PESTICIDE EXPOSURE AND DIABETES MELLITUS IN A SEMI-URBAN NEPALI POPULATION

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RAMAZZINI SEMINAR
OCTOBER 26TH 2017

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Introduction

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BACKGROUND 1/5

What are pesticides?

- Diverse group of chemicals used for killing organisms considered unwanted by humans.
- Differ with regards to the organisms targeted (plants, fungi, insects, rodents) and the mode of action.

Acute health effects of pesticides

- Pesticides are, by definition, toxic compounds.
- Intoxication due to high-level, acute pesticide exposure is well-known.

BACKGROUND 2/5

Suspected chronic health effects of pesticides

- Chronic neurologic disease.
- Developmental defects of the CNS.
- Lung function impairment
- Diabetes mellitus
- Cancer
- Etc.

BACKGROUND 3/5

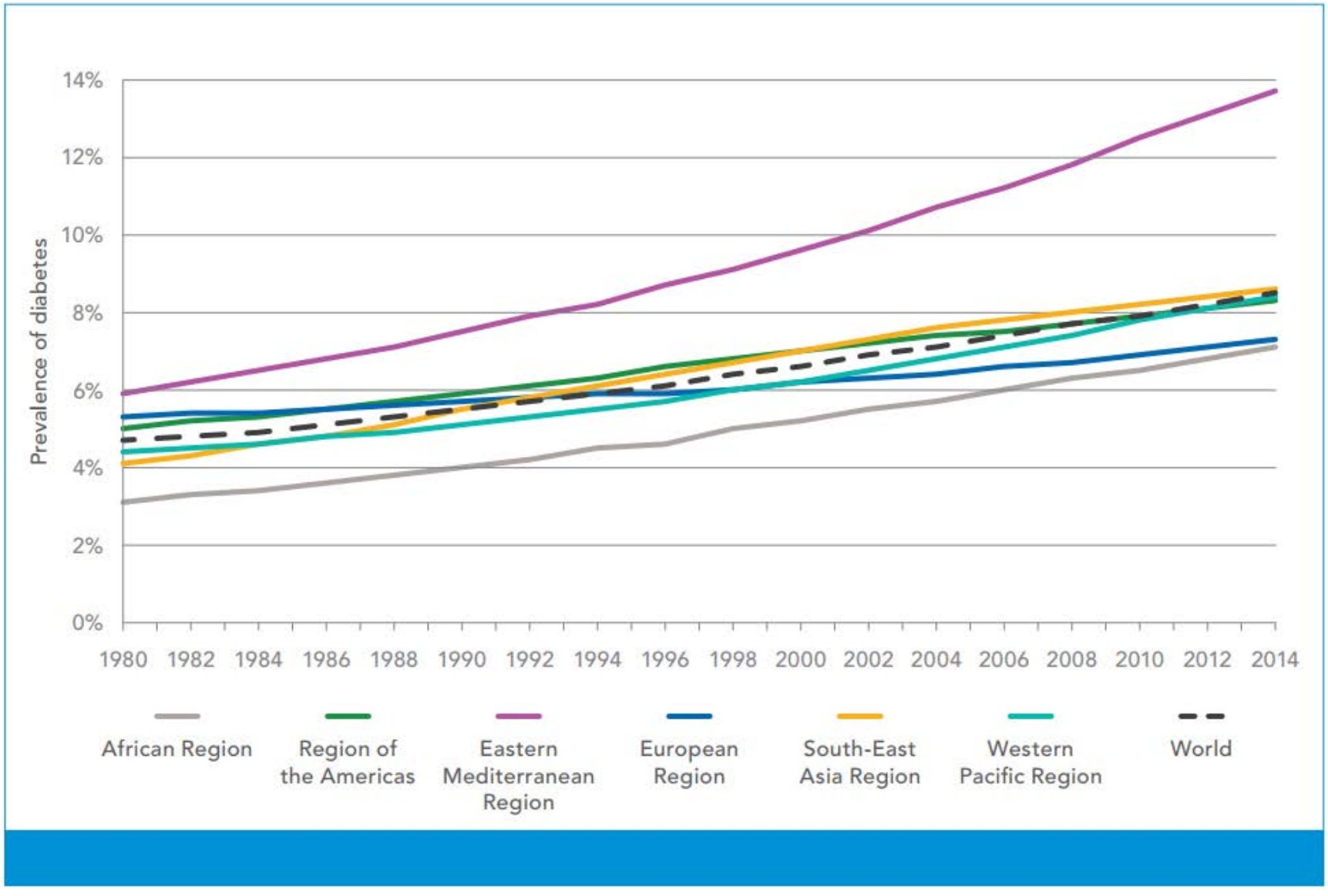
Pesticides and diabetes

- Recent systematic review on pesticides and diabetes: Exposure to organochlorine insecticides associated with increased risk of diabetes mellitus.[1]
- The authors found few studies on other classes of pesticides, and results cannot be extrapolated.
- However, some epidemiological studies also suggest associations with other classes of pesticides.[2,3]

1. Evangelou E, Ntritsos G, Chondrogiorgi M et al. Exposure to pesticides and diabetes: A systematic review and meta-analysis. *Environ Int* 2016;91:60-8.
2. Velmurugan G, Ramprasath T, Swaminathan K et al. Gut microbial degradation of organophosphate insecticides-induces glucose intolerance via gluconeogenesis. *Genome Biol* 2017;18:8.
3. Hansen MR, Jors E, Lander F, Condarco G, Schlunssen V. Is cumulated pyrethroid exposure associated with prediabetes? A cross-sectional study. *J Agromedicine* 2014;19:417-26.

BACKGROUND 4/5

FIGURE 4B. TRENDS IN PREVALENCE OF DIABETES, 1980–2014, BY WHO REGION



Source: Global report on diabetes. World Health Organization, 2016.


FORBRUG | MAD | SUNDHED
samvirke
LÆR AT ELSKE DIT LØSE MAVESKIND
SÅDAN BLIVER DU GOD TIL GRØD
VÆLG DEN RIGTIGE ELCYKEL
56%
af den konventionelle salat fra udlandet indeholder rester af sprøjtegift
0%
af den økologiske salat indeholder rester af sprøjtegift
Sprøjtegift er HVERDAGSKOST
Salaten indeholder rester af sprøjtegift. Det samme gør andre grøntsager, frugter, brød og vin. Giften er lovlig på marken, men i kroppen mistænkes den for at give kræft og diabetes
coop
OKTOBER 2017. PRIS 49 KR.
GRATIS FOR COOP-MEDLEMMER
ISSN: 0036394-4
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BACKGROUND 5/5

So why don't we just apply the precautionary principle and stop using pesticides?

- Pesticides are important for both food security and public health.
- Malaria kills approximately 429,000 persons per year, 70% of which are children under 5.[1]
- Indoor residual spraying (IRS) and insecticide-treated bednets are considered important factors in the fight against malaria.[1]
- When IRS was stopped in some provinces of Uganda, malaria incidence among children soared to epidemic heights.[2]

1. World malaria report 2016. World Health Organization, 2016.
2. Okullo AE, Matovu JKB, Ario AR et al. Malaria incidence among children less than 5 years during and after cessation of indoor residual spraying in Northern Uganda. *Malaria Journal* 2017;16:319.

BACKGROUND 5/5

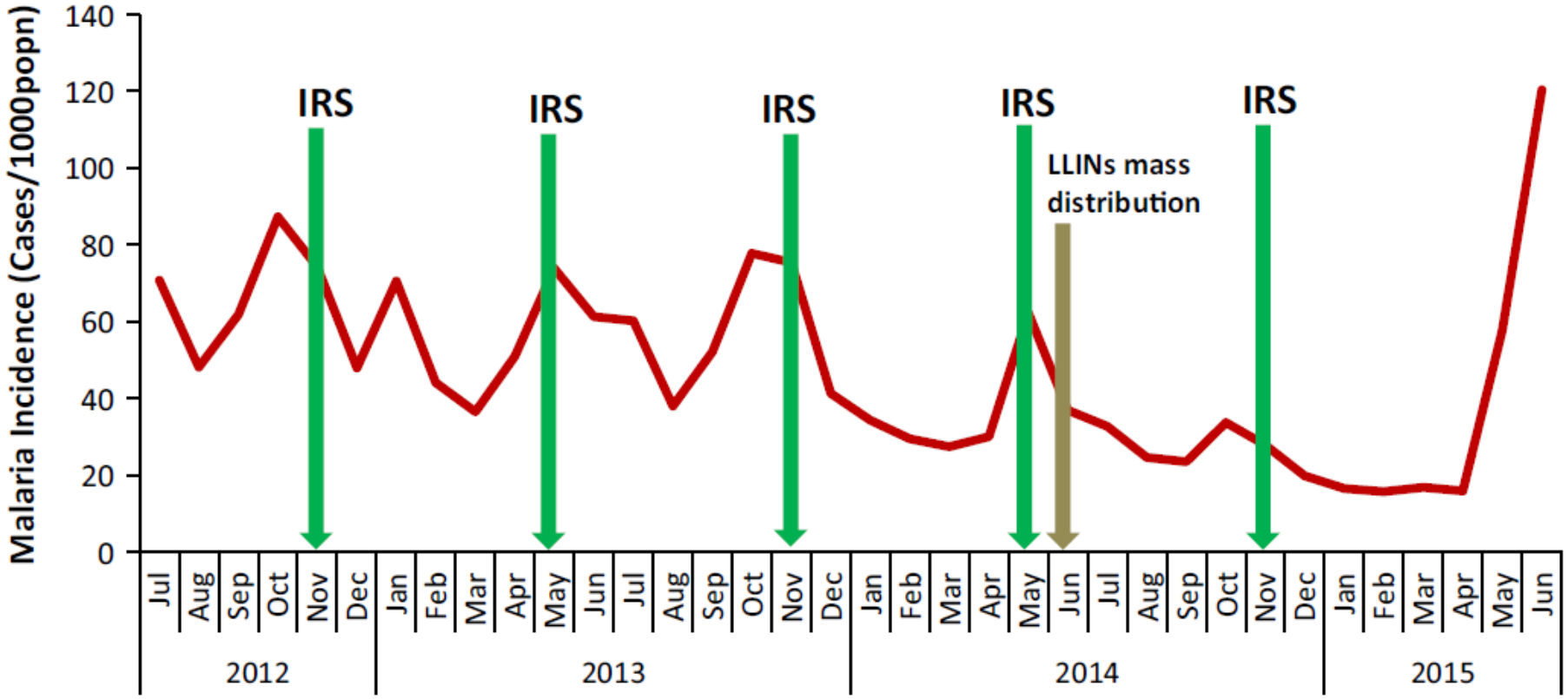


Fig. 2 Malaria incidence among under-5 year-olds vis-à-vis control interventions in five districts that ended IRS in November 2014 for period July 2012 to June 2015

Source: Okullo AE, Matovu JKB, Ario AR et al. Malaria incidence among children less than 5 years during and after cessation of indoor residual spraying in Northern Uganda. *Malaria Journal* 2017;16:319.

RESEARCH NEEDS 1/2

We need more information for proper risk assessment and management

- Which pesticides and classes of pesticides might be associated with diabetes mellitus?
- Establish exposure-response relationships.

RESEARCH NEEDS 2/2

Pesticide-exposed persons in developing countries need to be investigated, because .....

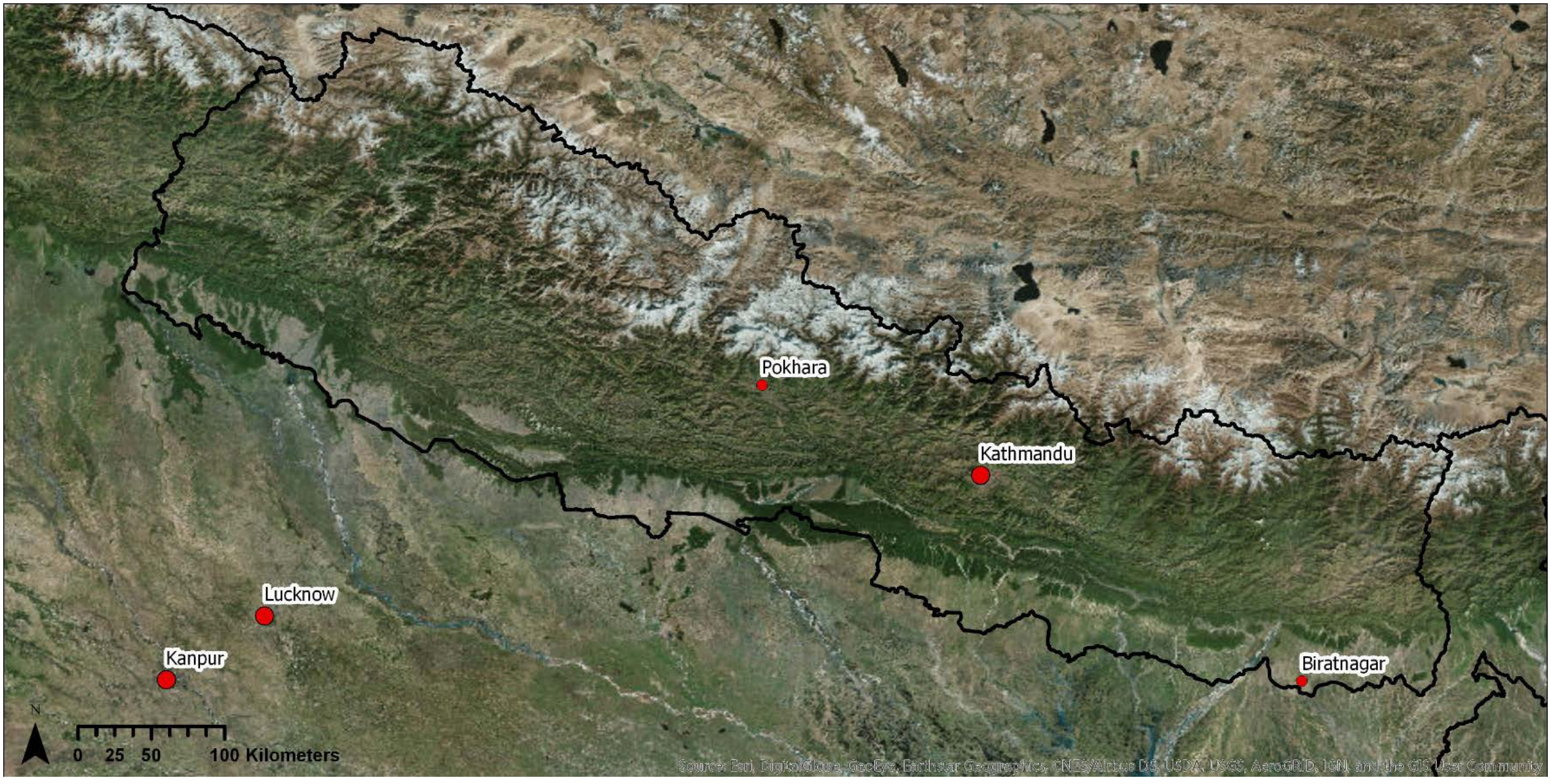
- Often...
  - Poorly educated on use of pesticides.
  - Poor use of personal protective equipment
- Result: Expected to have relatively high pesticide exposure levels.

ENTER THE "COBIN" PROJECT

COBIN (Community-Based Intervention in Nepal)

- Cluster-randomized population study on the effect of education on diabetes and hypertension in Lekhnath community, Nepal.
- 2310 participants tested, clusters randomized to intervention by female community health volunteers or control.
- Intervention started in May 2017.
- *A priori*, 60% of the population expected to be occupationally exposed to pesticides (small-scale farmers).

WHERE IN THE WORLD IS LEKHNATH?



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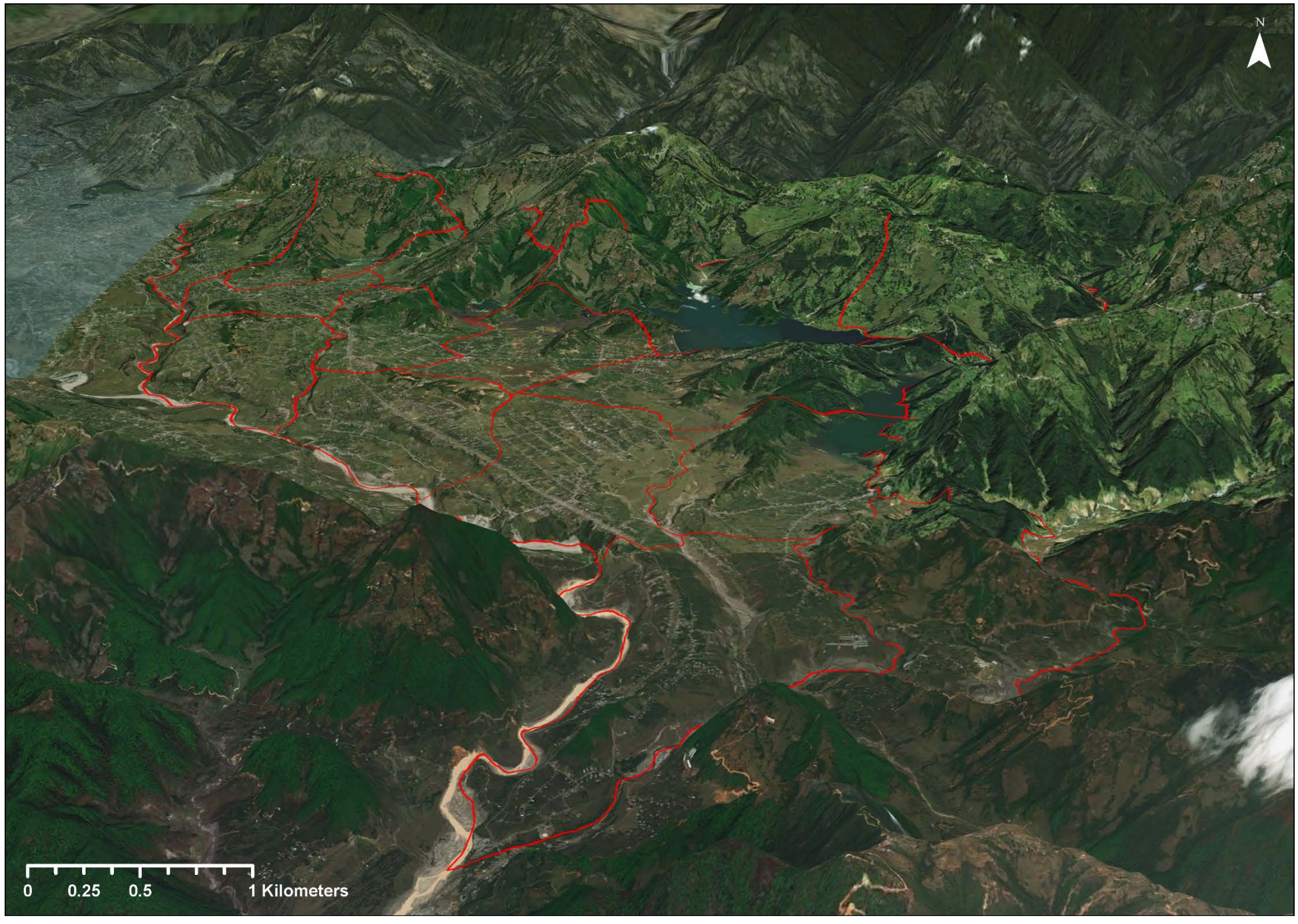
WARDS OF LEKHNATH MUNICIPALITY



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Methods

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NESTING A PILOT STUDY ON PESTICIDES IN THE COBIN PROJECT 1/2

October-December 2016: Baseline data collection for diabetes part of COBIN project

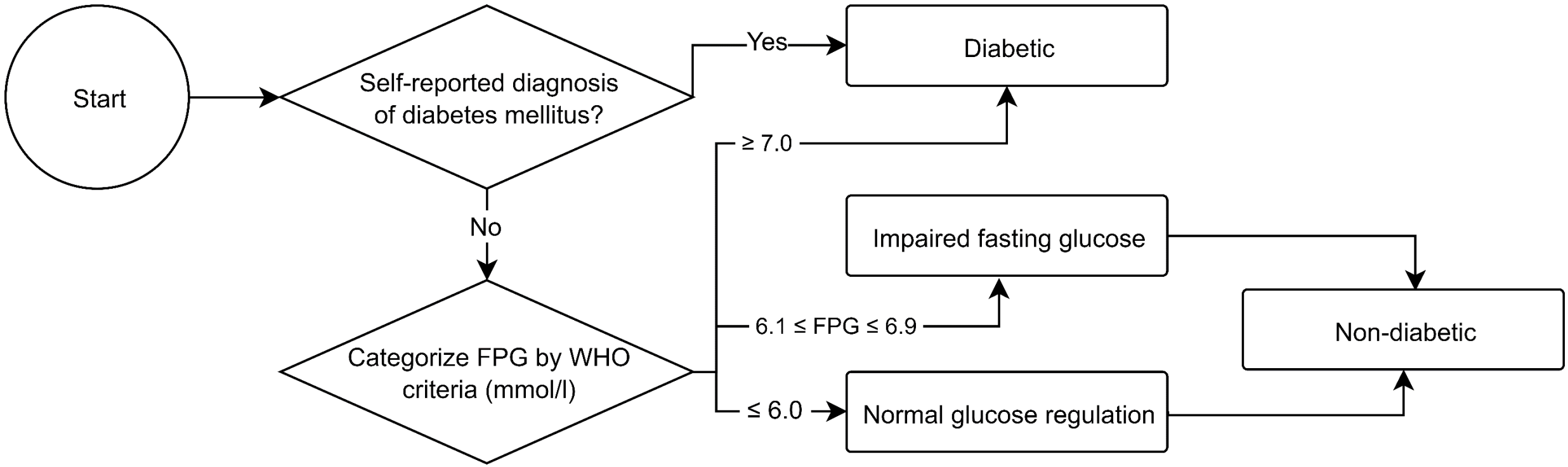
- Blood glucose measurements.
  - Original plan: Random plasma glucose (RPG), followed by fasting sample for persons with RPG in grey zone interval.
  - Carried out: Random plasma glucose measurements for everyone.
- Questionnaire data on pesticide exposure and demographics
- Original plan: Use data for power calculations for a second phase with better glucose assessment (HbA_{1c}), more detailed pesticide exposure information and objective measures of exposure (urine samples).

NESTING A PILOT STUDY ON PESTICIDES IN THE COBIN PROJECT 2/2

Example questions

- Do you use or have you used pesticides with/without relation to your job?
- In total, how long have you been using pesticides?
- How many weeks a year are you spraying?
- In the weeks that you spray, how many hours are you spraying?

CLASSIFICATION OF PARTICIPANTS AS DIABETIC OR NON-DIABETIC



CATEGORIZATION OF CONTINUOUS EXPOSURE METRICS

- Analyses showed that the continuous pesticide exposure metrics had severe digit preference.
- It was decided to categorize each metric (cut-points chosen *a priori* without looking at associations with diabetes).

Category	Years of pesticide exposure (Y)	Weeks of pesticide exposure per year (W)	Hours of pesticide exposure per week (H)
1	$Y \leq 5$	$W \leq 1$	$H \leq 0.25$
2	$5 < Y \leq 10$	$1 < W \leq 2$	$0.25 < H \leq 0.5$
3	$Y > 10$	$W > 2$	$H > 0.5$

Results and discussion

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DEMOGRAPHICS 1/3: BASIC INFORMATION

Parameter	Non-exposed	Exposed	p
n (% of n_{total})	868 (37.6)	1442 (62.4)	-
Sex**			
Female	538 (62.0)	1036 (71.8)	< 0.01
Male	330 (38.0)	406 (28.2)	
Age in years*	49.6 [40.0 ; 57.1]	46.4 [39.3 ; 54.5]	< 0.01
Years of school*	5.5 [0.0 ; 10.0]	7.0 [1.0 ; 10.0]	0.19
Farming main occupation**	255 (29.4)	583 (40.4)	< 0.01
Ethnicity**			
Upper caste	463 (53.3)	791 (54.9)	0.01
Janajati	262 (30.2)	480 (33.3)	
Others	143 (16.5)	171 (11.9)	
Currently married**	768 (88.5)	1325 (91.9)	0.01

* categorical variable. Numbers are counts (percentage). p-values calculated with Fischer's exact test.
** continuous variable. Numbers are median [interquartile range]. p-values calculated with Wilcoxon rank-sum test.

DEMOGRAPHICS 2/3: HOUSING STANDARDS

Parameter	Non-exposed	Exposed	p
Poor wall materials**	95 (10.9)	85 (5.9)	< 0.01
Poor floor materials**	111 (12.8)	95 (6.6)	< 0.01
Poor fuel type**	212 (24.4)	193 (13.4)	< 0.01
Poor stove type**	186 (21.4)	169 (11.7)	< 0.01
Separate kitchen in house**	812 (93.5)	1374 (95.3)	0.09

** Categorical variable. Numbers are counts (percentage). p-values calculated with Fischer's exact test.

Definitions for categories of housing standards

- Walls: Poor = grass, weeds, wood, bamboo, soil, raw bricks. Good = baked bricks, stone, cement, other.
- Floor: Poor = soil, bamboo. Good = wood, cement, brick, stone, sandstone.
- Fuel type: Poor = firewood, cow dung, plants, grass, weeds. Good = kerosene, LPG gas, biogas, other.
- Stove type: Poor = open stove, traditional oven. Good = improved oven, kerosene stove, gas stove, other.

DEMOGRAPHICS 3/3: HEALTH VARIABLES

Parameter	Non-exposed	Exposed	p
Body Mass Index*	24.9 [21.8 ; 27.8]	25.5 [22.6 ; 28.6]	< 0.01
Waist-to-hip ratio*	0.91 [0.88 ; 0.96]	0.91 [0.87 ; 0.95]	0.03
Known cardiovascular disease**	38 (4.4)	37 (2.6)	0.02
Family history of diabetes**	162 (18.7)	293 (20.3)	0.36
MET-minutes per week, thousands*	8.400 [5.04 ; 12.00]	8.40 [5.32 ; 13.44]	0.01
Ever smoking**	269 (31.0)	311 (21.6)	< 0.01
Current smoking**	173 (19.9)	192 (13.3)	< 0.01
Pack-years, current smokers*	13.5 [4.3 ; 29.1]	10.1 [4.0 ; 21.5]	0.10

* categorical variable. Numbers are counts (percentage). p-values calculated with Fischer's exact test.
** continuous variable. Numbers are median [interquartile range]. p-values calculated with Wilcoxon rank-sum test.

DESCRIPTIVE STATISTICS, GLYCEMIC STATUS

	Non-exposed	Exposed
Diabetes**	128 (14.7%)	143 (9.9%)
Impaired fasting glucose**	106 (12.2%)	196 (13.6%)
Normal**	634 (73.0%)	1103 (76.5%)

** Categorical variable. Numbers are counts (percentage).

CRUDE ANALYSES OF ODDS OF HAVING DIABETES

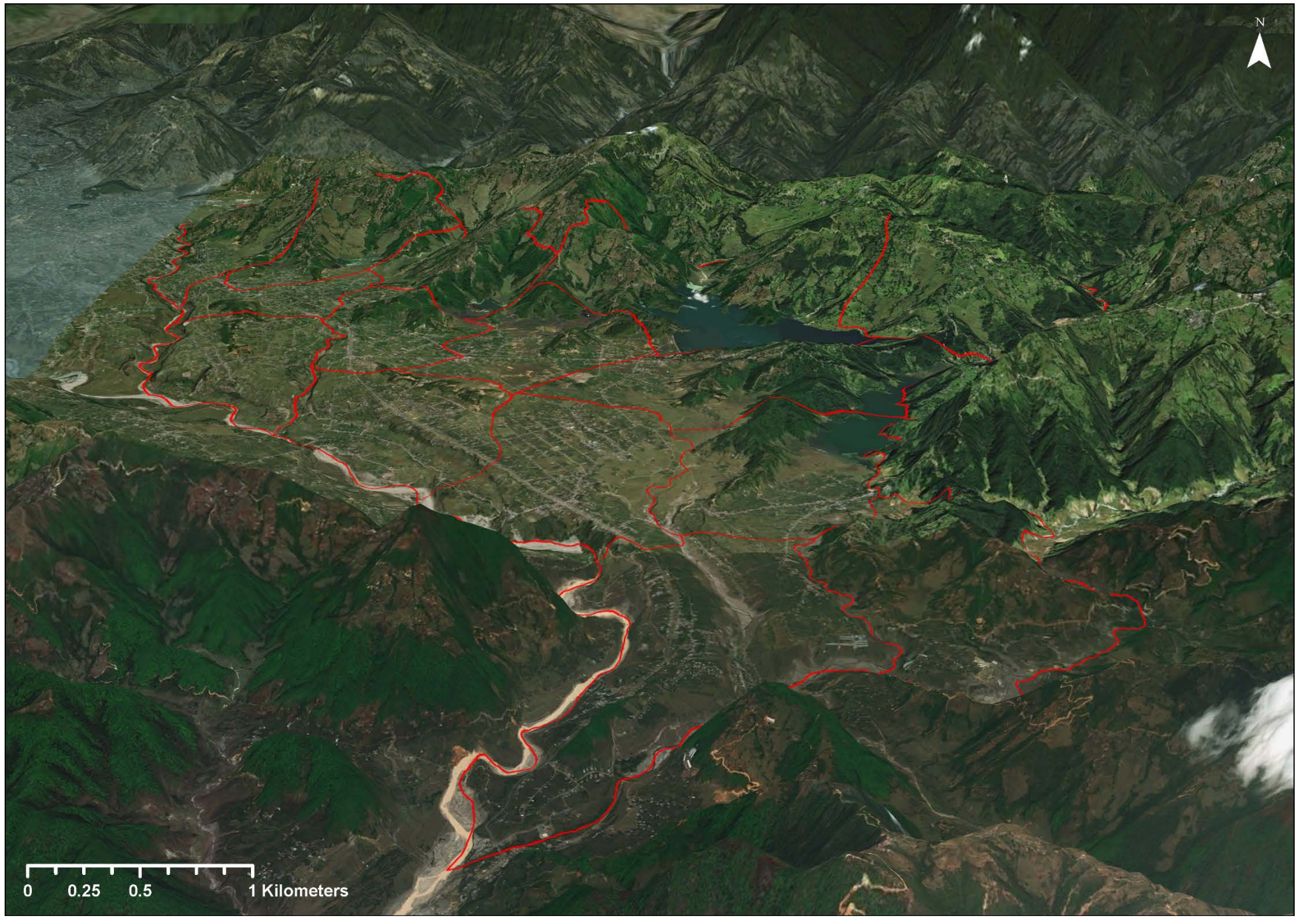
Independent variable	OR(diabetes)
Age in years / 10	1.67 [1.46 ; 1.92]
Body Mass Index	1.06 [1.03 ; 1.09]
Waist-to-hip ratio * 10	2.40 [1.98 ; 2.90]
MET-minutes per week / 1000	0.96 [0.94 ; 0.98]
Male sex	1.63 [1.25 ; 2.11]
Family history of diabetes	3.17 [2.42 ; 4.15]
Known cardiovascular disease	3.31 [1.98 ; 5.54]
Pesticide exposure (yes/no)	**0.64 [0.49 ; 0.82]**
Spraying duration, trend	**0.96 [0.78 ; 1.18]**
Spraying intensity, trend	**0.97 [0.77 ; 1.22]**
Spraying weeks, trend	**0.92 [0.75 ; 1.13]**

ADJUSTED ANALYSES OF PESTICIDE EXPOSURE VS. ODDS OF HAVING DIABETES

		aOR(diabetes)
Any pesticide exposure		0.68 [0.52 ; 0.90]
Trend across categories	Spraying duration	0.85 [0.68 ; 1.06]
	Spraying intensity	0.94 [0.74 ; 1.21]
	Spraying weeks	0.95 [0.76 ; 1.19]

Estimates adjusted for age in years, BMI, waist-to-hip ratio, physical activity level (MET-minutes per week), sex, family history of diabetes and known cardiovascular disease.

WARDS OF LEKHNATH MUNICIPALITY



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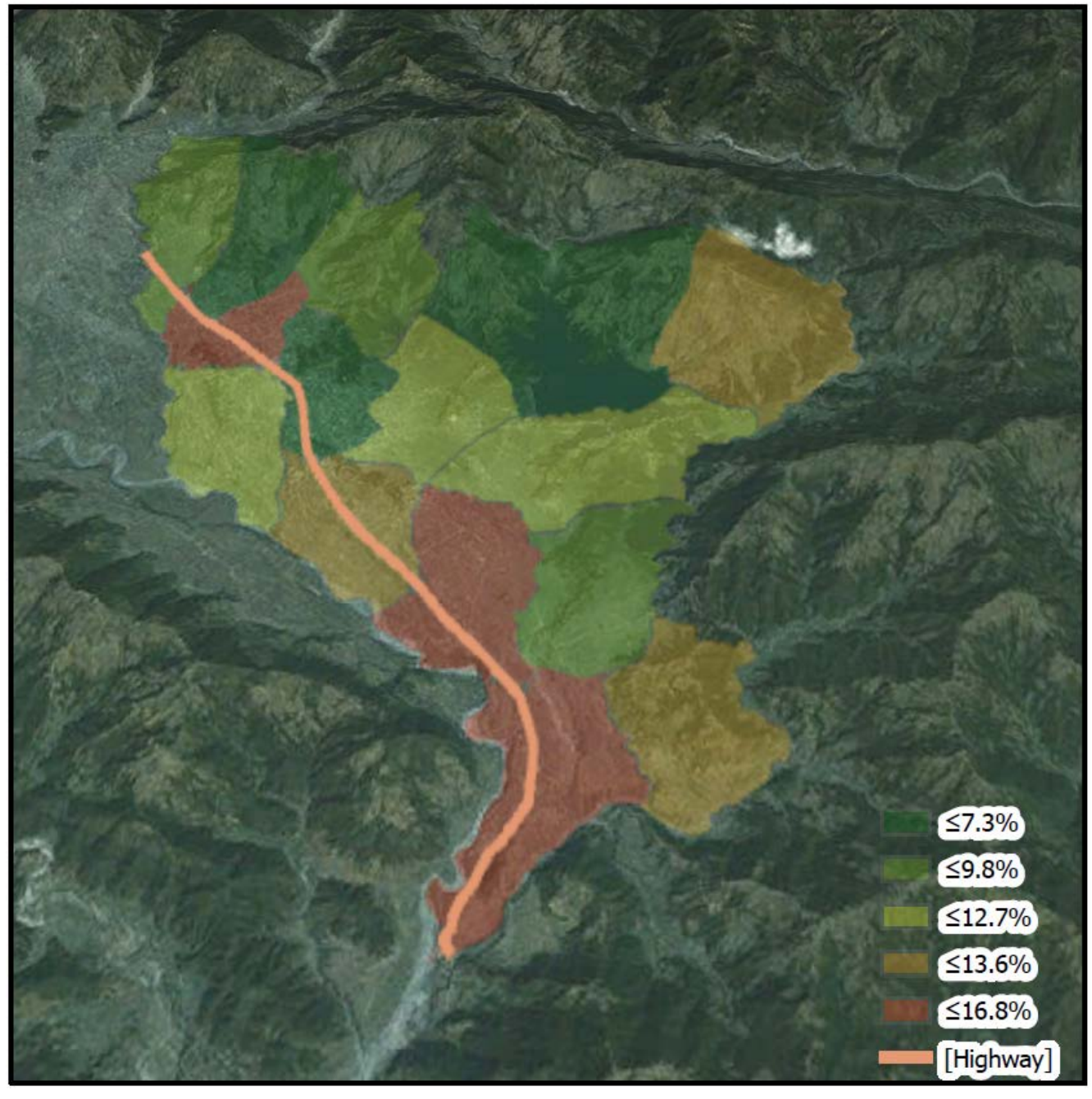
PREVALENCE OF DIABETES PER WARD



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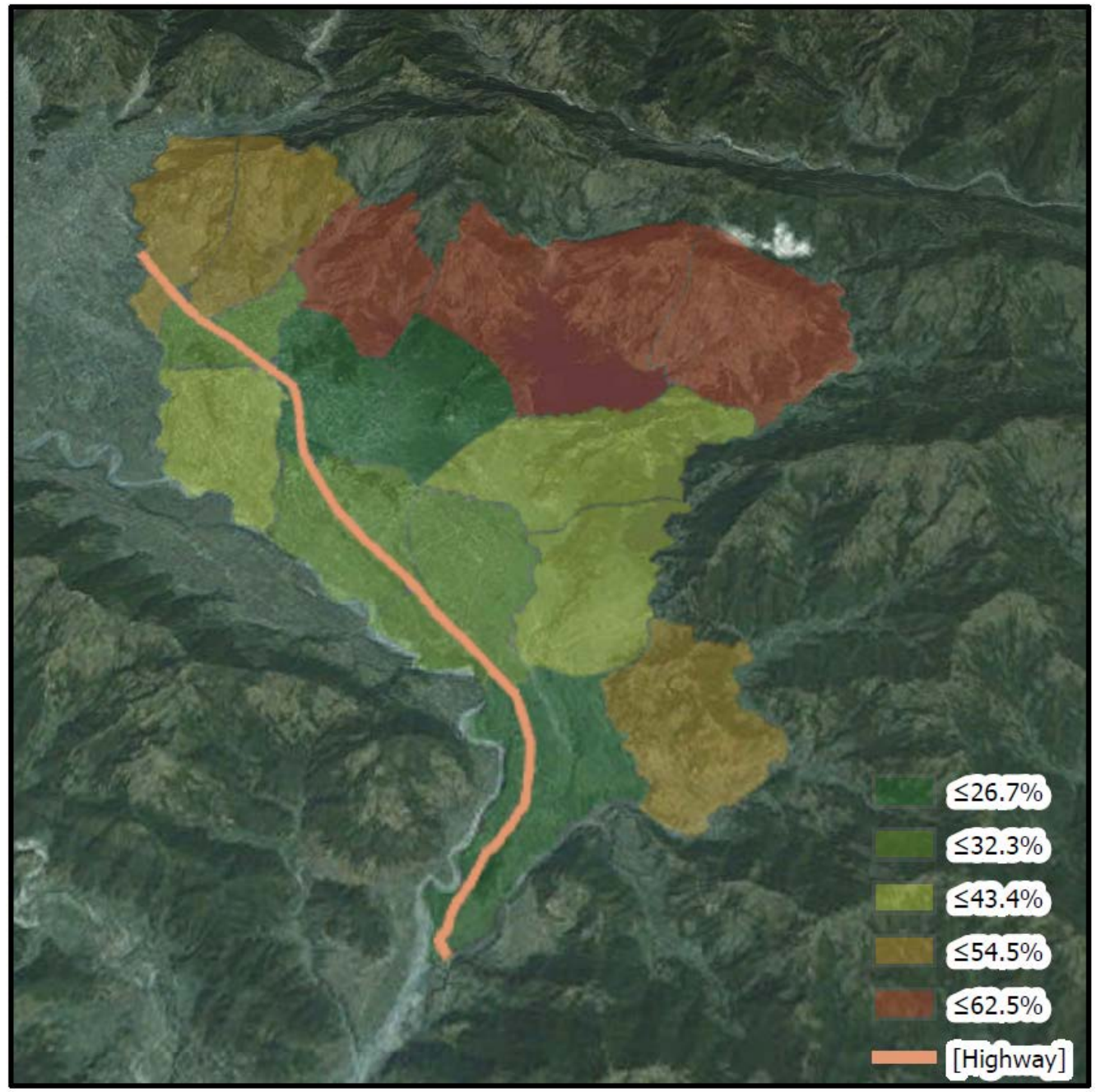
PERCENTAGE FARMERS PER WARD



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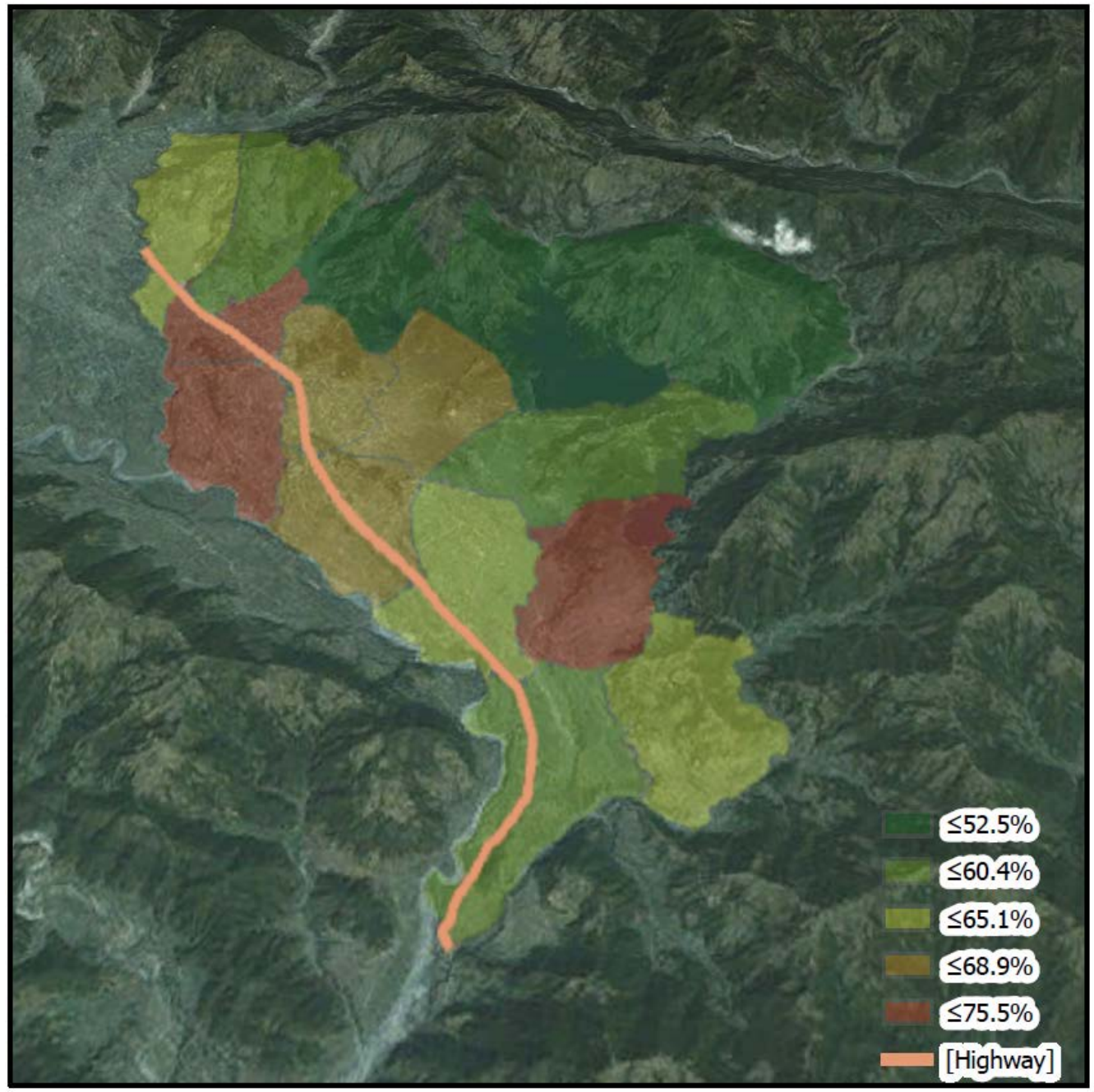
PERCENTAGE PESTICIDE-EXPOSED PER WARD (OUT OF ALL PARTICIPANTS)



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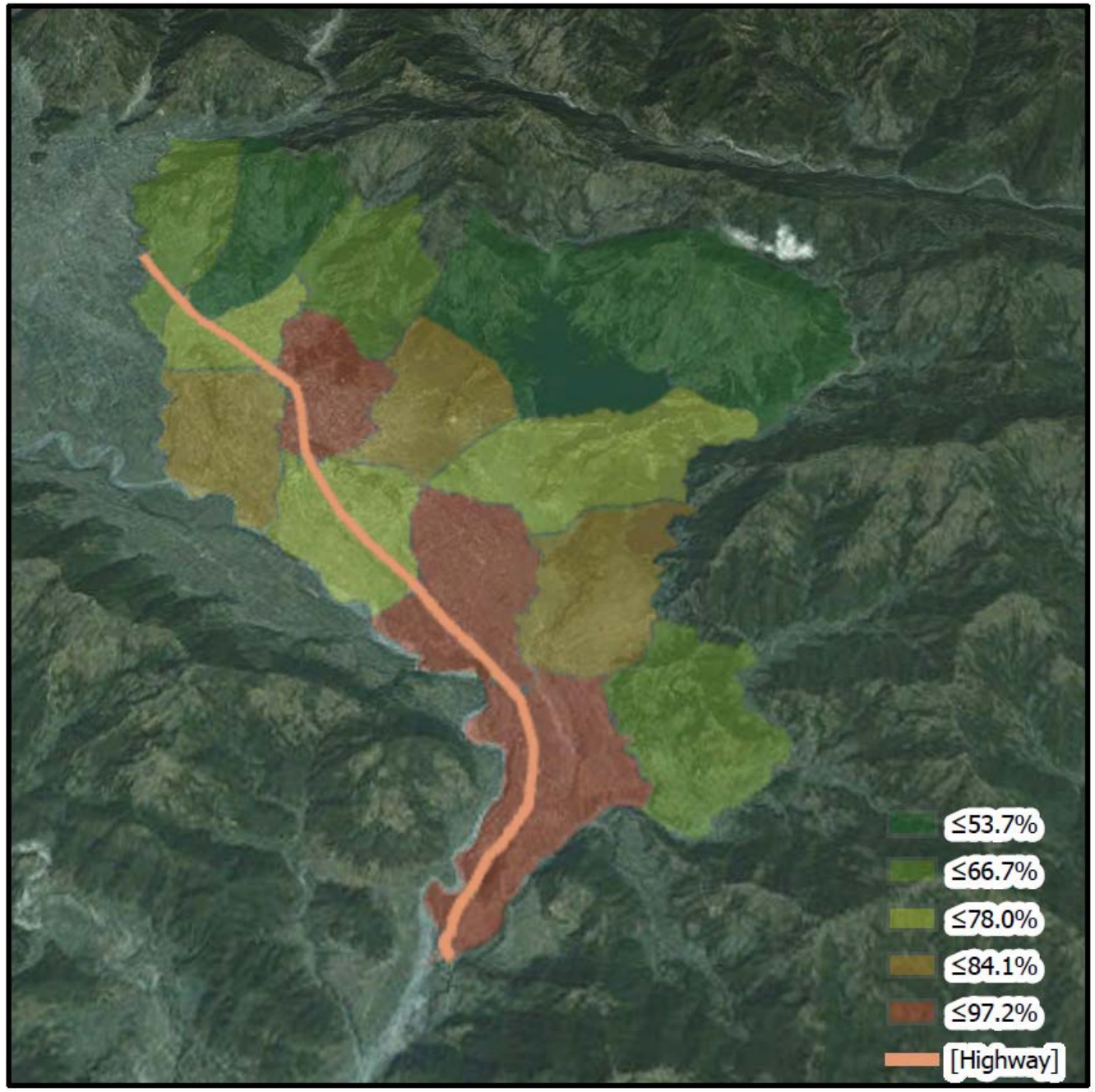
PERCENTAGE PESTICIDE-EXPOSED PER WARD (OUT OF FARMERS)



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FIELDS, FIELDS, EVERYWHERE

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SUMMARY OF ANALYSES ON ACUTE SYMPTOMS OF PESTICIDE INTOXICATION

- Participants had been asked if they had experienced any of 19 specific symptoms within the last month.
- The prevalences were significantly higher for females compared to males, and for older compared to younger individuals.
- Few associations were seen with pesticide exposure (yes/no).
- After adjusting for age and sex, only *muscle cramps* were significantly associated with pesticide exposure.
- These results suggest that pesticide exposure levels in this population are too low to cause acute symptoms.

CONCLUSIONS

- In the COBIN population, pesticide-exposed persons had lower odds of diabetes, adjusted OR = 0.68 [0.52;0.90].
- No clear exposure-response relationships were seen.
- Pesticide exposure levels were so low that few acute symptoms of pesticide exposure were seen.
- There were significant demographic differences between exposed and non-exposed persons with considerable risk of residual confounding.
- Spatial patterns and demographic information suggest we are seeing complex socio-economic and urban-rural gradients, not the effect of pesticides *per se*.

RESEARCH DIRECTIONS

Epidemiological study among workers with high-level, well-characterized pesticide exposure

- Under consideration
  - Vector control workers in Uganda
  - Farmers working in intensive agriculture in southern Nepal.
- Data collection in 2018.

Systematic review and meta-analysis on non-organochlorine insecticides and diabetes

- Protocol:
  - Submitted to the PROSPERO database.
  - Under revision for publication in peer-reviewed journal.
- Planned for 2018.

THANKS

Acknowledgements for our partners

- We wish to thank the staff of Nepal Development Society for their assistance with the field work.
- We also wish to thank Morten Frydenberg for his statistical advice.

Funding

- Data collection was supported by the International Centre for Occupational and Environmental Medicine and Public Health at the Clinic of Occupational and Environmental Medicine, Odense University Hospital.
- MRHH and BG are supported by PhD scholarships from Aarhus University.

Map credits

- Satellite image sources: Esri, DigitalGlobe, GeoEye, Earthstart Geographics, CNES/Airbus DS, USDA, USGS, AeroGrid, IGN and the GIS User Community.
- Administrative areas and road source: National Geographic Information Infrastructure Programme (Kathmandu, Nepal).


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