements. Back-calculated birth measurements are equivalent to z-scores (WHO 2006) measured at enrollment, except for weight measurements done 1–5 days after birth, when weight was multiplied by 100/98, 100/96, 100/96, 100/98, and 100/99, respectively, due to a change in hydration status after birth (Cheung 2013; Greenwood et al. 1992). Newborn size at birth z-scores based on GA were calculated using the INTERGROWTH-21st Newborn Size at Birth Chart (Villar et al. 2014) and back-calculated birth measurements. These measures were used for descriptive analysis of the sample.

2.6 Maternal Reports of Rearing Environment

Mothers provided information about their life situation and their children's living environment through interviews conducted during visits at the health center and each participant's home. Interviews included in the spatial analyses are described below.

1. In the social and demographic environment questionnaire, the mother was asked about her child's socio-demographic background. This questionnaire included questions about the age, literacy, and education level of the child's parents and about the child's family structure, such as the total number of children and people living in the household. A parent had to be able to write or read fluently in any language to be considered literate (all cases were Chewa or Yao). If a mother's reading and writing skills were not obvious, she was asked to read a piece of text and to write a piece of text.

2. Maternal cognition was assessed during the 15-week home visit with a digit span forward and backward test, a verbal fluency test (listing foods and girls' names), and a mental rotation test.

   - On the digit span forward and backward test, the mother was asked to repeat sequences of digits, increasing in length from two to nine digits. There were two sequences for each length and direction of digits. First, in the digit span forward test, the mothers were asked to repeat each digit in the sequence in the same order until the mother failed both sequences with a given number of digits. Second, in the digit span backward test the mothers were asked to repeat each digit in the sequence in backward order, and the test was terminated when the mother failed both sequences with a given number of digits. The total number of correct responses was calculated for each test (digit span forward score and digit span backward score).

   - On the verbal fluency test, the mother was first asked to name as many foods as possible in 60 seconds and then as many girls' names as possible in 60 seconds. For both conditions, each unique word in the category was counted as one point and a total number of unique words was calculated for each category.

   - The mental rotation test consisted of five rows of figures. For each row, the first figure was the original figure and the next eight figures were either rotated or flipped versions of the original figure. The mother was asked to point out the rotated figures (total of four to six rotated figures in a row). The number of rotated figures correctly identified and the number of flipped figures correctly not identified as rotated were summed to obtain a total test score (for a maximum of 40).

   For the maternal cognition score, all five scores (digit span forward, digit span backward, food names, girl's names, and mental rotation) were standardized (mean 0, SD 1) and then summed, and standardized again.

3. The socioeconomic status (SES) was a mean of the following standardized items:

   - The food security questionnaire focused on the household's access to food. The household food insecurity access scale (HFIAS) questionnaire was used. The questionnaire includes a total of nine questions that ask about the household's ability to access food, the variety and amount of food consumed, and the hunger experienced by household members. For each question, the respondent was asked if the event occurred "Never," "Rarely," "Sometimes," or "Often" in the past 30 days. Items experienced rarely, sometimes, and often receive a score of 1, 2, and 3, respectively. Scores across all nine items are summed to give a total score for household food insecurity. Thus, the possible range of scores on the questionnaire is 0 to 27 (Coates et al. 2007).

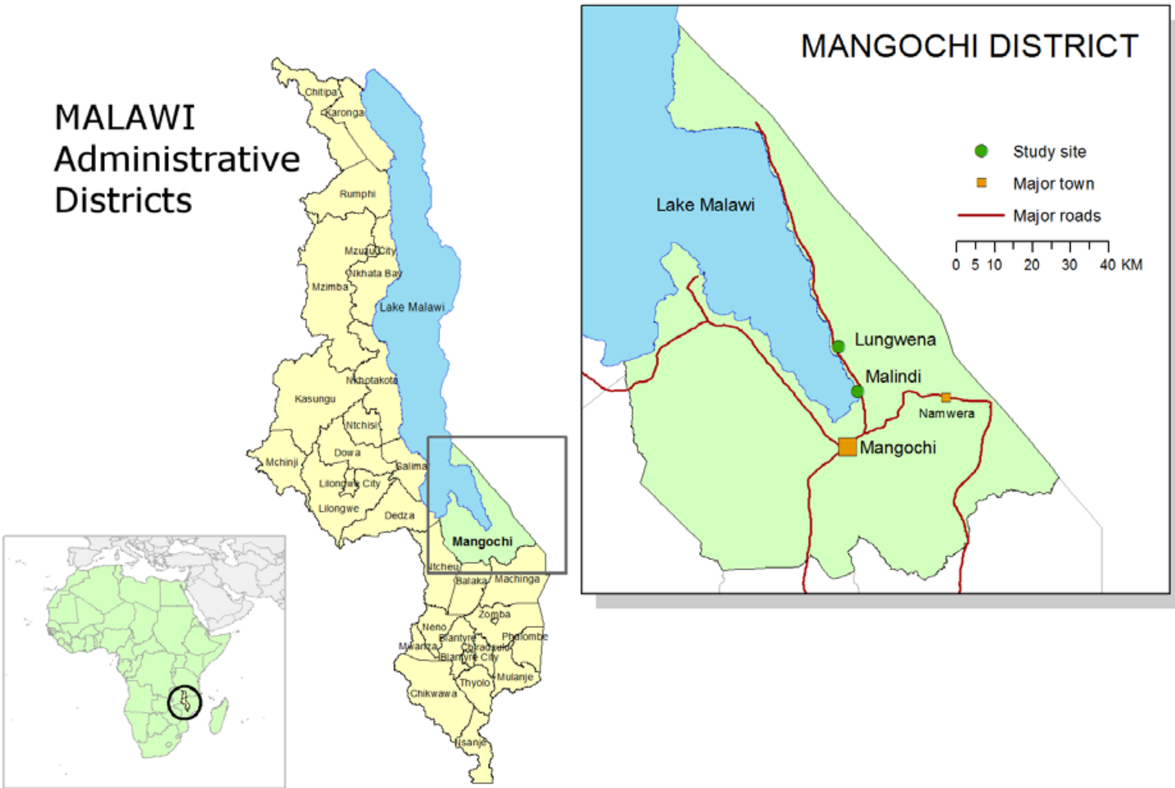
   - The living environment questionnaire included six questions about the building material of the house and the roof, the main source for drinking water, the sanitary facilities, the light source, and the main source for cooking oil. For each question, response options were ranked, with a higher score indicating more-developed construction. Based on the collected answers, each question was standardized (mean 0, SD 1) to represent the variety of housing conditions. Responses to the questions were then summed as a living environment score.

   - The social and demographic environment questionnaire included an assessment of subjective social status, specifically, nine questions about the mother's well-being in the past month. The first three questions asked the mother how often she ate three meals every day, how often her children ate three meals every day, and how often she had enough money for everyday needs. The response options (with their scores in parentheses) were "Never" (0), "Rarely" (1/3), "Sometimes" (2/3), and "Often" (1). The last six questions asked whether the mother had been able to buy food, clothes, and soap for laundry or washing for her or her children and whether she had been working in the past month. The response options were "Yes" (1) or "No" (0). Scores from the nine questions were summed to form a subjective social status score for the mother.

2.7 The Study Site

The trial area comprised a stretch of rural land on the eastern shore of Lake Malawi. Roughly, the area stretches 22 km from south to north and about 8 km from west to east, narrowing both toward the north and south end. It is bordered by Lake Malawi on the west side and the Namizimu Forest Reserve on the east, where the area's altitude increases. Further to the north, the Malawian territory eventually ends between Lake Malawi and the national border with Mozambique. Lungwena Health Center is located more or less in the middle of the area. There is one main road (S129) leading through the area that goes north. Other roads exist as well, but they start and end at the main road. Directly to the south of the trial area in the town of Malindi is St. Martin's Hospital. Further south is the district center of Mangochi with the district hospital (Figure 2-1).

Figure 2-1. Map of Study Site in Mangochi District, Malawi



2.8 Methods for GPS Data Collection and GPS Data Handling

A data collector visited each participant's home and, while there, recorded each home's global positioning system (GPS) coordinates given by a Garmin eTrex 10 GPS location device (Universal Transverse Mercator [UTM] coordinate system 'arc 1960 UTM Zone 36S'). UTM coordinates can be entered straight into the ArcGIS Desktop 10.5 package and used for analysis. The GPS dataset was checked for logical and recording errors.

2.8.1 Segmenting the Study Area—Areal Location

To get an idea of whether the *residential area* was associated with the main outcomes of the trial, we segmented the study area into five areas. For this we used an areal segmentation we constructed for another research into the influence of residential area on outcomes from the Lungwena Antenatal Intervention Study (LAIS) (Poelman et al. 2018). We extended the segmentation from that research with one extra area to the south. We constructed the segments based on previous knowledge of the area and its size. Five areas would yield areal units large enough to roughly understand the variability in the area. The main road through the area was taken as natural border for dissecting the area into a western and an eastern part. Areas 1–3, and 5 are located along the lake, and Area 4 is located east of the road and has a higher altitude. Lungwena Health Center is in Area 2, and St. Martin's Hospital is in Area 5. The participants living near the main road were allocated to the areas that border the lake. We hypothesized that the lake's vicinity may be an influence on the local diet, type of employment, and possible household assets. The five areas were drawn as polygon features, and the main road going through the trial area was a line feature in the ArcGIS software based on the World view areal satellite picture of the area.

2.8.2 Residential Location

After investigating the outcomes by residential area, we proceeded to investigate the outcomes by residential location, referred to as *household level clustering*. For this we used the GPS coordinates collected for each participant's home. These were imported into the ArcMAP software and a file geodatabase was constructed.

We executed a cluster analysis for each selected outcome by using the Hot Spot Analysis (Getis-Ord Gi*) tool[3] in ArcMap Desktop software. For the results reported here we used the following tool settings: "Conceptualization of Spatial Relationships" based on "Spatial Weights From File," "Distance Method" set to "Euclidean," "Standardization" set to "None," and no false discovery rate correction applied. The environment settings were left at default. Other settings were also tried and essentially presented similar cluster outcomes although the size of the clusters varied.

The Getis-Ord Gi* tool analyzes each residential location (of a participant) within the context of neighboring locations within the specified distance band. The Hot Spot Analysis tool returns a feature layer that includes a confidence-level variable indicating whether the feature is part of a statistically significant cluster of high (hot spot) or low (cold spot) variable values. The value of a feature and its neighboring features within the specified distance band is compared to the average for the variable within the whole dataset. The null hypothesis states that the values are spread through the area in accordance with complete spatial randomness (CSR). Significant differences from CSR are reported as Hot and Cold spots, with an accompanying confidence level (at 90%, 95%, and 99% confidence). For the household cluster level analyses in this report, we used the 90% confidence level as an indication that a participant's residential location is part of a cluster.

2.8.3 Spatial Weights Matrix

An important setting for the Hot Spot Analysis tool is how the spatial relationships among the residential locations are defined. For this we created a spatial weights matrix using the "Generate Spatial Weights Matrix" tool in the ArcMap desktop 10.5 software. A spatial weights matrix is a representation of the spatial structure of the data and consists of an NxN (N is the number of features [participants] in the dataset) table with one row and one column for each feature. The cell value for any given row/column combination is the weight that quantifies the spatial relationship between those row and column features. We used the following settings while constructing the spatial weights matrix: "Fixed Distance Band" set to 1,000 meters, a minimum of eight neighbors, and "Row" set to "standardized".[4]

The distances between the participants' residential locations were calculated using the Geographic Distance Matrix Generator software.[5] Four participants in the set were located more than 1 km from their nearest neighbor. These participants were considered to be spatial outliers, and their influence was

[3] For background, see: http://desktop.arcgis.com/en/arcmap/latest/tools/spatial-statistics-toolbox/hot-spot-analysis.htm.

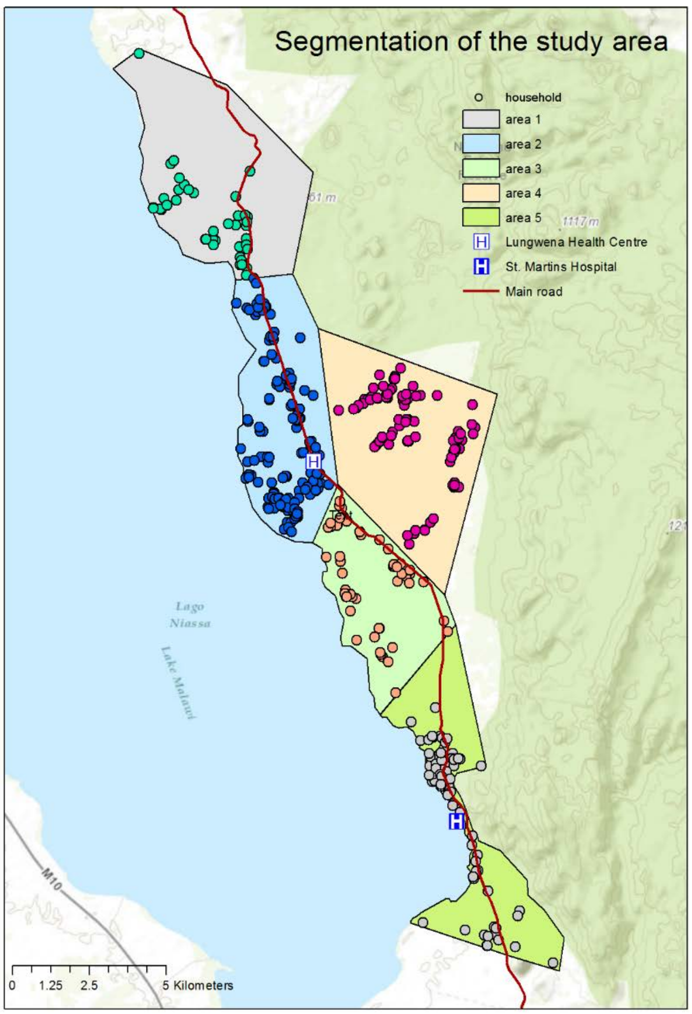
[4] These settings mean that during the cluster analysis, each participant is compared to neighbors within a distance circle of 1,000 meters. If there are fewer than eight neighbors within this circle, the distance restriction is relaxed until there are eight neighbors. "Row standardized" means that the spatial weights are standardized by row—each weight is divided by its row sum (1/number of neighbors included in the cluster analysis for a particular participant). For further background, see: http://desktop.arcgis.com/en/arcmap/latest/tools/spatial-statistics-toolbox/generate-spatial-weights-matrix.htm.

[5] Software v.1.2.3, downloaded on 5/18/2016 from http://biodiversityinformatics.amnh.org/open_source/gdmg/.

reduced by setting the distance band at 1,000 meters. The average distance to the nearest neighbor was 137 meters.

The output of the cluster analysis was exported to maps that show the five predefined residential areas. The standard layer output from the tool shows blue symbols for clusters of low (cold) outcome values and red for high (hot) outcome values. The meaning of low and high outcome values is ambiguous: For example, a low value on a growth outcome indicates a "bad" outcome, while a low value on preterm birth indicates a "good" outcome. In the study area maps in the next section, clusters of outcomes that can be considered "good" are indicated in green while clusters of "bad" outcomes are in red.

Figure 2-2. Segmentation of the Study Area and Household Locations



2.9 Statistical Analyses

We calculated group means and used analysis of variance (ANOVA) to calculate differences between the five areas for continuous outcomes. We adjusted for multiple comparisons using Tukey's method. For dichotomous outcomes, we calculated percentages and used log binomial regression to estimate risk ratios between the five areas. We rejected the hypotheses of the groups being equivalent if $P < 0.05$.

We used least squares regression to calculate differences in means for continuous outcomes and log-binomial regression models to estimate risk ratios for binary endpoints. In case there were no positive observations in one of the groups for dichotomous outcomes, we used exact logistic regression to estimate odds ratios. We also calculated 95% confidence intervals for differences in means and risk ratios and tested null hypotheses that the groups were equivalent. We rejected the hypotheses of the groups being equivalent if $P < 0.05$. All results are shown without covariate adjustments.

The ArcGIS tool produced a variable that indicates at 90%, 95%, or 99% confidence whether the location was part of a cluster of high or low outcome values. This output was categorized into three classes, indicating whether a location was part of a cluster with 90% or more confidence.

2.10 Software

Geospatial analysis, map creation, and data storage in a file geodatabase were done with ArcGIS Desktop (v.10.5, Environmental Systems Research Institute [ESRI] 2017, Redlands, CA.

A distance matrix was created using the Geographic Distance Matrix Generator (v. 1.2.3, downloaded on 18.05.2016 from http://biodiversityinformatics.amnh.org/open_source/gdmg/).

Statistical analyses, other than spatial statistical analyses, were done with Stata 13.1 (StataCorp, College Station, TX, USA).

3 Results

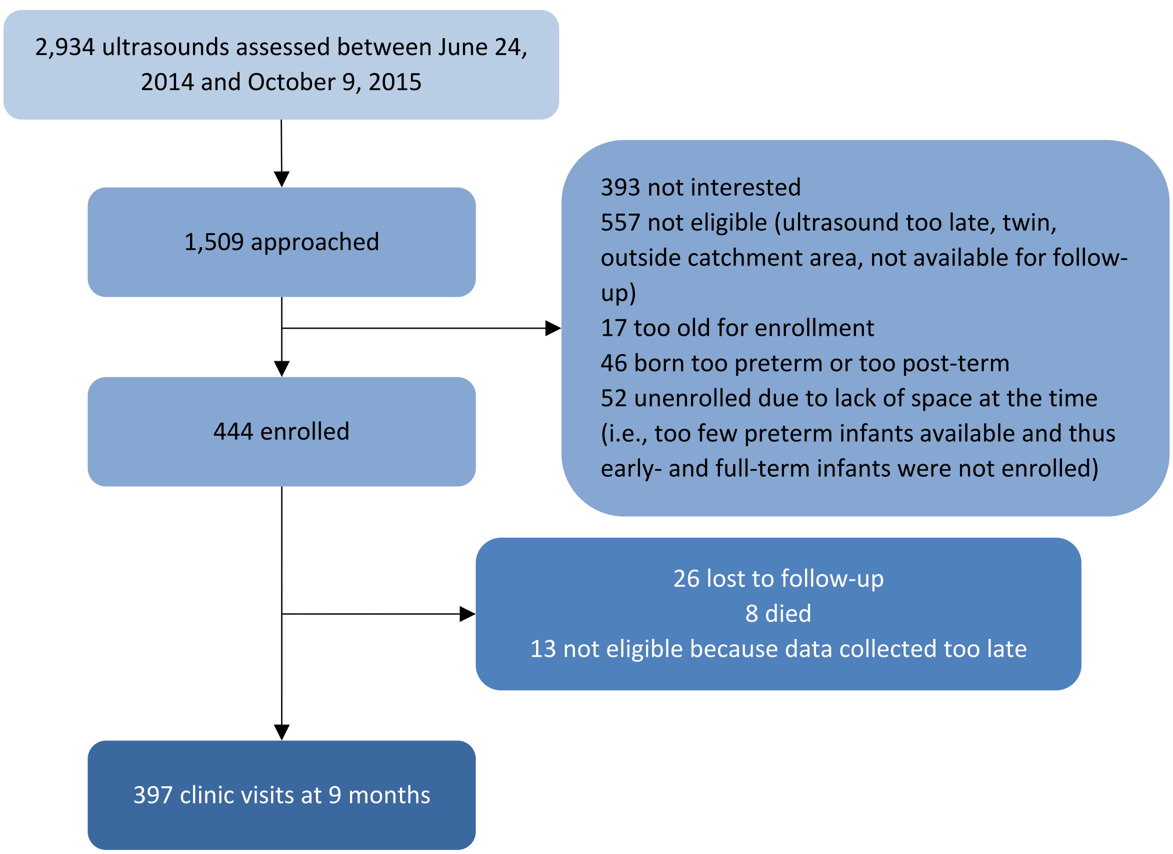
3.1 Characteristics of the Study Sample and Success of Follow-Up

Between November 2014 and October 2015, the MiTrack team approached 1,509 mothers after the birth of their children for participation in the study. A total of 444 children born to 444 mothers were enrolled. Between enrollment and the 9-month visit, 34 (7.7%) participants were lost to follow-up or died. The 9-month clinic visit was done too late for 13 participants. There were 397 9-month clinic visits done (Figure 3-1).

Women who were approached but whose infants were not included in the study had the same mean age (24 vs. 24, $P = 0.90$) and number of children currently living in the household as women whose infants formed the study cohort (2.9 vs. 2.8, $P = 0.22$) (data not shown).

Infants who were lost to follow-up had smaller head size at enrollment than infants continuing in the study at 9 months (difference in HCZ: −0.51, $P = 0.007$), whereas there was no statistically significant difference in LAZ or WAZ. There were no differences between mothers of infants lost to follow-up and the analyzed participants in terms of mean maternal age (24 vs. 24, $P = 0.89$) or number of children (alive) in the family (2.9 vs. 2.9, $P = 0.99$) (data not shown).

Figure 3-1. Participant Recruitment and Enrollment



3.2 Geographic Clustering of Maternal Background Characteristics

For all participants, the mean (SD) maternal age was 24 (7) years, and the mean number of years of maternal schooling was 3.2 (3.2) years. Among the mothers, 29.1% were primiparous and 35.4% were literate (Table 3-1).

Table 3-1. Rearing Environment Variables: Maternal and Family Characteristics

Characteristic	N	Mean (SD) or %
Mother's age, years	444	24 (7)
Mother's years in school	424	3.2 (3.2)
Mother's literacy, %	424	35.4
Primiparous women, %	444	29.1
Children alive (born to mother)	444	2.9 (1.8)
Children under 5 living in the household	424	1.7 (0.7)
People living in the household	424	5.2 (1.9)
Maternal height	444	155.8 (5.6)

Area 5 had the highest proportion of primiparous women, highest maternal cognition score, highest socioeconomic status, and highest proportion of literate mothers (Table 3-2). The second "best" outcomes were generally in Area 3 and third "best" outcomes in Area 2. Area 4 had the second "worst" outcomes and Area 1 the "worst." Except for the proportion of primiparous women, the differences between areas were statistically significant.

Table 3-2. Maternal Background Characteristics by Area

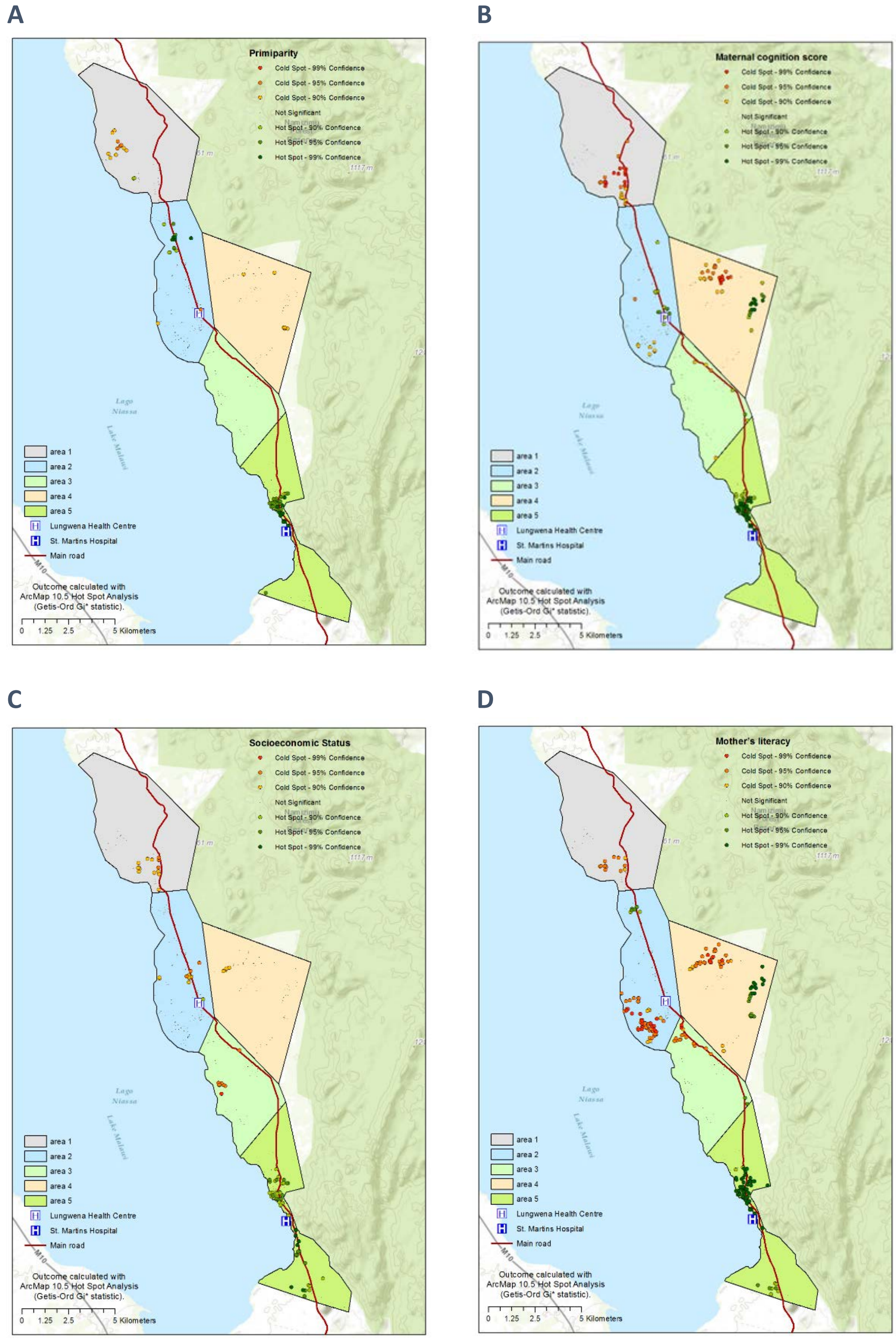
	Area 1	Area 2	Area 3	Area 4	Area 5	*
Primiparous, n/N (%)	13/44 (29.6)	49/168 (29.2)	19/94 (20.2)	14/55 (25.5)	34/83 (41.0)	0.050
Maternal cognition score (standardized), mean (SD)	-0.47 [a] (0.85)	0.00 [b] (0.96)	-0.04 [ab] (0.98)	-0.05 [ab] (1.16)	0.34 [b] (0.96)	0.001
Socioeconomic status, mean (SD)	-0.17 [a] (0.59)	-0.04 [a] (0.65)	-0.01 [ab] (0.73)	-0.11 [a] (0.70)	0.27 [b] (0.76)	0.002
Mother's literacy, n/N (%)	9/42 (21.4)	44/156 (28.2)	30/92 (32.6)	15/54 (27.8)	52/80 (65.0)	<0.001

*For continuous outcomes, *P* values were derived by ANOVA; for dichotomous outcomes, *P* values were derived by log binomial regression.

Notes: Green indicates "best" values; yellow second "best"; light orange third "best"; dark orange second "worst"; red "worst." Groups that do not share a common superscript differ significantly from each other ($P < 0.05$).

There was a household-level cluster of fewer primiparous women in Area 1 and smaller clusters of fewer primiparous women in Area 4. There were small clusters of more primiparous women in Area 2 and a very clear cluster of more primiparous women in Area 5 (Figure 3-2, panel A). There were small household-level clusters of "better" maternal cognition scores in Areas 2 and 3 and very clear clusters of "better" scores in Areas 4 and 5. There were two big clusters of "worse" scores in Areas 1 and 4 and several small clusters in Areas 2 and 3 (Figure 3-2, panel B). Areas 1, 2, 3, and 4 had several small clusters of lower socioeconomic status and Area 5 had clusters of higher socioeconomic status (Figure 3-2, panel C). There were clear clusters of less literacy in Areas 1, 2, 3, and 4. There were small clusters of higher literacy in Areas 2, 3, and 5 and clear clusters of higher literacy in Areas 4 and 5 (Figure 3-2, panel D).

Figure 3-2. Household-Level Clusters of Maternal Social and Demographic Background Variables



3.3 Geographic Clustering of Birth Outcomes

Among all participants, the mean (SD) duration of pregnancy was 38.7 (1.7) weeks, and 15.8% of babies were born preterm. The mean (SD) birth weight was 2.95 kg, and 11.2% of babies had low birth weight.

Area 1—which had the shortest mean duration of pregnancy, the lowest mean birth weight, and the highest incidence of preterm birth and low birth weight—scored worse on all the selected birth outcomes. The longest mean duration of pregnancy and the lowest incidence of preterm births occurred in Area 4. The highest mean birth weight and the lowest incidence of low birth weight occurred in Area 3. However, none of these differences were statistically significant (Table 3-3).

Table 3-3. Birth Outcomes by Area

	Area 1	Area 2	Area 3	Area 4	Area 5	*P* value*
Duration of pregnancy (weeks), mean (SD)	38.1 (1.8)	38.8 (1.7)	38.7 (2.0)	38.9 (1.9)	38.8 (1.5)	0.151
Preterm delivery (<37 weeks), n/N (%)	13/44 (29.6)	23/168 (13.7)	15/94 (16.0)	5/55 (9.09)	14/83 (16.9)	0.087
Birth weight (kg), mean (SD)	2.87 (0.41)	2.93 (0.42)	3.04 (0.39)	2.96 (0.45)	2.95 (0.40)	0.187
Low birth weight (<2,500 g), n/N (%)	7/44 (15.9)	18/167 (10.8)	9/94 (9.6)	8/55 (14.6)	8/83 (9.6)	0.702

* For continuous outcomes, *P* values were derived by ANOVA; for dichotomous outcomes *P* values were derived by log binomial regression.

Notes: Green indicates “best” values; yellow second “best”; light orange third “best”; dark orange second “worst”; red “worst Areas that shared the same rank are given the same color, starting from the “best” side of the scale.*P* < 0.05)

For pregnancy duration, there were occasional small household-level clusters of shorter duration in Areas 1, 3, and 4, and small clusters of longer duration in Areas 2, 3, and 4 (Figure 3-3, panel A). There was a small cluster of higher incidence of preterm birth in Area 1 and a small cluster of lower incidence in Area 3 (Figure 3-3, Panel B). There were small clusters of lower and higher birth weight in Areas 2, 3, and 4. Areas 1 and 5 did not show clustering of birth weight (Figure 3-3, panel C). There were small clusters of higher incidence of low birth weight in Areas 1, 3, and 4, and small clusters of low incidence in Areas 2 and 5 (Figure 3-3, panel D).

Figure 3-3. Household-Level Clusters of Birth Outcomes

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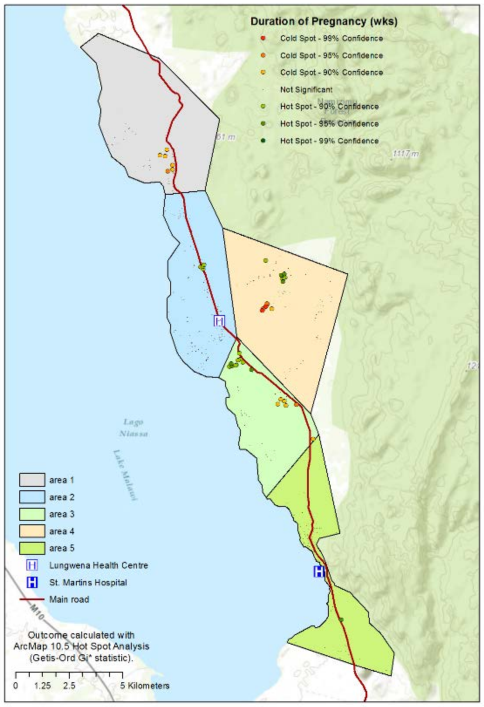

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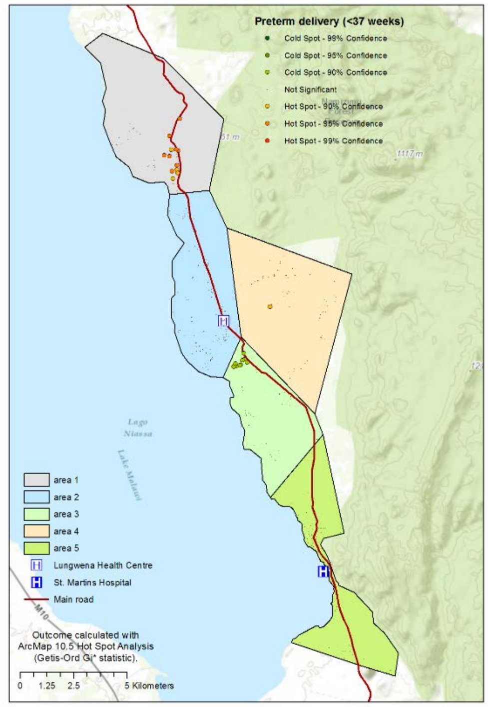

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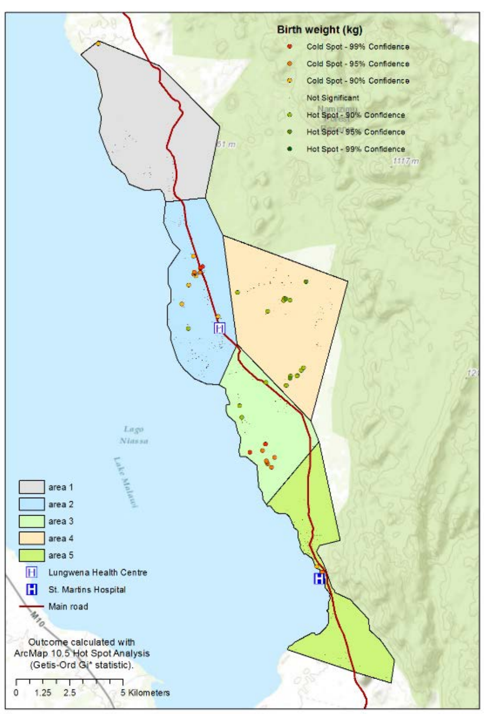

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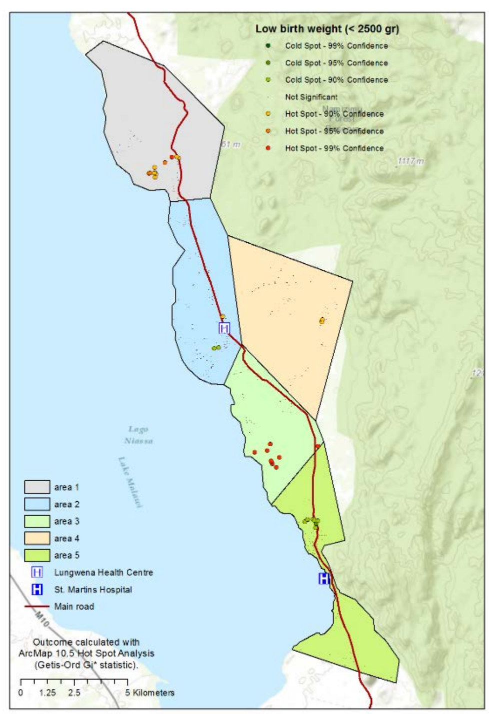


3.4 Geographic Clustering of Child Growth Outcomes

At 9 months of age, the mean (SD) WAZ, LAZ, HCZ, and WLZ among all participants were -0.72 (1.01), -1.45 (0.98), -0.52 (0.94), and 0.16 (0.96), respectively.

Area 1 had the lowest or second-lowest z-scores at 9 months of age except for WLZ, for which the z-score was the highest. Second "worst" was Area 2. Area 3 had both "good" and "bad" z-scores. Area 4 generally had the second-highest Z-scores. Area 5 had the highest WAZ and LAZ scores but the lowest HCZ. The only statistically significant difference between groups was found for LAZ (Table 3-4).

Table 3-4. Child Growth Outcomes by Area, at 9 Months of Age

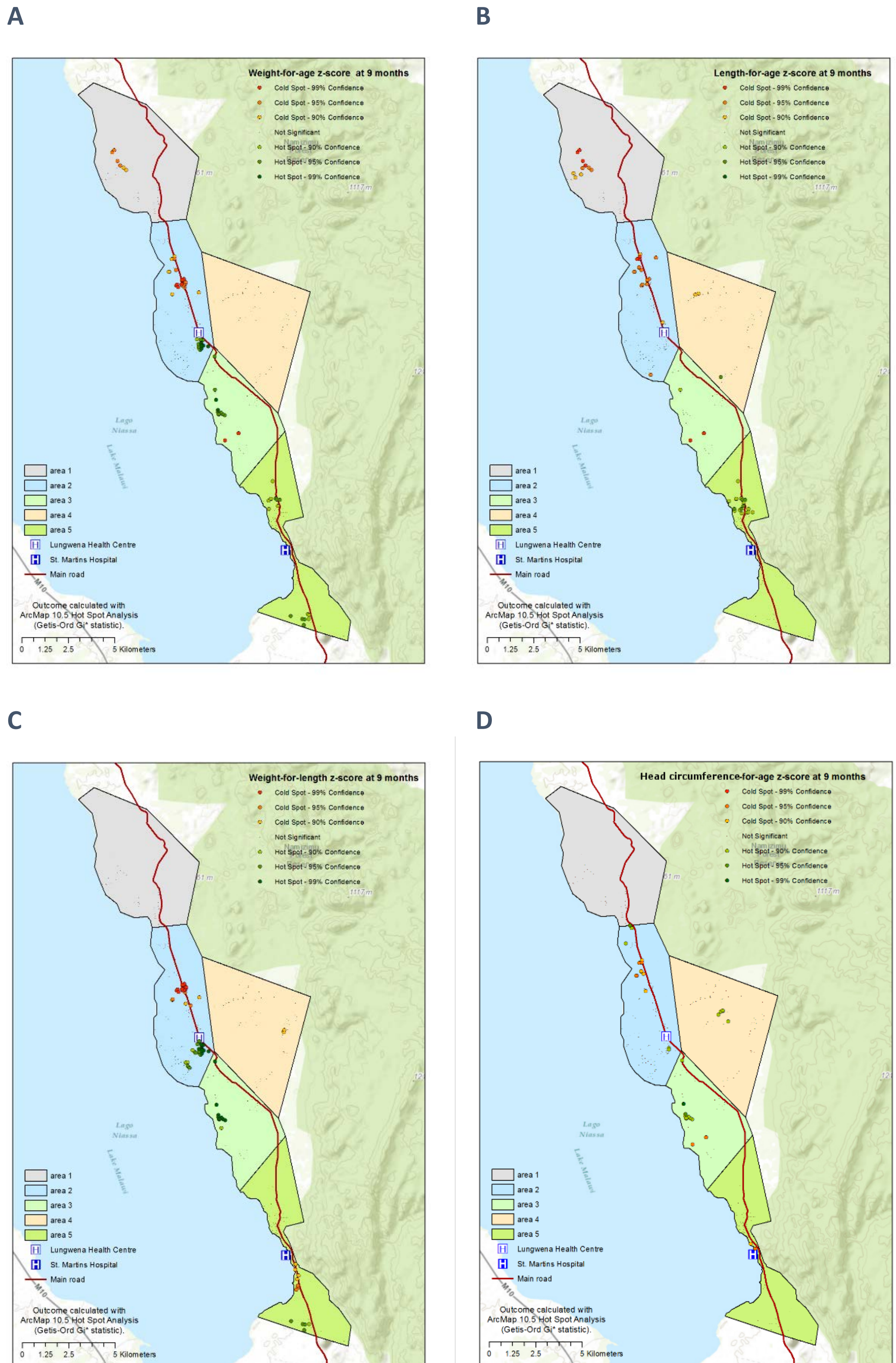
	Area 1	Area 2	Area 3	Area 4	Area 5	*P* value*
Weight-for-age (z-score), mean (SD)	-0.83 (1.00)	-0.77 (1.06)	-0.75 (1.05)	-0.70 (1.01)	-0.56 (0.88)	0.612
Length-for-age (z-score), mean (SD)	-1.80 [a] (0.99)	-1.55 [ab] (1.03)	-1.36 [ab] (0.98)	-1.44 [ab] (0.98)	-1.20 [b] (0.82)	0.016
Weight-for-length (z-score), mean (SD)	0.29 (0.91)	0.18 (1.02)	0.05 (0.97)	0.18 (0.88)	0.17 (0.93)	0.773
Head circumference-for-age (z-score), mean (SD)	-0.56 (0.93)	-0.54 (1.02)	-0.45 (0.91)	-0.47 (0.87)	-0.57 (0.84)	0.920

* For continuous outcomes, *P* values were derived by ANOVA; for dichotomous outcomes, *P* values were derived by log binomial regression.

Notes: Green indicates "best" values; yellow second "best"; light orange third "best"; dark orange second "worst"; red "worst." Areas that shared the same rank are given the same color, starting from the "best" side of the scale. Groups that do not share a common superscript differ significantly from each other ($P < 0.05$)

For WAZ at 9 months, there were small household-level clusters of lower WAZ in Areas 1, 2, and 3 and clusters of higher WAZ in Areas 2, 3, and 5 (Figure 3-4, panel A). There were small clusters of lower LAZ in Areas 1, 2, 3, and 4. Two very small clusters of higher LAZ were in Areas 3 and 4 and one slightly bigger cluster in Area 5 (Figure 3-4, panel B). There were no clear clusters of low or high WLZ in Areas 1 and 4. There were small clusters of low WLZ in Areas 2 and 5 and small clusters of high WLZ in Areas 2, 3, and 5 (Figure 3-4, panel C). There were no clear clusters of high or low HCZ in Areas 1 and 5. Small clusters of low and high HCZ were scattered around Areas 2 and 3. There was a small cluster of higher HCZ in Area 4 (Figure 3-4, panel D).

Figure 3-4. Household-Level Clusters of Child Growth Outcomes at 9 Months



3.5 Geographic Clustering of Eye-Tracking Outcomes

The mean (SD) VPS across all participants was 454 (50) ms. The mean (SD) proportion of successful visual search tasks was 0.92 (0.16) for one object, 0.62 (0.22) for multiple objects, and 0.45 (0.20) for conjunction. The mean (SD) proportion of successful anticipation in the switch-task was 0.72 (0.27) for pre-switch and 0.54 (0.28) for post-switch. The mean (SD) proportion of occurred shifts for attention disengagement was 0.71 (0.26) with a central happy face and 0.67 (0.26) with a central fearful face. The mean (SD) dwell time of gaze on faces before gaze transition to a new object (lateral stimulus) was 1,261 (513) ms.

Area 3 scored "best" on VPS, Area 5 second best, Area 2 third best, Area 1 the second worst, and Area 4 the worst. Area 5 scored best on all three visual search outcomes, and Area 2 scored second best. The visual search and attention disengagement outcomes did not show clear patterns for Areas 1, 3, and 4 (Table 3-5). For switch-tasks, the best results were in Areas 3 and 4, and the second best in Area 2. Attention disengagement tasks scores were best in Area 5, and second best in Area 1. Area 4 scored worst on the attention disengagement tasks with happy stimulus, and Area 2 scored worst on the attention disengagement tasks with the fearful stimulus. The differences between the areas were statistically significant for the visual search outcomes (one object and multiple objects). Area 3 scored best on the dwell time result, while Area 1 scored worst (Table 3-5).

Table 3-5. Child Eye-Tracking Variables by Area, at 9 Months of Age

	Area 1	Area 2	Area 3	Area 4	Area 5	*P* value*
Visual processing speed, mean (SD) ms	457.3 (42.3)	453.3 (55)	446.7 (49.2)	467.7 (48.1)	447.5 (44.3)	0.193
Visual search—one object, mean (SD) % of successful search	90 [ab] (15)	91 [ab] (18)	88 [a] (21)	88 [ab] (18)	96 [b] (9)	0.046
Visual search—multiple objects, mean (SD) % of successful search	54 [a] (25)	64 [ab] (25)	63 [ab] (21)	57 [ab] (23)	66 [b] (22)	0.027
Visual search—conjunction, mean (SD) % of successful search	42 (25)	45 (24)	42 (22)	44 (25)	49 (21)	0.386
Switch-task—pre-switch, mean (SD) % of correct anticipation	72 (26)	73 (26)	69 (27)	76 (23)	72 (29)	0.679
Switch-task—post-switch, mean (SD) % of correct anticipation	49 (29)	55 (29)	58 (28)	52 (28)	52 (27)	0.380
Attention disengagement—happy stimulus, mean (SD) % of occurred shifts	75 (27)	72 (28)	73 (28)	66 (28)	76 (27)	0.416
Attention disengagement—fearful stimulus, mean (SD) % of occurred shifts	68 (31)	65 (29)	68 (28)	67 (26)	71 (26)	0.700
Dwell time of gaze on faces before gaze transition to a new object (lateral stimulus), mean (SD) ms	1110.5 (565.6)	1219.7 (524.5)	1317.3 (565.9)	1209.1 (578.6)	1225.5 (533.3)	0.396

*For continuous outcomes, *P* values were derived by ANOVA; for dichotomous outcomes, *P* values were derived by log binomial regression.

Notes: Green indicates "best" values; yellow second "best"; light orange third "best"; dark orange second "worst"; red "worst." Areas that shared the same rank are given the same color, starting from the "best" side of the scale. Groups that do not share a common superscript differ significantly from each other ($P < 0.05$)

There were two clear household-level clusters of lower VPS in Areas 2 and 3 and clusters of higher VPS in Areas 2, 4, and 5 (Figure 3-5, panel A). There were small clusters of lower scores on the one-object visual search in Areas 2, 3, and 4 and a clear cluster of higher scores in Area 5 (Figure 3-5, panel B). For the multiple-objects visual search, there were small clusters of lower scores in Area 1 and even smaller clusters in Areas 3 and 4. Area 5 had a small cluster of higher scores (Figure 3-5, panel C). The conjunction visual search had small clusters of lower scores in Areas 1 and 4 and small clusters of higher scores in Areas 2 and 5 (Figure 3-5, panel D). There were very small clusters of lower scores in the pre-switch switch-task in Areas 1, 2, and 5 and very small clusters of higher scores in Areas 4 and 5 (Figure 3-5, panel E). For switch-task post-switch, there were very small clusters of lower scores in Areas 2, 3, 4, and 5 and clusters of higher scores in Areas 2 and 4 (Figure 3-5, panel F). There were very small clusters of lower scores for happy-stimulus attention disengagement in Areas 3 and 4 and very small clusters of higher scores in Areas 1, 4, and 5 (Figure 3-5, panel G). For fearful-stimulus attention disengagement, there were very small clusters of lower scores in Areas 1 and 4, a very small cluster of higher scores in Area 4, and a bigger cluster of higher scores in Area 5 (Figure 3-5, panel H). For dwell time of the gaze on faces before gaze transition to a new object, there was a bigger cluster of better outcomes in Area 4 and some very small clusters in Area 5. Area 1 had two small clusters of shorter dwell time (Figure 3-5, panel I).

Figure 3-5. Household-Level Clusters of Eye-Tracking Variables

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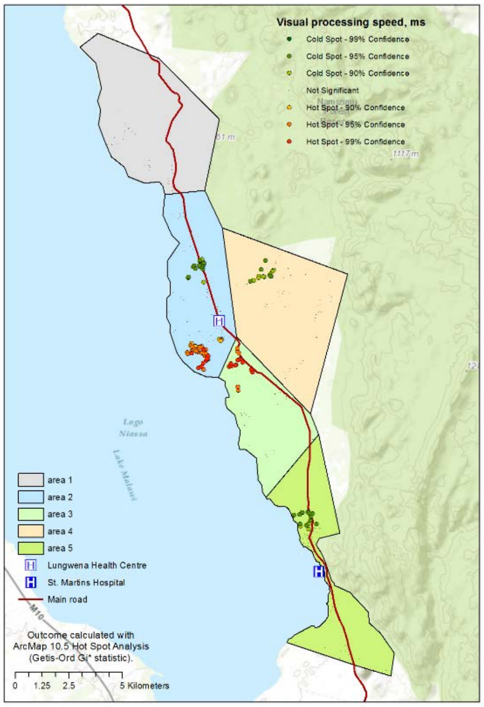

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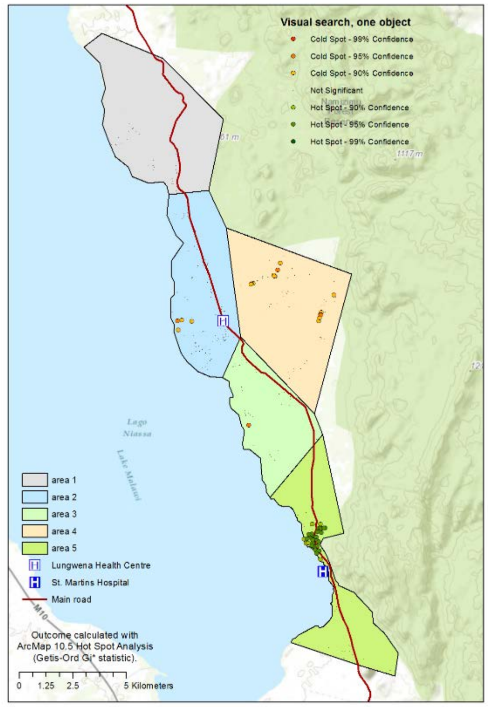

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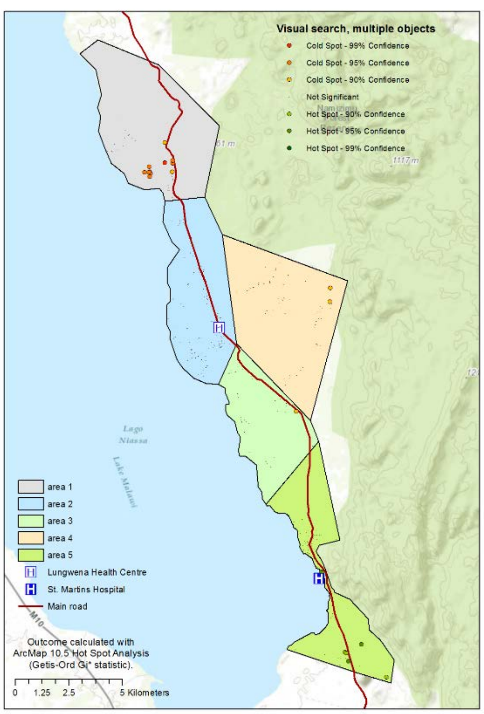

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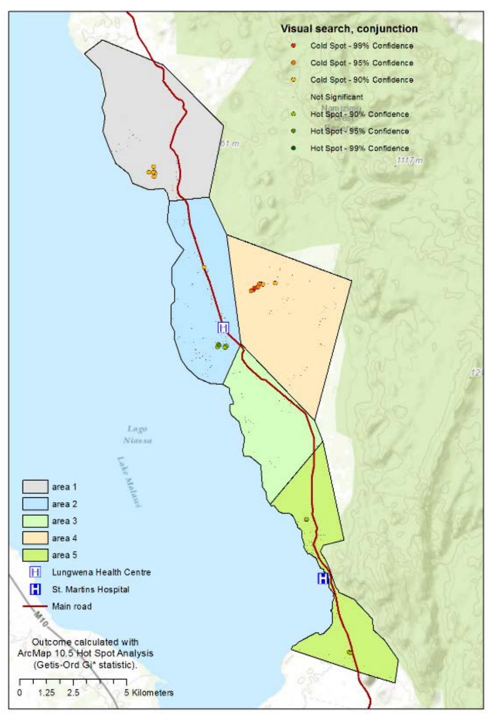

Figure 3-5. Household-Level Clusters of Eye-Tracking Variables (continued)

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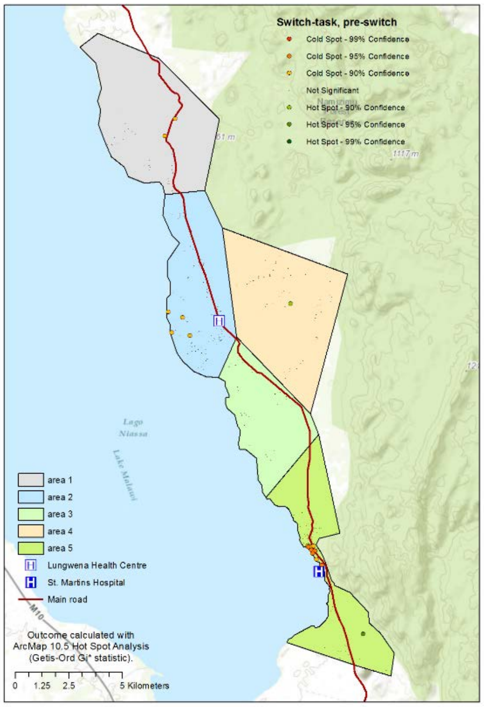

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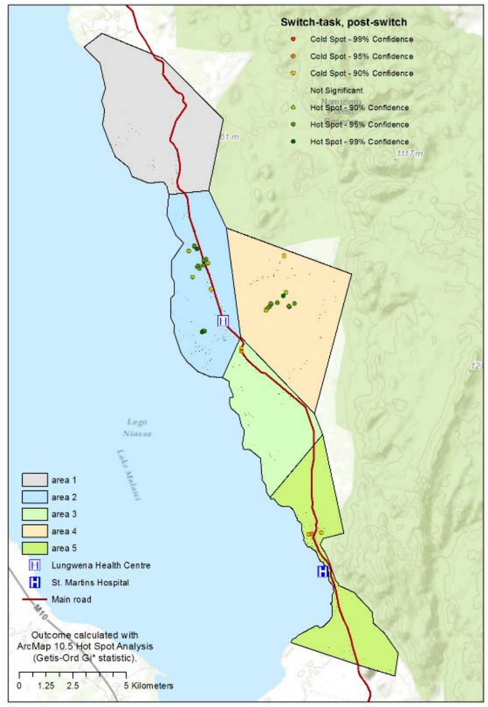

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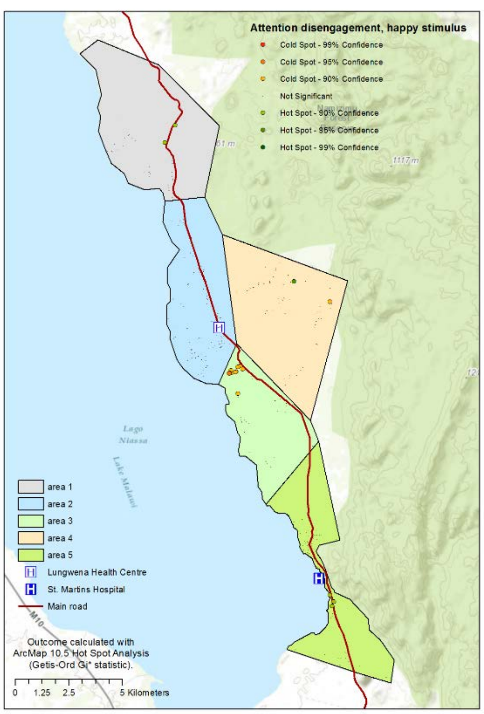

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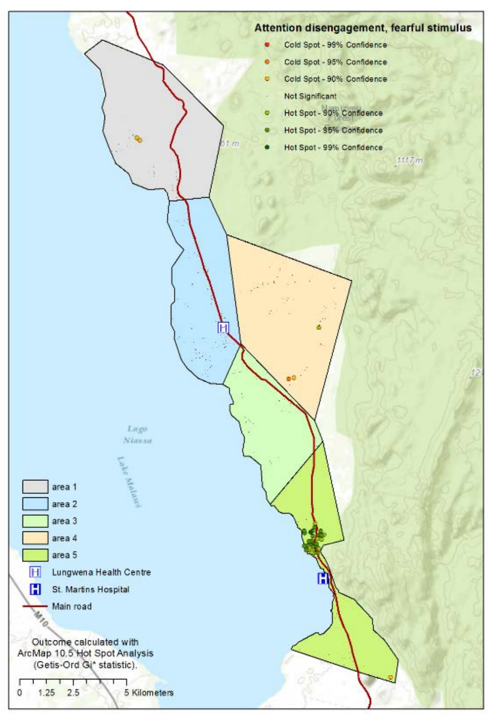
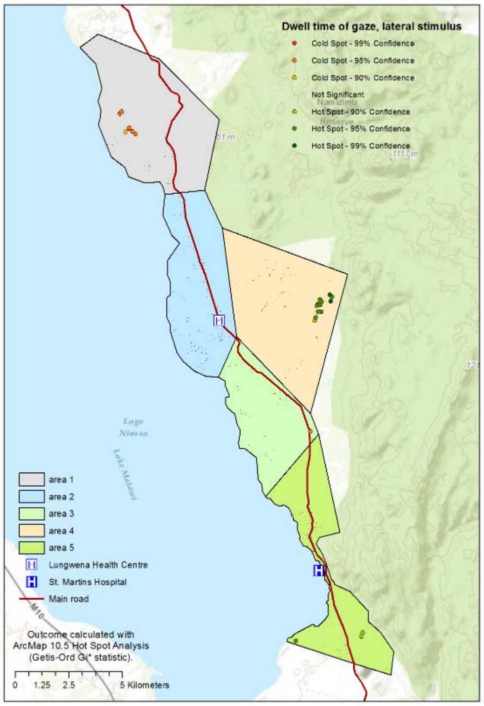


Figure 3-5. Household-Level Clusters of Eye-Tracking Variables (continued)



4 Discussion

In this study, we were interested in the geographic distribution of outcomes related to child growth and cognitive development, as well as some selected maternal factors in the area around Lungwena Health Center and St. Martin's Hospital in Malawi's Mangochi district. We focused on a few broad groups of outcomes; maternal socioeconomic background and well-being, birth outcomes, child growth at 9 months of age, and cognitive development at 9 months of age, as assessed by eye-tracking tests.

In general, our results confirm the idea that maternal and child health outcomes show geographical heterogeneity. The outcomes clustered geographically, both by residential area and household cluster.

4.1 Residential Areas

Looking at all outcomes generally, Area 1, in the northern part of the study area, scored worst for over half of the outcomes (13 of 21 outcomes), whereas Area 5, around St. Martin's Hospital in Malindi village in the southern part of the study area, had the highest number of best outcome scores (11 of 21 outcomes). This pattern of areal differences was especially evident in the distribution of maternal background characteristics, and to a lesser extent, in LAZ and certain eye-tracking measures at 9 months.

Of the 21 outcomes considered in this study, six outcomes showed statistically significant ($P < 0.05$) differences between the areas, and for five of these outcomes, Area 1 scored worst and Area 5 scored best. This pattern was less consistent for the eye-tracking outcomes as for the other outcomes, although Area 5 did score best on five and second best on two of the nine eye-tracking outcomes considered. However, the eye-tracking data did not show consistent, statistically significant differences between areas.

4.2 Household Clusters

Our data-driven analyses of the spatial clustering of outcome markers showed some hot and cold spots with relatively higher concentrations of better and worse outcomes. Area 1, the southern part of Area 2, and the northern part of Area 4 had a higher number of worse outcomes, whereas the east of Area 4 and the center of Area 5 had a higher number of better outcomes.

There were correlated clusters between maternal cognition scores and the mother's literacy, with better scores on both outcomes north of Malindi in Area 5, a cluster of better scores in the north of Area 4, a cluster of worse scores in the south of Area 4, and a cluster of lower scores in the south of Area 1. Also, in Area 2 near the lake and southwest from Lungwena Health Center, mother's literacy and cognition are indicated as clusters of worse outcomes. The same household cluster appears as a bad VPS cluster, whereas there were no other household clusters on eye-tracking variables except in Area 5, north of St. Martin's Hospital. The presence of good and bad household clusters (e.g., the worse and better maternal cognition and literacy clusters in Area 4) suggests that dividing the study area into five residential areas in our original analyses may have been too broad. A different number of residential areas and different boundaries of areas might have revealed differences that did not show up in the current form.

4.3 Evaluation

Area 5 around St. Martin's Hospital in Malindi village can be considered as a town center; it is the most expensive housing area of the study area and home to more educated and wealthier people, who also have better access to the health services. The findings of relatively higher maternal literacy rate and highest infant LAZ at 9 months in this area are consistent with previous research showing that mother's literacy is positively associated with children's health (LeVine 2012). These results leave open the possibility that maternal SES and schooling could relate to the child's cognitional development. For these outcomes, the best scores were found in Area 5, and the worse (visual search with multiple objects) in Area 1.

Consistent with these results, our previous analysis of the current data indicated that mother's literacy is positively associated with infants' visual attention, as measured by the probability of orienting to discrepant visual stimuli among various distractor stimuli (Pyykkö et al. 2017). However, these results should be treated tentatively, given that, apart from visual search performance, the other eye-tracking markers did not show statistically significant differences between the residential areas as maternal SES and literacy did.

Elsewhere, it has been seen that home learning environment attenuates negative impacts of stunting on child's cognitive development (Nguyen et al. 2017) and nutrition importantly affects brain development in the first 1,000 days (Cusick and Georgieff 2016).

Overall, the analyses of household-level clustering give an interesting insight into the areal distribution of maternal and child health indicators and may prove useful for designing targeted interventions.

4.4 Strengths and Limitations

The strengths of this study include precise collection of GPS data. Household locations were collected and confirmed by experienced data collectors with vast local knowledge.

Our study has a number of limitations. First, we used the same areal division for all outcomes. This segmentation was based on a segmentation we created for another study, the Lungwena Antenatal Intervention Study (LAIS). For the LAIS, we constructed a four-way segmentation of the area based partly on our knowledge of the area—and certain assumptions on what could influence the outcomes considered—and partly on the segmentation's usability for future research in the area. We added one extra area to the division (Area 5) for this study. It is possible that a smaller or larger number of areas might lead to different results. It is feasible that the processes or background variables causing clustering of outcomes in some areas are not the same for all those outcomes. For example, distance to the health center might have a more direct influence on duration of pregnancy than on eye-tracking outcomes, even though duration of travel might fatigue children and affect their eye-tracking results.

Also, to look for consistent areas of outcome clustering in the analysis on the household level, we used the same setting for the spatial relationship on the Hot Spot Analysis tool for all outcomes. It could be that the spatial processes causing clustering in some of the outcomes operate on different spatial levels within the area and therefore do not show up as spatial clusters.

The data we used were not collected with the present purpose in mind; this is a post-hoc analysis. Preferably, data would have been collected over a larger area and with more equal representation over the whole trial area.

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