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Geographical variation and associated factors of infant vaccination in Japan: a spatial and multilevel analysis

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Abstract

Background

There were few geographical studies of child immunization coverage and the potential factors associated to geographical disparities in Japan.

Methods

An ecological study was performed. We estimated 17 doses vaccine coverage rates in approximately 1700 Japanese municipalities from 2013 to 2018. Multivariate and multilevel analysis were conducted to estimate the effect of 9 compositional factors and 4 contextual factors.

Results

Metropolitan areas(Tokyo, Osaka, Nagoya) showed relatively high vaccination coverage. Income per capita and Average number of children per household showed association on many doses of vaccines.

Discussion

Social inequities may associate with immunization coverage. Addressing access barriers can reduce Vaccine Hesitancy and enhance vaccination rates.

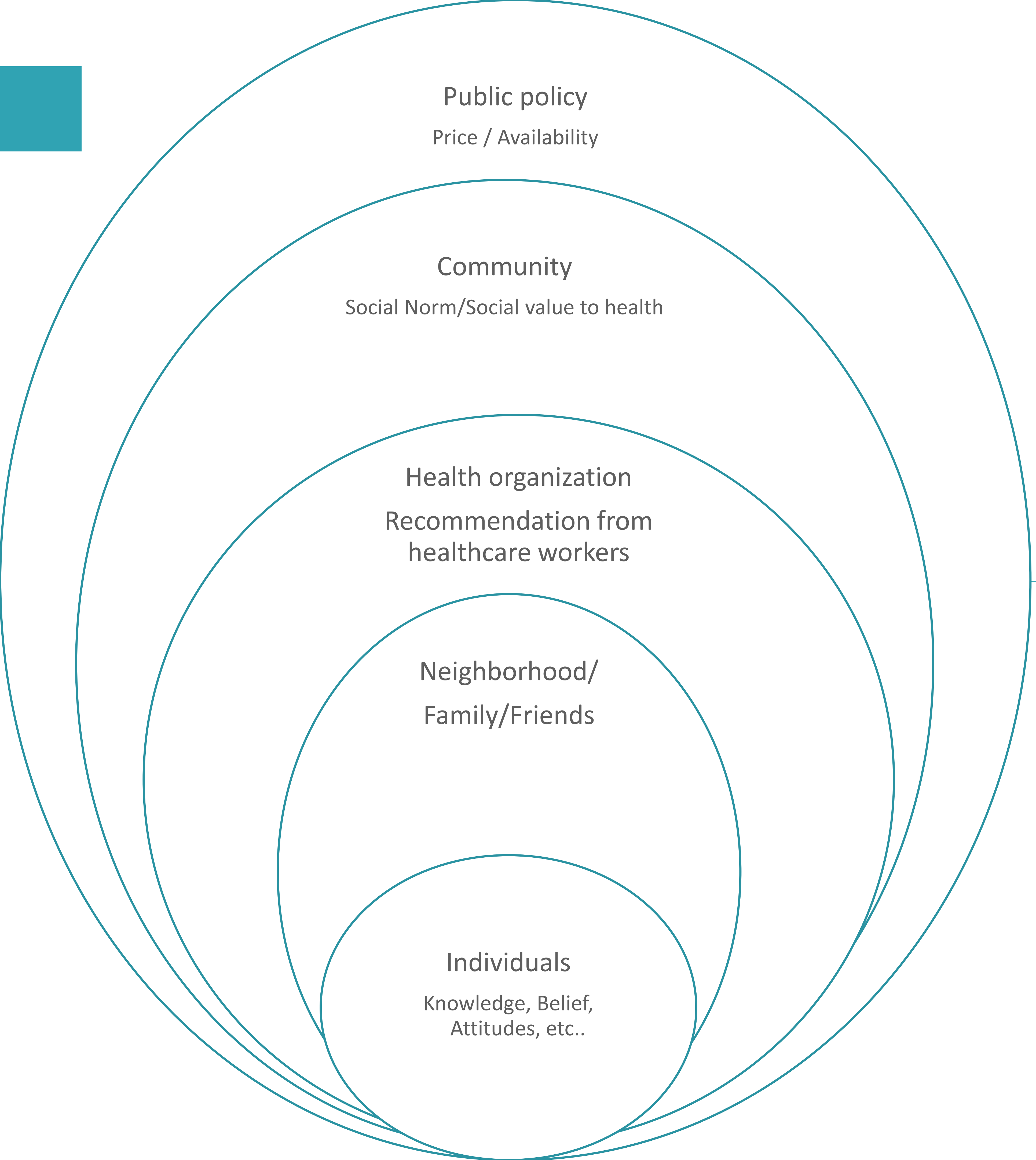
Objective

Examining geographical variation and the factors of infant immunization coverage in Japan.

Background

1． Multiscale disparities of vaccination coverage

- Low vaccination coverage can contribute to the spread of infectious diseases.
  - The Global Vaccine Action Plan(GVAP) set the goal to reach 90% national vaccination coverage and 80% vaccination coverage in every district or equivalent administrative unit with DTP three doses.
- Many existing studies presented spatially heterogeneous vaccination rate.
  - Ex) Figueiredo et al. (2016） :Global scale , Mosser et al. (2019) : African Continental with administrative data, Holipah et al. (2020） : National- subnational- local government levels in Indonesia, Delameter et al. (2018） :State – school ward levels in California states, the U.S. .
- However, There were few studies or governmental statistics estimating child vaccination coverage in multi-geographical levels.
  - Most Japanese studies have focused on individual levels. The government have ceased publishing vaccine rates of each administrative units since 2015, except for MR(Measles-Rubella) vaccines rate.



2. What makes disparities? ≒ What prevents people from vaccines ?

- Vaccine Refusal ： Very few deny all vaccines.
- Vaccine Hesitancy: Some delay , others fail to complete all vaccines.
  - This is a major problem at the global scale.

  ← Hesitancy model(Dube et al. 2018）。

3. Previous studies suggested the association the coverage and…

- **Compositional effects** ： When inter-group (or inter-context) differences in an outcome are attributable to differences in group composition(Roux 2002).
  - In this study ：Income（Sakai et al. 2015）, Mother age（大澤他 2019）, single-parents（Sugishita et al. 2019）、mother working (double- income)（Ueda et al. 2014）, nationality （磯野他 2004）, using nursery or not/other （根路銘他:2006）, parental knowledge（Saitoh et al. 2013）, social migrations （Sugishita et al. 2019）、Birth order （Matsumura et al. 2005）, etc…
- **Contextual effects**：”when group differences are attributable to the effects of GROUP LEVEL VARIABLES or properties” (Roux 2002)
  - In this study ：local pediatrics （江原 2015）, 接種体制（杉下他 2012), city/ rural （Yahata et al. 2007）, public information （羽田・大日 2010）, etc …

4． Research in context

- Most existing studies in Japan focused on individual level.
- Local vaccine coverage estimates are also needed to apply to public policy.
  - Municipalities are essential units of vaccination policy in Japan.
- This ecological study examines how much / whether factors which have investigated in existing study on individual level have significant association with regional vaccination coverage.

Methods

1. Dependent variables

- 2013 and 2014 : Governmental Statistics were used.
- 2015-2018: number of target population were not collected/ published.
- Estimates of target population.
  - Ex) HBV1st , Hib1st and PCV1st doses : 2mth old
  - 2017 estimated target population for 2mth : (N of born in 2017) * 11/12 + (N in 2018)*1/12
  - For 12mth – 24mth child vaccines : target population of MR vaccines were used as proxy number.
- Mean immunization rate from 2013 to 2018 were calculated on every municipalities.
  - To control year variation(error).
- An analysis on each dose included about 1700 municipalities having less than 2 years missing coverage rate and below Std. dev <4 (Grubbs test for outlier, n = 1500).

2. Independent variables

Individual factors （Compositional effects）

- Number of children per household
- single-parent rate
- mother working rate
- Mean of mother age
- Nursery children's rate (by population of 0 ~6 years old)
- child health checkup rate(as a proxy variable of trust in health sector)
- Social migration rates
- Birth rate of foreigners
- Per capita income (Logarithmic transformation)

Environmental factors (Contextual effects)

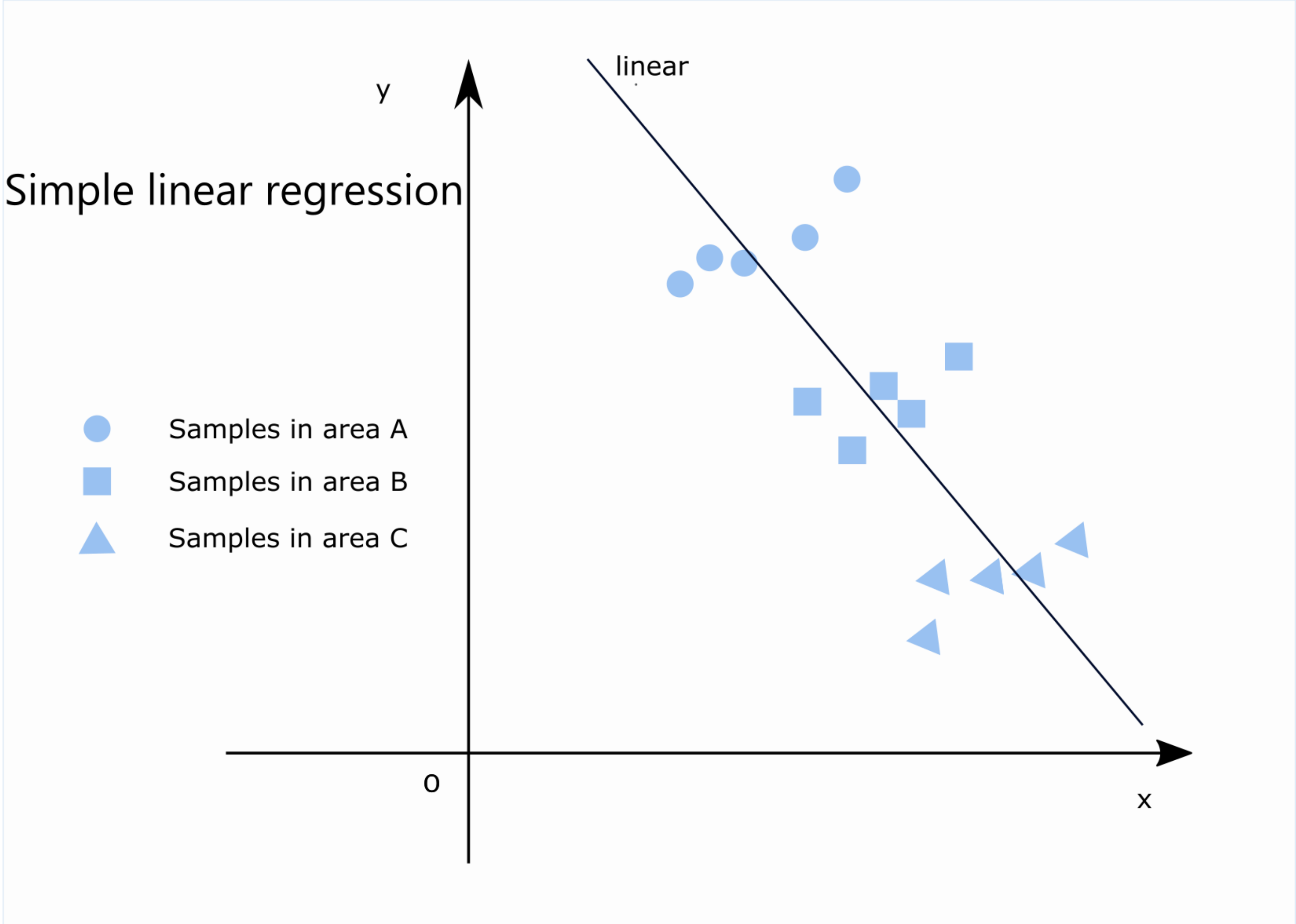
- There is more than one pediatrics doctors(Y/N binomial)
- Mass vaccination was conducted in 2018(Y/N binomial)
- Percentage of public health workers in local staffs （as a proxy variable of adequacy to public information)
- City or county(City = 1, county = 0)

All variables were from Japanese Government Statistics

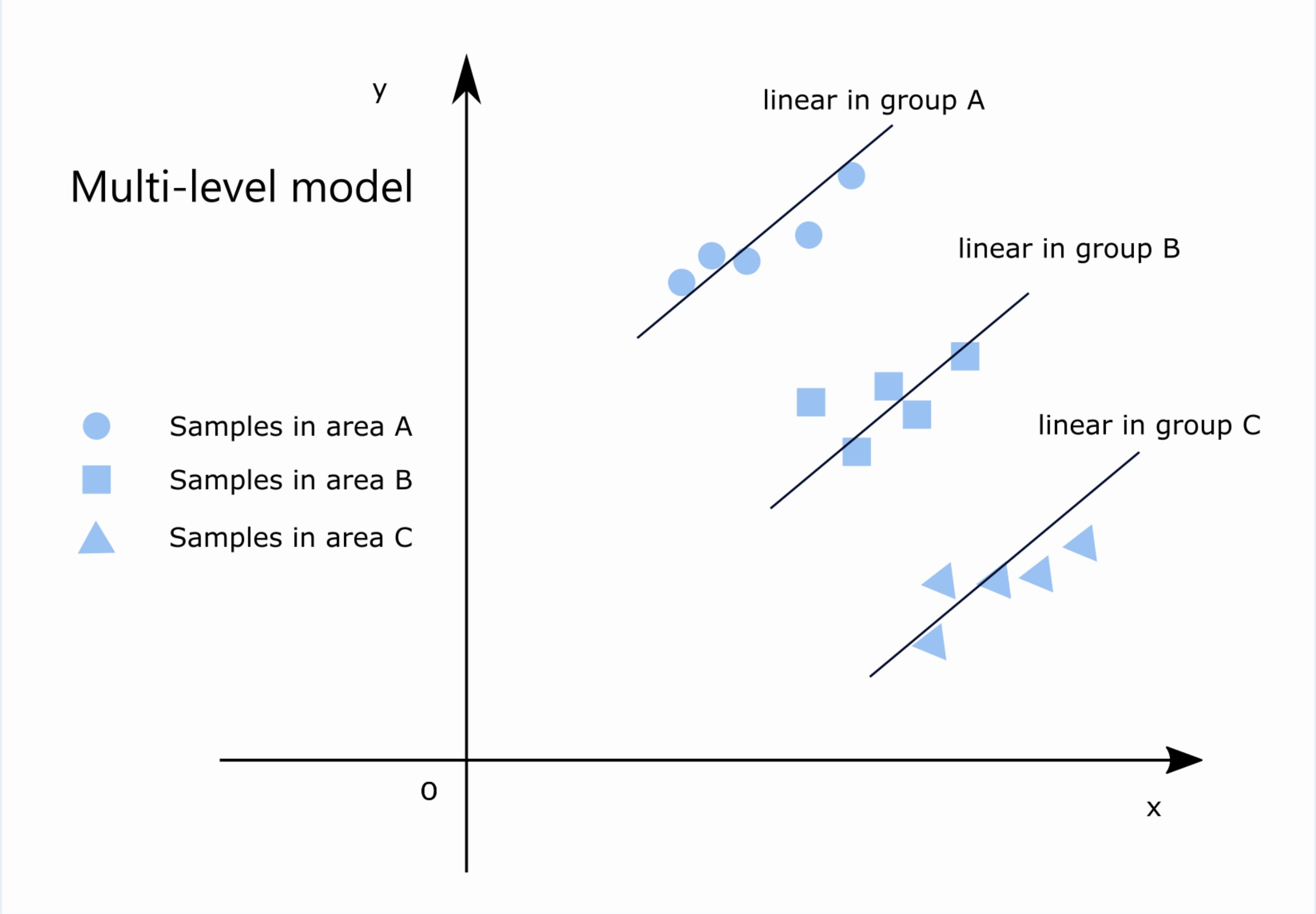
- National census, Annual Report on Health and Welfare, Report of Vital Statistics, Statistics of Physicians, Dentists and Pharmacists, Survey of Social Welfare Institutions.

3. Multivariate (+ multilevel) analyses

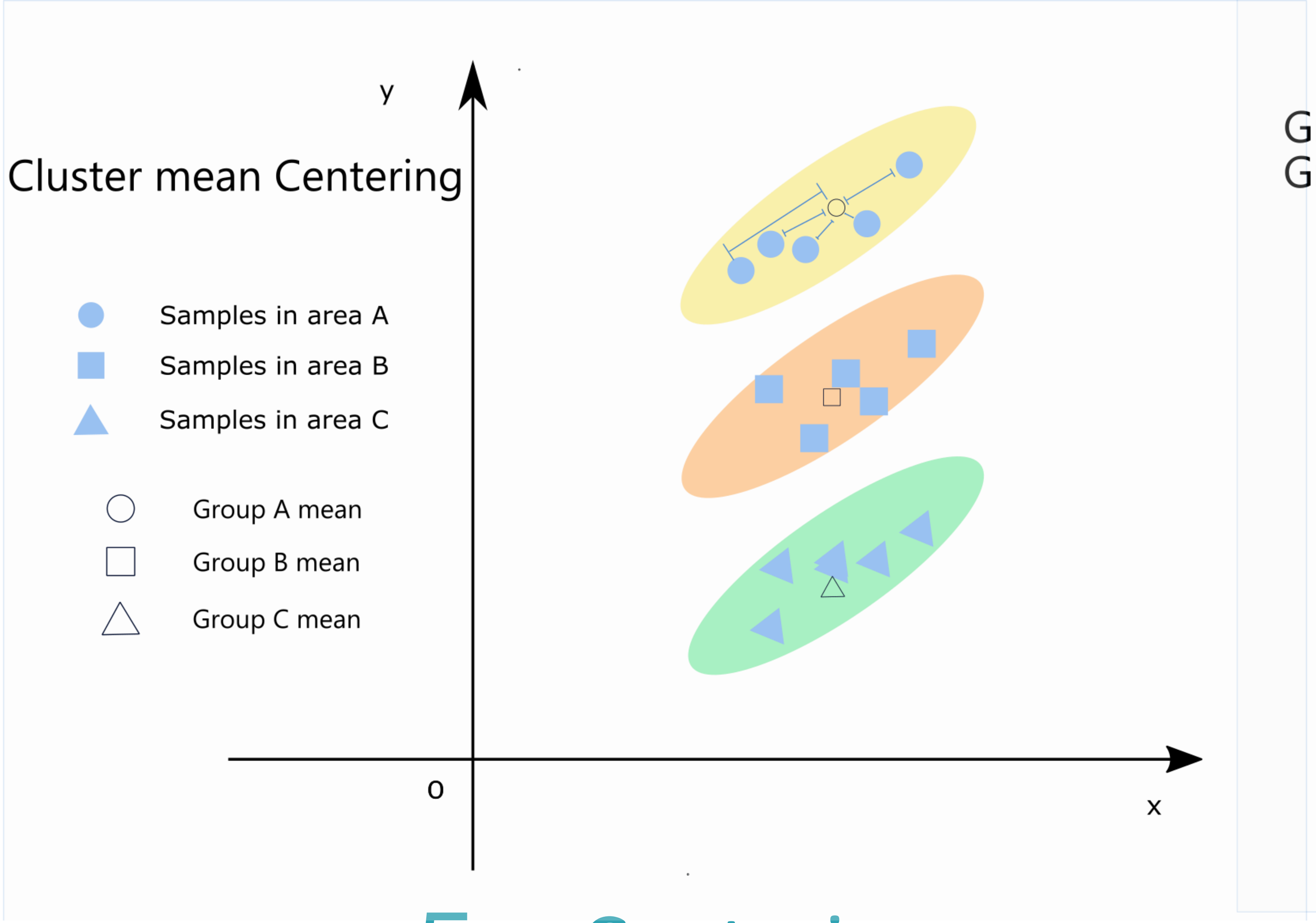
- Model 1 : multivariate regression analysis with all independent variables.
- Model 2 : AIC stepwise method applied Model 1.
  - Cut-off point : P <0.05
- Model 3 : random intercept , no independent variables (null model)
  - If ICC showed <0.05 or Design Effect (DE) showed less than 2, we no hierarcal data
- Model 4 : random intercept, fixed coefficients model (multi-level model)
  - Cut-off point : P <0.05

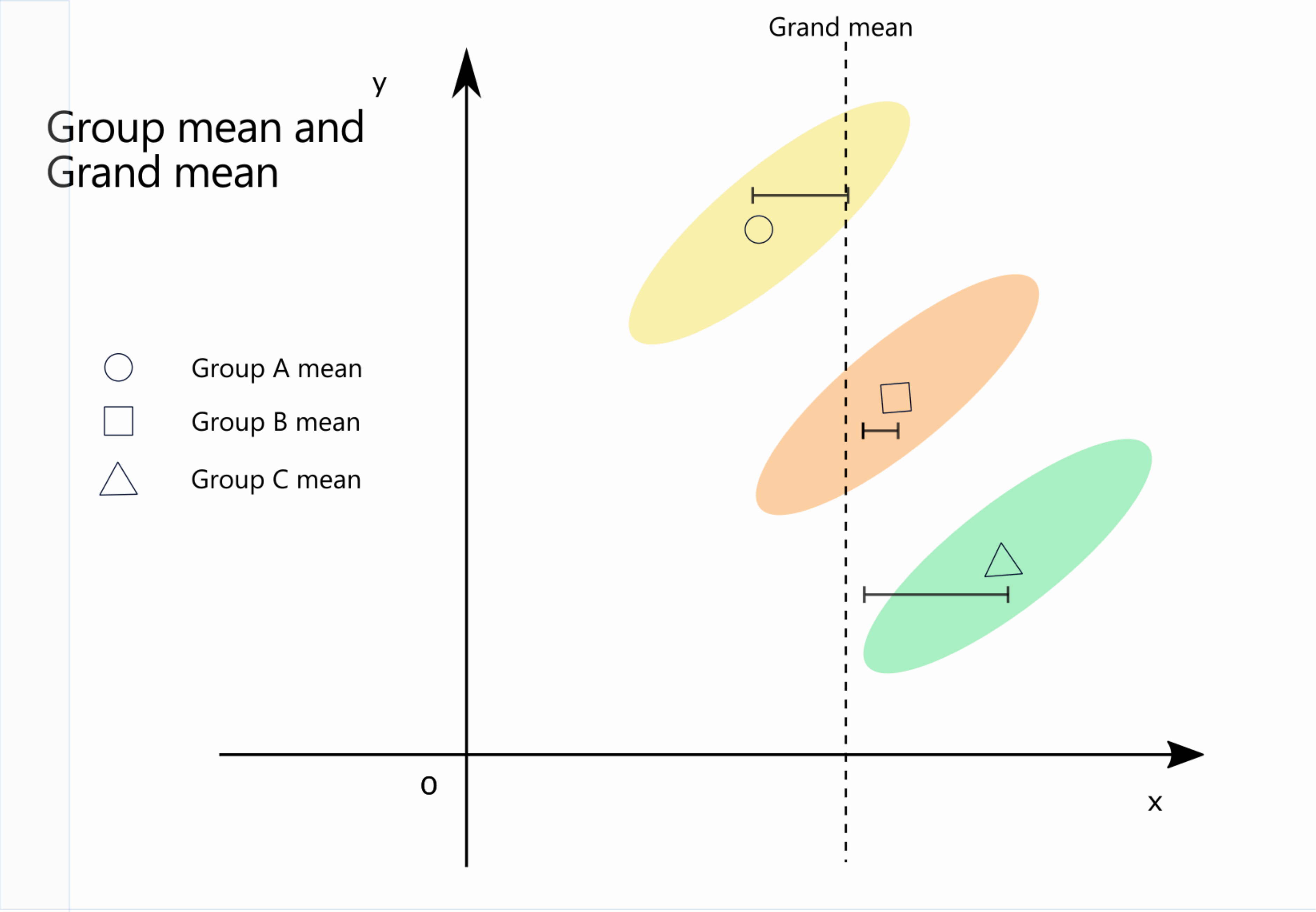


4. Importance of multi-level model analyses



- Prefectures include municipalities.
  - When samples nested in the same category, they have same characteristics (clustered).
- Model 3 and 4 set municipalities as level 1 and prefectures as level 2.
  - Many studies apply multi-level model between individuals and subnational(environmental) groups.





5． Centering

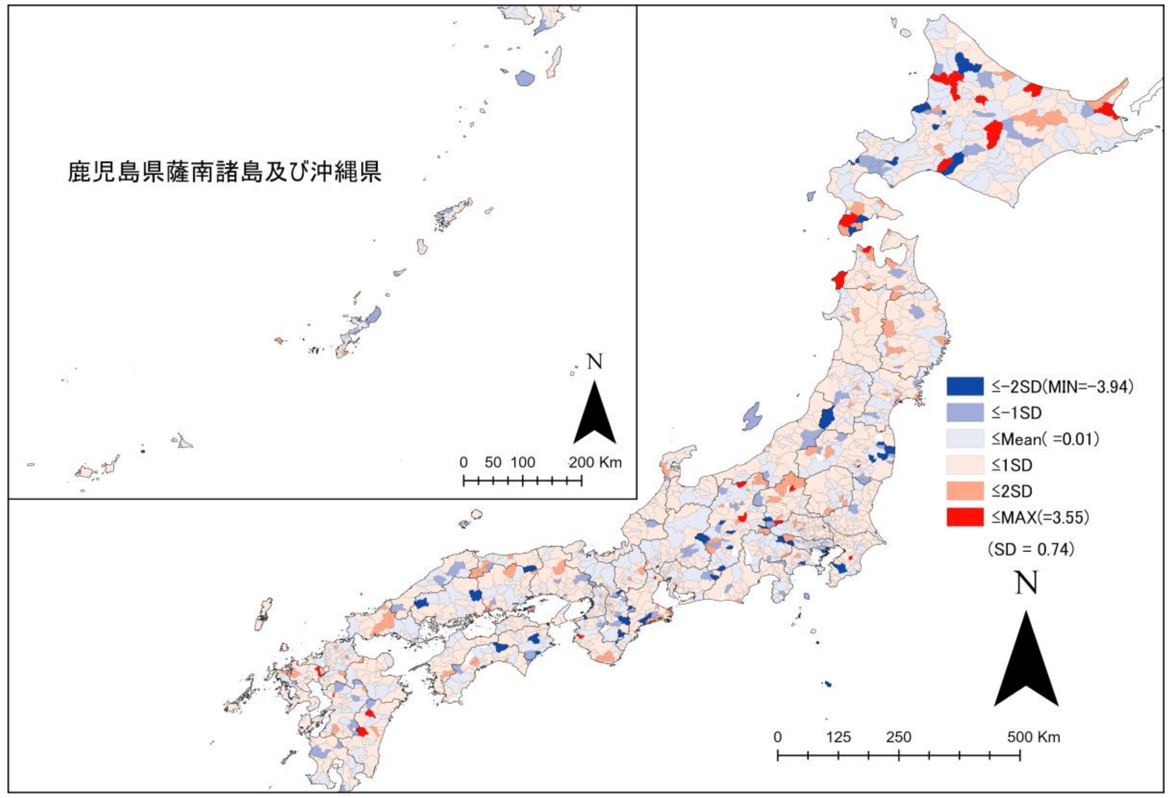
- (←) Level 1 (municipalities level): Centering within cluster(CWC)

  To compare municipalities without group effects.

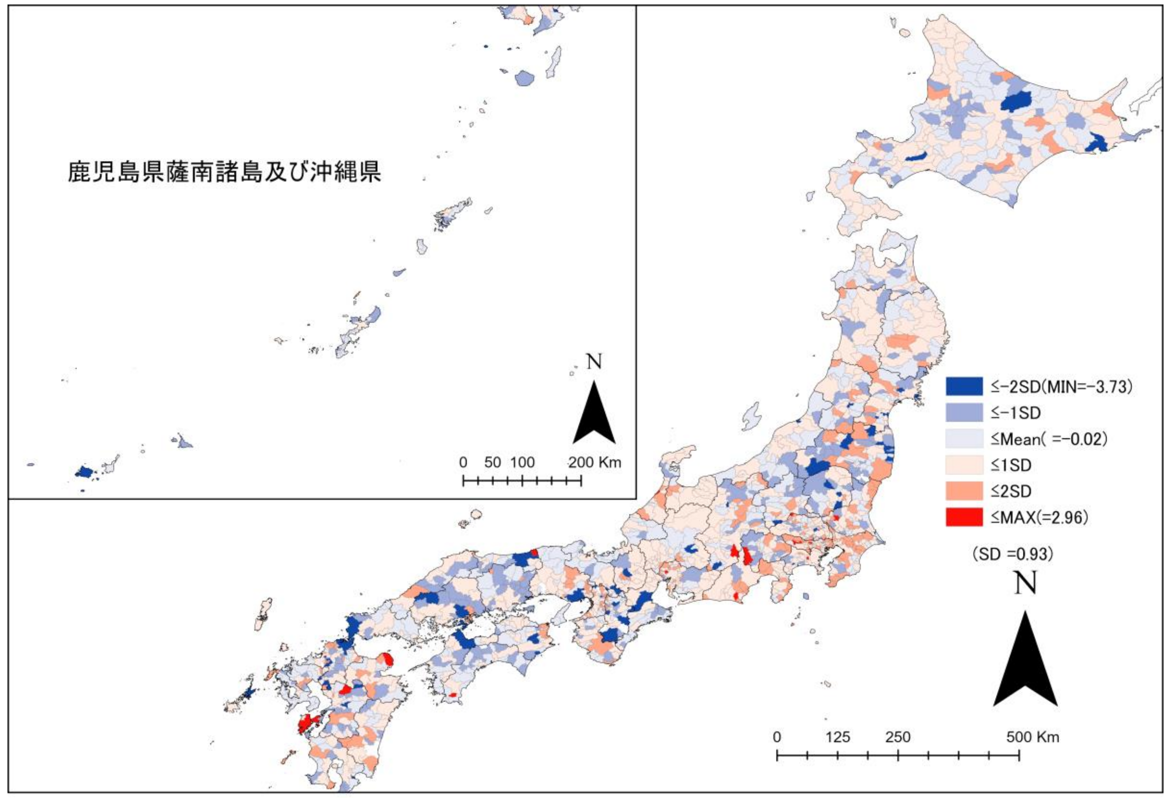
- (→) Level 2 (Prefecture level): Comparison of prefecture mean.

Results

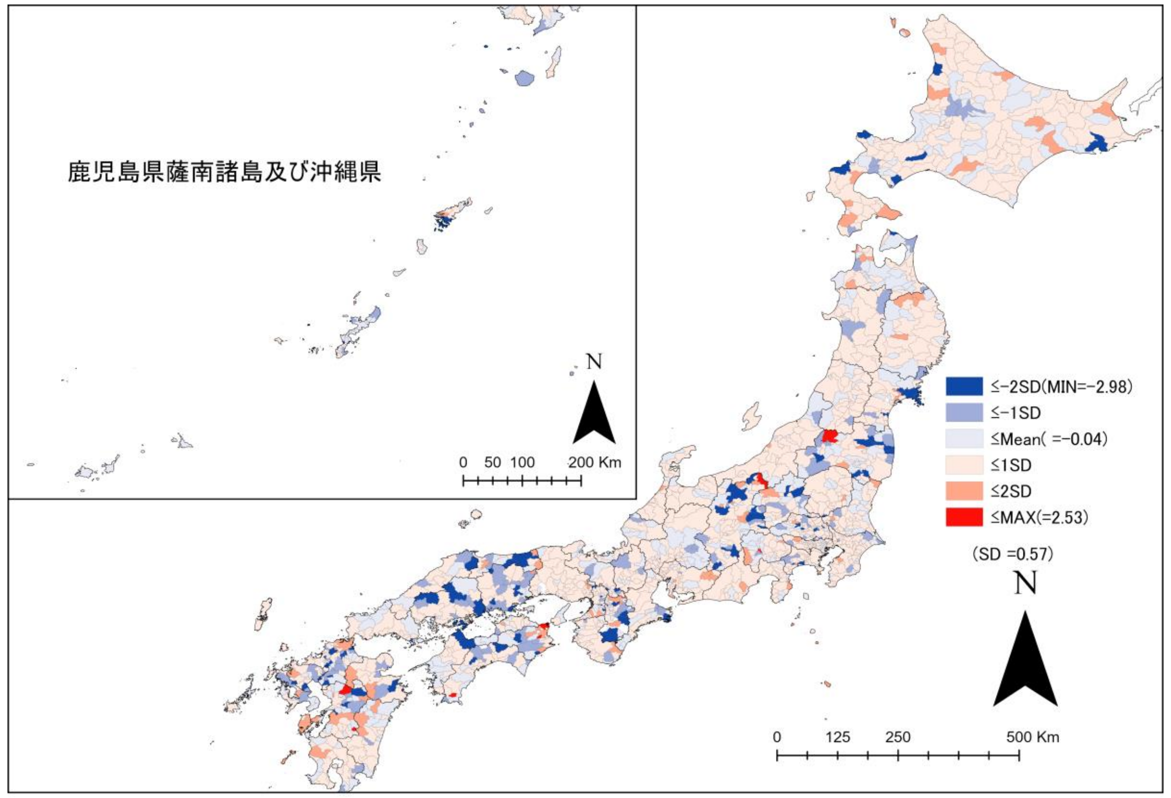
1. Geographical distribution of coverage rates (standardized)



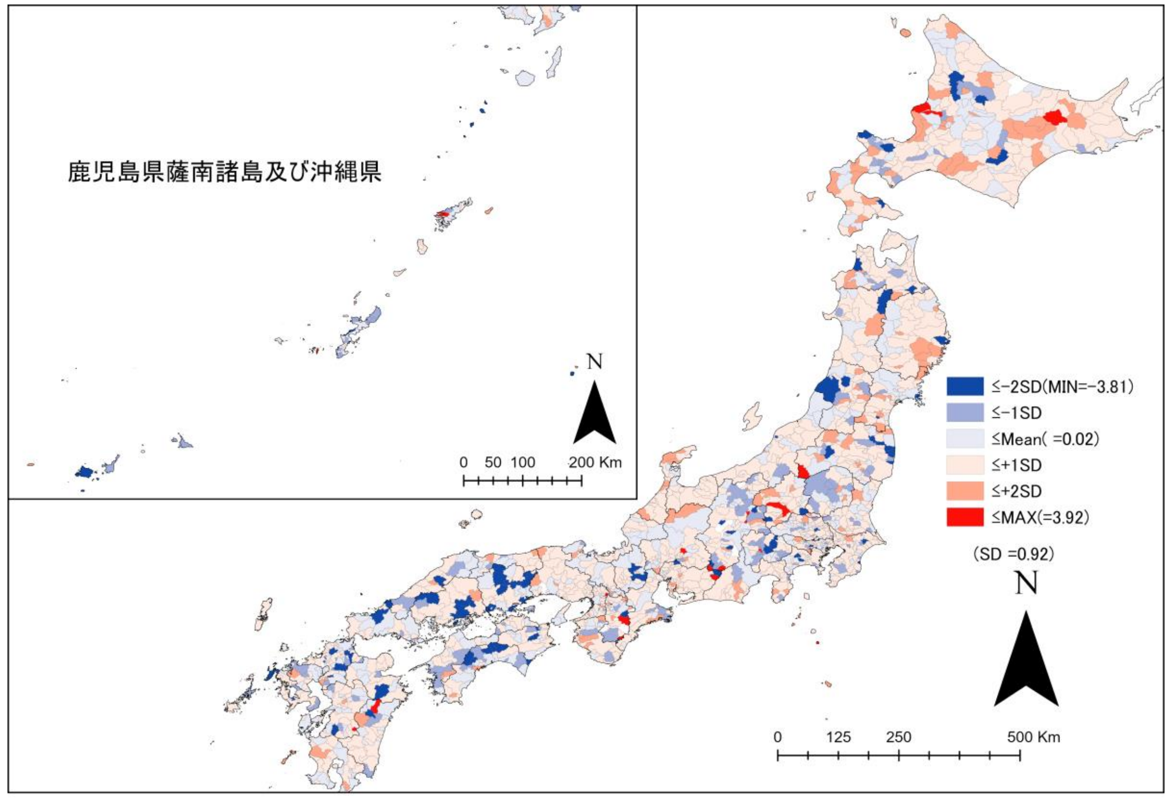
HBV1（Hepatitis B 1st dose，2mth old）



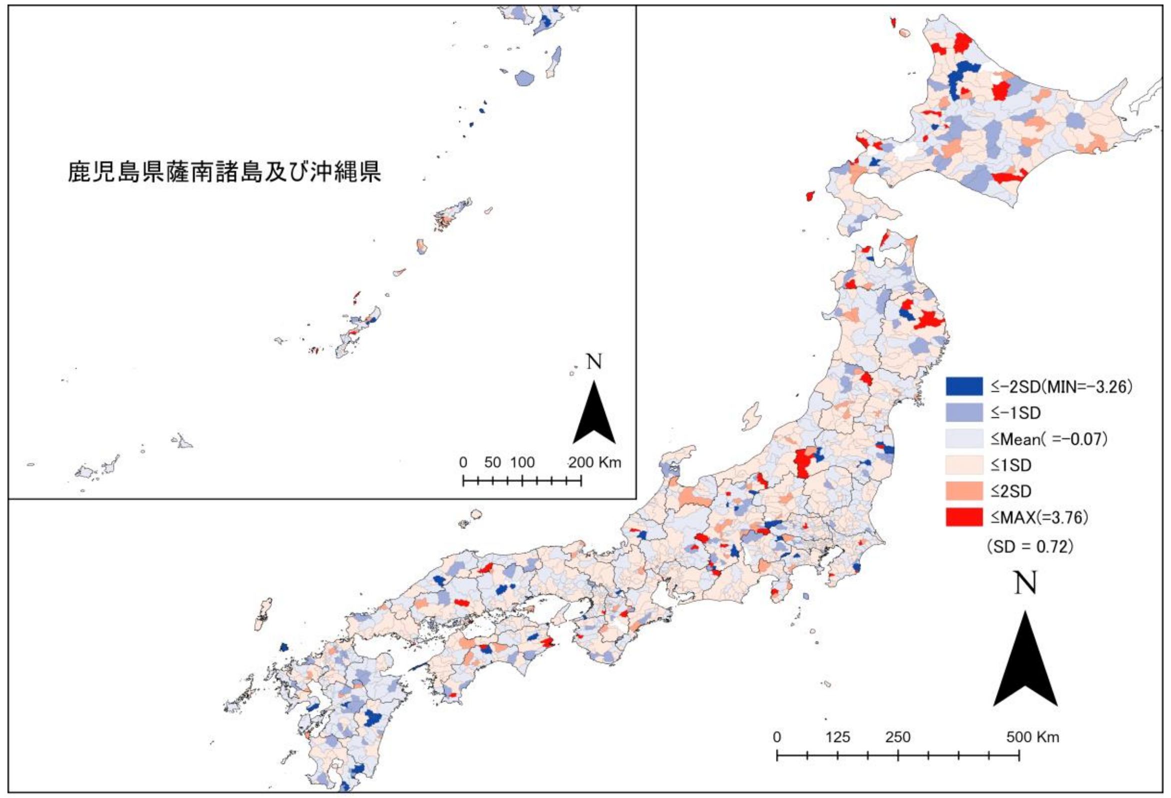
PCV1（Pneumonia 1st，2mth old）



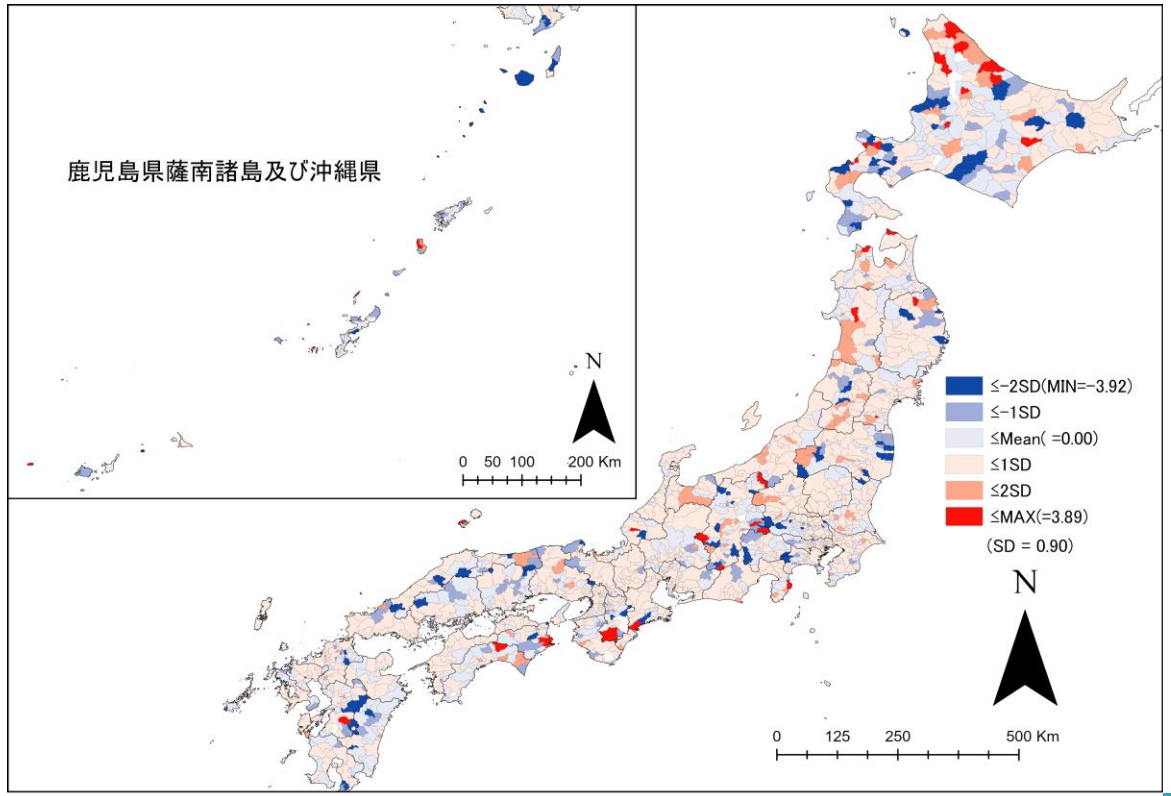
DPT-IPV1（diphtheria, pertussis, tetanus &polio 1st, 3mth old）



BCG（ Tuberculosis, 5mth old）

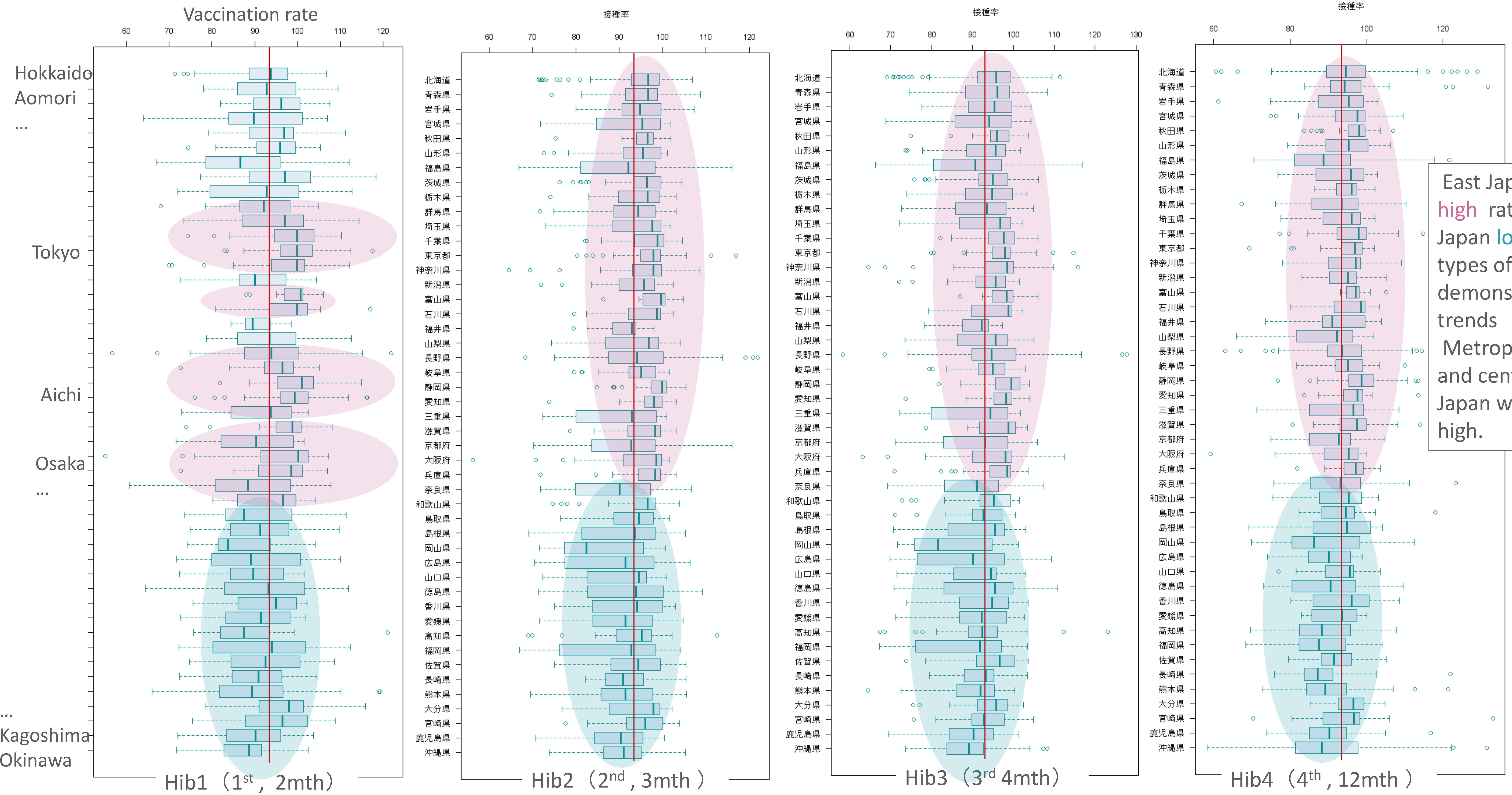


VAR1（varicella 1st，12mth old）



MR（Measles and Rubella, 12mth old）

2. Box plot of rates by prefectures (Haemophilus influenzae type b 1^{st} ~4^{th})
*Red lines denote mean rate



East Japan showed high rate and West Japan low. Other types of vaccines demonstrated same trends

Metropolitan areas and central-north Japan were relatively high.

3. Coefficients of multivariate regression analysis (model2)

モデル2

	Tuberculosis	diphtheria, pertussis, tetanus, and polio				Hepatitis B			Haemophilus influenzae type b				Measles & Rubella	Pneumonia				varicella	
変数名（単位）	BCG	DPT-IPV1	DPT-IPV2	DPT-IPV3	DPT-IPV4	HBV1	HBV2	HBV3	Hib1	Hib2	Hib3	Hib4	MR	PCV1	PCV2	PCV3	PCV4	VAR1	VAR2
Individual factors																			
Mother year avg (yrs old)		-0.63**			0.56*	-0.80***	-0.49*		-0.47 †				-0.58***	-0.66*				-0.52*	1.40***
N of children per family		-12.04***	-5.40	-6.29 †		-4.81 †	-7.49*	-9.69*		-6.07	-6.36	-14.34***	-11.35***	-7.77	-7.58*	-8.70*	-17.09***	-12.77***	
single-parent rate(%)	-0.25**	-0.22*	-0.18	-0.32**				-0.60***	-0.28*	-0.38***	-0.40***	-0.19	-0.24***	-0.33**	-0.35***	-0.35**	-0.18	-0.35***	-0.86***
Mother&father working rate(%)		0.06**				0.05***	0.06***											-0.07***	-0.13***
Nursery children's rate(%)	0.12***	0.06*	0.07*	0.06*	0.29***	0.05*	0.05*	0.11**			0.05	0.26***	0.20***				0.28***	0.21***	0.49***
child health checkup rate(%)									0.38*			0.35*		0.32					0.33
Social migration rate(%)																			-0.02**
foreigners birth rate (%)	-0.51				-0.98*				0.73					1.04*					-1.36*
Per capita income (logx)	2.49*	6.74***	3.47**	3.89**	5.30**		2.40		8.75***	5.81***	7.69***	4.97**	3.46***	8.7***	6.99***	7.74***	5.81***		
Environmental factors																			
Pediatrics(Y/N)		0.80							1.57**				0.90**	1.51**				-0.94*	-2.56***
Mass vaccination(Y/N)					0.14		0.10					0.16*	0.10					0.13 †	0.24 †
Health workers rate(%)	2.24***			0.72	1.31*	-0.93*							1.00**			0.87			2.65**
City/County(binominal)		-0.94 †			-1.89***	1.54***	0.99**	1.74**	0.92				0.96**	1.10			-0.86		

注：† p<0.1, * p<0.05, ** p<0.01, ***p<0.001

- P value less than 0.05 was considered statistically significant.
- Dark gray background color denotes no hierarchal data. We did not apply multilevel model to these 4 doses.
- AIC stepwise method selected average number of children per household, single-parent rate, health check rate, and per capita income on most analyses.

4. Fixed effect(coefficients) of multi-level model analysis(model 4)

レベル1（CWC）

変数名（単位）	BCG	DPT-IPV1	DPT-IPV2	DPT-IPV3	DPT-IPV4	HBV1	HBV2	HBV3	Hib1	Hib2	Hib3	Hib4	MR	PCV1	PCV2	PCV3	PCV4	VAR1	VAR2
Individual factors																			
Mother year avg (yrs old)		-0.71**				-0.44*			-0.82**					-0.93**					1.10**
N of children per family		-4.99	0.73	0.07		-1.58		0.23		4.59	4.54	-7.66 †		3.35	2.27	2.11	-10.73		
single-parent rate(%)	-0.09	-0.13	-0.03	-0.16				-0.60***	-0.12	-0.24 †	-0.21 †	-0.06		-0.14	-0.22 †	-0.19			-0.68***
Mother&father working rate(%)		0.04				0.06**													-0.08*
Nursery children's rate(%)	0.08**	0.07*	0.07*	0.07*		0.04		0.12**			0.06	0.23**					0.22**		0.36***
child health checkup rate(%)									0.15			0.37*		0.14					0.10
Social migration rate(%)																			-0.02**
foreigners birth rate (%)	0.29								1.34**					1.74***					-0.66
Per capita income (logx)	1.89	5.30**	3.59*	4.07*					3.99 †	4.76*	7.10***	5.34**		4.86*	5.71**	7.48***	5.67**		
Environmental factors																			
Pediatrics(Y/N)		0.58							1.34*					1.37*					-2.80***
Mass vaccination(Y/N)												0.11							0.16
Health workers rate(%)	1.96***			0.16		-0.81 †										0.22			2.25**
City/County(binominal)		-0.65				1.75***		2.00***	0.91					1.27*			-0.55		

注：† p<0.1, * p<0.05, ** p<0.01, ***p<0.001, CWC =集団平均中心化。

- Level 1 (Municipalities level). P value less than 0.05 was considered statistically significant.
- Per capita income and child health checkup rate widely had association with coverage rates.
- Other independent variables were not significant.

4. Fixed effect(coefficients) of multi-level model analysis(model 4)

レベル2（Mdev）	BCG	DPT-IPV1	DPT-IPV2	DPT-IPV3	DPT-IPV4	HBV1	HBV2	HBV3	Hib1	Hib2	Hib3	Hib4	MR	PCV1	PCV2	PCV3	PCV4	VAR1	VAR2
Individual factors																			
Mother year avg (yrs old)		0.01				-2.63***			1.42					0.99					2.57
N of children per family		-31.55*	-19.32	-22.03 †		-16.29*		-32.67*		-37.60*	-36.16*	-27.16 †		-39.07*	-35.13*	-40.45**	-22.34 †		
single-parent rate(%)	0.83**	-0.11	-0.54	-0.74 †				-0.33	-0.56	-0.39	-0.55	-0.53		-0.14	-0.43	-0.52	-0.70		-1.27
Mother&father working rate(%)		0.11				0.02													-0.20 †
Nursery children's rate(%)	.15*	0.05	0.03	0.01		0.10 †		0.09			0.01	0.25					0.31		0.87 †
child health checkup rate(%)									1.02			0.15		1.00					0.17
Social migration rate(%)																			-0.02
foreigners birth rate (%)	4.78**								-2.54					-1.28					-2.64
Per capita income (logx)	.71	4.18	0.77	-0.55					5.64	2.25	4.27	3.99		-0.31	3.97	1.85	3.44		
Environmental factors																			
Pediatrics(Y/N)		2.50							3.10					1.88					-0.11
Mass vaccination(Y/N)												0.33							1.18
Health workers rate(%)	.11*			3.21		-1.51										3.53			3.02
City/County(binominal)		0.23				1.93		4.07 †	4.33					6.28			-0.04		

注：† p<0.1, * p<0.05, ** p<0.01, *** p<0.001, Mdev =都道府県平均の偏差化。

- Level 2 (Prefecture level).
- Average number of children per household showed significant negative association.
- Only BCG rate significantly associated with multiple independent variables.
- No independent variables showed significance on several vaccines in level 2.

Discussion, Limitation and Conclusion

1. Discussion: health inequalities and small depopulation areas

- Immunization rates of Metropolitan areas (Tokyo, Osaka and Nagoya) were generally higher than those of national average.
  - High income and small numbers of births in large cities may be informative of high rates.
  - Regional differences may come from multi-level inequalities of social/economic resources to children.
- Relatively large areas of low coverage were identified in West Japan
  - The trend possibly depends on low accessibility.
- There were large residuals in inland areas on residual plots.
  - The spatial distribution was similar to the geographical prevalence trend of depopulated small villages（藤田 2007）.
  - Quite few studies focused on immunization program in small villages. This study probably failed to consider potential factors in independent variables

2. Limitation

1. Estimated vaccination coverage
   - Some administrative units were estimated more than 100%.
   - Small number of births may lead to quite large/ small immunization rate.
2. Missing dataset
   - The government did not collect nor publish some statistics each year. (e.g. Census are conducted every 5 years.)
3. Statistical model variation
   - Some vaccines were not hierarchical structure. Model were likely to be under fitting.
4. Possibility of ecological fallacies

3. Conclusion

- Although immunization rates were generally high, there were geographical disparities in inter-prefectures and in inter-municipalities in Japan.
- Social Inequality are likely to associate with vaccination coverage.
  - This may lead to Health Inequalities.
- It is required to investigate small- size and depopulation municipalities to find potential factors.

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