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Living in an urban environment and non-communicable disease risk in Thailand: Does timing matter?

Background: This paper uses a life-course approach to explore whether the timing and/or duration of urban (vs rural) exposure was associated with risk factors for NCDs.

Methods: A cross-sectional survey was conducted among health care workers in two hospitals in Thailand. Two measures of urbanicity were considered: early-life urban exposure and the proportion of urban life years. We explored four behavioural NCD risk factors, two physiological risk factors and four biological risk factors.

Results: Both measures of urbanicity were each independently associated with increases in all behavioral and physiological risk factors. For some biological risk factors, people spending their early life in an urban area may be more susceptible to the effect of increasing proportion of urban life years than those growing up in rural areas.

Conclusion: Urbanicity was associated with increases in behavioral and physiological risk factors. However, these associations may not translate directly into increases in biological risk factors. It is likely that these biological risk factors were results of a complex interaction between both long term accumulation of exposure and early life exposures.

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Introduction

Thailand, like many countries in Southeast Asia and developing regions, faces a growing burden of non-communicable diseases (NCDs) (Dans et al., 2011, Abegunde et al., 2007). One of the main drivers of non-communicable disease is urbanization. Urbanization is thought to be associated with a range of socio-economic, cultural and environmental changes which may contribute to the development of NCDs (World Health Organization, 2005).

Most research on the link between urbanization and risk factor for NCDs unfortunately does not offer insight into the mechanisms driving the associations (Harpham, 2009). In recent decades, a life course approach to chronic disease epidemiology (Lynch and Smith, 2005) has been suggested as a way forward in the understanding of urbanization and health (Kinra, 2004). A life course approach considers the effect of an exposure (such as urbanization) during different periods of life (from gestation to adult life) on later health-related risks and outcomes. Two main conceptual life-course models exist (Ben-Shlomo and Kuh, 2002). The first is the critical period or sensitive period model. This model emphasizes the importance of the timing of the exposure. It is based on theories that there may be a limited period in which an exposure may effect structural or functional development (the critical period model) or that there is a time period when an effect of an exposure may be stronger than other time periods (the sensitive period model). An example of a critical/sensitive period model is the association between intrauterine growth retardation (IUGR) and low birth weight with many chronic diseases such as coronary heart disease and diabetes (Darnton-Hill et al., 2004). Urbanization is associated with IUGR and low birth weight through many mediating factors such as maternal nutritional status and smoking (Ohmi et al., 2001, Kramer, 1987). The second main conceptual life course model is the accumulation of risks model. This model emphasizes the importance of cumulative exposure over time. An example of an accumulation model is where the risk of obesity and diabetes rises with the time spent in urban environments (Sobngwi et al., 2004).

Evidence from life course models can help identify targets for, and timing of, public health interventions. Evidence for critical/sensitive period models would favour interventions during these critical time frames; interventions at others times would be less effective. Evidence for accumulative models would suggest that interventions across the lifespan would be effective (Liu et al., 2010).

In Thailand, recent studies have explored the associations between urbanization and risk factors for NCDs. These studies suggest that urban residence was associated with obesity and high blood pressure, but they did not use a life course approach (Lim et al., 2009, Banwell et al., 2009). Two life-course studies were conducted in a cohort of Thai university students (Sleigh et al., 2008). Using urban residence at two or three different points in time, the studies found that people who had spent more time in an urban area had higher prevalences of smoking, alcohol consumption, obesity (BMI≥25) and a higher incidence of self-reported medical diagnosis of hypertension and dyslipidemia than those spending more time in a rural area (Yiengprugsawan et al., 2011, Zhao et al., 2014). However, the authors did not explicitly differentiate between life-course models and did not have actual measurements for blood pressure and laboratory investigations.

This paper utilized survey data from the Chiang Mai University (CMU) Health Worker Study (Angkurawaranon et al., 2014). The overall aim of the CMU Health Worker Study was to generate evidence on the links, and potential life course mechanisms, between urban environments, NCD risk factors, and development of NCDs. The aim of this paper is to explore the association of urban (vs. rural) residence with risk factors for NCDs in Thailand using two different life course models, the early life critical/sensitive period model and the accumulation of risk model. The study will also explore whether the associations between growing up in urban areas and NCD risk factors are modified by later accumulation of urban exposure.

Methods

Study population

A cross sectional survey of health care workers in two government hospitals in Northern Thailand was conducted between January and June 2013. The first hospital was Chiang Mai University (CMU) Hospital, employing over 5000 workers. The details of the study population, methods, strengths and limitations of the survey conducted in CMU Hospital have been published (Angkurawaranon et al., 2014) . The survey utilized a periodic health check up program offered to health care workers. Questionnaires, interviews, physical and laboratory examinations were used to collect data on detailed migration history from birth to current age and information on behavioral, physiological and biological risk factors for NCDs. Using a similar protocol, the survey was extended to a rural hospital in Fang District. The leading investigators of the study trained researchers at both sites to use standard measurement protocols.

Measurements and variable definitions

Urban exposure

The classification of urban areas in Thailand is defined using government administrative criteria largely driven by population density. In 1970, only three areas were considered 'cities': Bangkok, Thonburi (a suburb of Bangkok) and Chiang Mai (Goldstein and Goldstein, 1978). For our study, all districts in Bangkok and the ten districts in Chiang Mai Metropolitan Area, consisting of Muang (Chiang Mai Province), Sarapi, Sanpatong, Hang Dong, Mae Rim, Sansai, Doi Saket, Mae On, Sang Kampang, Muang (Lumphun Province), were considered urban. The remaining districts in Thailand, such as Fang, were classified as rural. By tracking the location (district) of residence during each participant's life, two exposures related to living in an urban environment were defined:

(i) Early life urban exposure was defined by using the main location (district) of residence while participants were aged between 0-5 years. This variable was used to represent the early life critical/sensitive period model (Kuh et al., 2003)

(ii) The proportion of urban life years was calculated as total years of urban exposure divided by current age, expressed as a percentage. This was used to represent the accumulation of risk model (Kuh et al., 2003). Small differences in the proportion of urban life years were unlikely to produce notable differences in levels of risk factors for NCDs, thus the variable 'proportion of urban life years' was classified into four categories: <25%, 25-50%, 50-75%, >75%.

Risk factors for NCDs

Using the World Health Organization's framework (World Health Organization), the risk factors for NCDs were classified into three categories: behavioral , physiological and biological . This classification reflects assumed causal pathways between urbanization and development of NCDs. Behavioral risk factors were considered as more distal, physiological risk factors as intermediate and biological risk factors as more proximal towards the development of NCDs (World Health Organization, 2005).

Behavioral Risk factors for NCDs were obtained using questionnaires derived from the WHO STEPS instrument (World Health Organization). The four behavioral risk factors consisted of current smoking, heavy alcohol consumption, inadequate fruit and vegetable intake, and inadequate physical activity. Information on

behavioral risk factors was obtained through interviews at CMU Hospital and through self-answered questionnaires at Fang Hospital. Literature has suggested that for behavioral factors such as alcohol and physical activity, the two methods of administration can provide similar results (Bongers and Van Oers, 1998, Craig et al., 2003) . Both smoking and tobacco chewing were considered as 'current smoking'. More than five standard drinks per sitting in men and more than four standard drinks per sitting in women were cutoff points for heavy alcohol consumption. Less than 35 units standard units of fruit and/or vegetable consumption per week was the cutoff point for inadequate fruit and vegetable intake. Less than 75 minutes of vigorous-intensity physical activity, 150 minutes of moderate-intensity physical activity, or an equivalent of 600 metabolic equivalent (MET) minutes per week were the cutoff points for inadequate physical activity.

Physiological risk factors for NCDs consisted of raised blood pressure and raised body mass index.
Three blood pressure readings were taken five minutes apart. The average of the second and third blood pressure reading was used as the blood pressure for each participant. Blood pressure readings were taken using digital sphygmomanometers in Chiang Mai University hospital and by manual mercury sphygmomanometers in Fang Hospital. A portable stadiometer and an electronic scale were used to measure standing height and body weight. Body mass index was calculated using weight (in kg) divided by height (in meters) squared.

Biological risk factors for NCDs were derived from participants' blood samples. They consisted of blood glucose level, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride (TG) levels. All participants were asked to fast at least eight hours before examination. All blood samples were handled at their respective hospitals' laboratory. Since both sites are government hospitals, they undergo the same external validation process from the Ministry of Public Health. Furthermore, 100 random samples from Fang Hospital were processed at Chiang Mai University hospital to assess agreement.

Analysis plan

Descriptive statistics were used to describe the socio-demographic patterns and urban exposure status for the study participants. Early life urban exposure and the proportion of urban life years, representing the two different life course models, were considered the main exposures of interest. Each exposure was modeled separately using logistic regression or linear regression depending on the outcome of interest. The proportion of urban life years was tested for general association, linear trend and departure from linearity.

Current age and sex were considered *a priori* confounders. We did not adjust for other variables such as income and education because we considered this might lead to over adjustment for mediating factors in the pathways between urbanization and risk factors for NCDs.

To account for the temporal ordering between the two exposure variables, the data were stratified by early life urban exposure and analyses conducted separately on each group. To formally test whether the associations differed by early life urban exposure, multivariable regression was used by modeling both exposure variables together along with their interaction term.

Sensitivity analyses:

We tested for interactions by sex as there was evidence that gender may modify associations between urbanicity and NCD risk factors, such as BMI and blood pressure (Kinra et al., 2011, Sovio et al., 2013). To explore potential non-differential information bias due to different methods of data collection and different blood pressure instruments used between the two sites, a sensitivity analysis was done using data from only the CMU hospital (larger sample size). Results from this restricted analysis were reported only if they yielded materially different conclusions from the original results. Bland-Altman plots (Bland and Altman, 1986) were used to assess agreement between laboratory measurements on one hundred blood samples chosen at random from Fang Hospital, which were also processed at Chiang Mai University Hospital.

Ethics

Informed consent was obtained from all participants. The study was approved by a institutional review board from Fang Hospital and Chiang Mai University (No 069/2012) and London School of Hygiene and Tropical Medicine (Ref. 6521).

Results

3,204 healthcare workers from CMU Hospital (58.3% of all eligible workers) and 312 healthcare workers in Fang Hospital (67.8% of all eligible workers) participated in the study. The sample from CMU hospital represented the source population well in terms of age and education level, although females were slightly over-represented. The sample from Fang hospital represented the population well in terms of age, gender and job distribution. Characteristics of responders and non-responders by study site can be found in Appendix 1.

In total, 3,516 participants were included in the study (59.0% of all eligible workers). The mean age of the study population was 39.6 years (sd=10.9), although the sample from CMU Hospital (mean 40.2,sd=10.7) was older than Fang Hospital (mean 33.1 years, sd=10.7). In both sites, the majority (63.7%) had at least a bachelor's degree or equivalent. Almost half (47.6%) spent their early life (between age 0 to 5) in a rural area. The majority from Fang Hospital (83.6%) had spent less than 25% of their lifetime in an urban area while more than half (57.9%) from Chiang Mai University Hospital had spent more than 75% of their life time in an urban area. (Table 1) Early life urban exposure was positively correlated with proportion of urban life years. Those spending their early life in an urban area were more likely to have spent higher proportions of their lives in an urban area than those spending their early life in a rural area (Table 2).

Table 1 Demographic characteristics and urban exposure in study population

	Chiang Mai University (CMU) Hospital	Fang Hospital	Total
Number of participants	3204	312	3,516
Mean age in years (sd)	40.2 (10.7)	33.1(10.7)	39.6 (10.9)
Female: N (%)	2,472 (77.1)	235 (75.3)	2,707 (77.0)
Highest education: N(col %)			
Below Bachelor's degree	1,134 (35.5)	143 (46.0)	1,277 (36.3)
Bachelor's degree/equivalent	1,690 (52.6)	152 (48.9)	1,842 (52.4)
Higher than Bachelor's degree	380 (11.9)	15 (5.1)	396 (11.3)
Monthly household income in baht*: N(col %)			
<20,000	1,196 (37.4)	133 (42.8)	1,329 (37.8)
20,000-40,000	927 (28.9)	106 (34.1)	1,033(29.4)
40,000-60,000	522 (16.3)	40 (12.9)	562 (16.0)
>60,000	559 (17.4)	32 (10.2)	591 (16.8)
Early life exposure (Age 0-5)** N(col %)			
Rural	1,397 (43.7)	272 (87.5)	1,669 (47.6)
Urban	1,797 (56.3)	39 (12.5)	1,836 (52.4)
Proportion of urban life years in percent[#]: N (col %)			
<25%	245 (7.7)	260 (83.6)	505 (14.4)
25-50%	445 (13.9)	20 (6.4)	465 (13.3)
50-75%	656 (20.5)	15 (4.8)	671 (19.1)
>75%	1,847 (57.9)	16 (5.1)	1,863 (53.2)

* 1 US dollar = approximately 32 baht; one missing value from Fang Hospital; ** 11 missing value, 10 from CMU hospital; [#] 12 missing value, 11 from CMU hospital

Table 2 Relationship between Early life urban exposure and Proportion of urban life years

Proportion of urban life years*	Early life Urban exposure (n, column %)	Early Life Rural Exposure (n, column %)	Total (n, column %)
<25%	6, 0.33%	499, 29.9%	505, 14.4%
25-50%	16, 0.87%	449, 26.9%	465, 13.3%
50-75%	41, 2.23%	630, 37.8%	671, 19.1%
>75%	1773, 96.6%	90, 5.4%	1,863, 53.2%
Total	1,836	1,668	3,504

* 12 missing values in proportion of urban life years

When modeling each exposure separately and adjusting for age and sex, both exposures of interest were associated with increases in all four behavioral and both physiological NCD risk factors (Table 3). For biological risk factors, both exposures were associated with increased glucose and LDL cholesterol but there was no evidence for association with HDL. For triglyceride levels, unlike other risk factors for NCDs, an increasing proportion of urban life years was associated with a lower triglyceride level. (Table 4)

Table 3 Association between Early life urban exposure (Age 0-5) and Proportion of urban life years with Behavioral and Physiological Risk factors for NCDs

	Behavioral Risk Factors				Physiological Risk factors	
	Current Smoking	Heavy alcohol drinking	Inadequate physical activity	Inadequate fruit and vegetable intake	BMI (kg/m^2)	Systolic blood pressure## (mmHg)
	Odds Ratio (95% CI) and p-value	Odds Ratio (95% CI) and p-value	Odds Ratio (95% CI) and p-value	Odds Ratio (95% CI) and p-value	Regression coefficient β (95% CI) and p-value	Regression coefficient β (95% CI) and p-value
Early Childhood (0-5) Urban exposure	1.87 (1.32 to 2.64) <0.001	2.35 (1.92 to 2.87) <0.001	1.16 (1.01 to 1.33) 0.034	1.29 (1.06 to 1.56) 0.010	0.69 (0.43 to 0.95) <0.001	2.54 (1.56 to 3.49) <0.001
Proportion of urban life years						
0-25%	Reference	Reference	Reference	Reference	Reference	Reference
25-50%	0.94 (0.48 to 1.86) 0.865	0.82 (0.55 to 1.21) 0.316	1.12 (0.87 to 1.45) 0.362	1.71 (1.19 to 2.45) 0.004	0.20 (-0.28 to 0.68) 0.421	0.23 (-1.86 to 2.32) 0.827
50-75%	0.61 (0.30 to 1.24) 0.171	1.02 (0.69 to 1.51) 0.919	1.10 (0.86 to 1.42) 0.449	1.65 (1.17 to 2.32) 0.004	0.38 (-0.09 to 0.86) 0.116	-1.61 (-3.74 to 0.51) 0.136
75-100%	1.58 (0.97 to 2.57) 0.069	2.12 (1.56 to 2.88) <0.001	1.34 (1.08 to 1.67) 0.007	1.92 (1.42 to 2.59) <0.001	0.90 (0.49 to 1.30) <0.001	1.52 (-0.38 to 3.44) 0.117
Overall p-value	0.003*	<0.001*	<0.003#	<0.001#	<0.001#	<0.001*

Reference group for early childhood urban exposure is early childhood rural exposure; Each exposure is modeled separately adjusting for age and sex; analysis performed separately for each NCD risk factors using logistic regression for behavioral risk factors and linear regression for physiological risk factors; More than five standard drinks per sitting in men and more than four standard drinks per sitting in women were cutoff points for heavy alcohol consumption; Less than 35 units standard units of fruits and/or vegetable consumption per week were the cutoff point for inadequate fruits and vegetable intake. Less than 75 minutes of vigorous-intensity physical activity or 150 minutes of moderate-intensity physical or an equivalent of 600 metabolic equivalent (MET) minutes per week was the cutoff point for inadequate physical activity; * p-overall association, #p-trend; ## data only from Chiang Mai University Hospital (n=3,194)

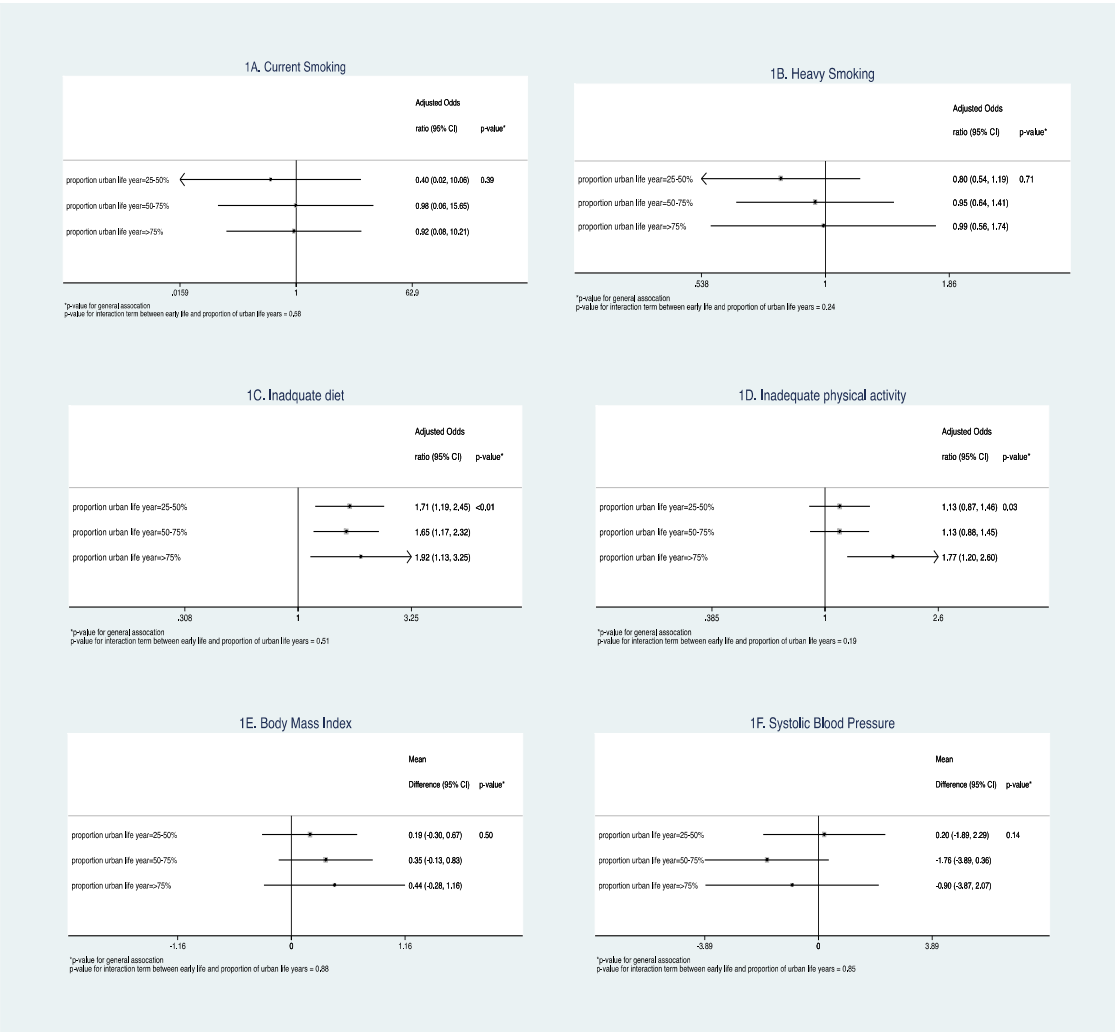
Table 4 Association between Early life urban exposure (Age 0-5) and Proportion of urban life years with Biological Risk factors for NCDs

	Blood glucose (mg/dL)	Low density lipoprotein (LDL) cholesterol (mg/dL)	Triglyceride (mg/dL)	High density lipoprotein (HDL) cholesterol (mg/dL)
	Regression coefficient β (95% CI) and p-value	Regression coefficient β (95% CI) and p-value	Regression coefficient β (95% CI) and p-value	Regression coefficient β (95% CI) and p-value
Early Childhood (0-5) Urban exposure	1.51 (0.41 to 2.61) 0.007	2.17 (-0.25 to 4.59) 0.079	-4.33 (-10.6 to 1.95) 0.176	0.31 (-0.58 to 1.20) 0.493
Proportion of urban life years in percent				
0-25%	Reference	Reference	Reference	Reference
25-50%	4.12 (2.10 to 6.14) <0.001	6.12 (1.66 to 10.5) 0.007	-4.75 (-16.3 to 6.83) 0.421	-0.07 (-1.70 to 1.57) 0.936
50-75%	3.56 (1.56 to 5.57) <0.001	7.10 (2.68 to 11.5) 0.002	-19.2 (-30.7 to-7.71) 0.001	0.48 (-1.13 to 2.11) 0.557
75-100%	4.50 (2.81 to 6.20) <0.001	6.81 (3.07 to 10.5) <0.001	-15.5 (-25.2 to -5.77) 0.002	0.63 (-0.74 to 2.00) 0.367
Overall p-value	<0.001*	0.003#	0.002#	0.279#

Reference group for early childhood urban exposure is early childhood rural exposure; Analysis performed separately for each NCD risk factor using linear regression. Each exposure is modeled separately adjusting for age and sex; * p-overall association, #p-trend

From modeling both exposures simultaneously, there was no evidence that the associations between proportion of urban life years with behavioral and physiological risk factors were modified by urban early life exposure. For inadequate physical activity and inadequate fruit and vegetable intake, early life urban exposure lost its statistical significance when adjusted for proportion of urban life years. Those having spent more than 75% of their lifetime in an urban area were more likely to have inadequate physical activity (OR 1.77, 95% CI 1.20 to 2.60) and inadequate fruit/vegetable intake (OR 1.92, 95% CI 1.13 to 3.25) compared to those who have spent less than 25% of their life time in an urban area. (Figure 1, Table 5). However, those spending their early life in an urban area were 2.2 times more likely to be heavy alcohol drinkers (OR 2.20; 95% CI 1.34 to 3.59) and the mean systolic blood pressure was 2.5 mmHg higher (95% CI 0.16 to 4.90) compared to those spending early their early life in a rural area, even when adjusting for their later proportion of urban life years (Table 5).

Figure 1 Associations between proportion of urban life years with behavioral and physiological risk factors for NCDs adjusted for age, sex and early life exposure



The reference group for all analysis was 'proportion of urban life year <25%; More than five standard drinks per sitting in men and more than four standard drinks per sitting in women were cutoff points for heavy alcohol consumption; Less than 35 units standard units of fruits and/or vegetable consumption per week were the cutoff point for inadequate fruits and vegetable intake. Less than 75 minutes of vigorous-intensity physical activity or 150 minutes of moderate-intensity physical or an equivalent of 600 metabolic equivalent (MET) minutes per week was the cutoff point for inadequate physical activity

Table 5 Mutually adjusted associations for early life urban exposure (Age 0-5) and proportion of urban life years with Behavioral and Physiological Risk factors for NCDs

Exposure	Behavioral Risk Factors								Biological Risk factors			
	Current Smoking		Heavy alcohol drinking		Inadequate physical activity		Inadequate fruit and vegetable intake		BMI (kg/m^2)		Systolic blood pressure## (mmHg)	
	Odds Ratio and p-value		Odds Ratio and p-value		Odds Ratio and p-value		Odds Ratio and p-value		Difference (Urban-Rural) and p-value		Difference (Urban-Rural) and p-value	
Early life (0-5) Urban exposure	1.37 (0.59 to 1.20)	0.468	2.20 (1.34 to 3.59)	0.002	0.75 (0.54 to 1.05)	0.094	1.00 (0.63 to 1.59)	0.985	0.48 (-0.15 to 1.10)	0.135	2.53 (0.16 to 4.90)	0.036
Proportion of urban life years												
0-25%	Reference		Reference		Reference		Reference		Reference		Reference	
25-50%	0.93 (0.47 to 1.83)	0.829	0.80 (0.53 to 1.19)	0.270	1.14 (0.88 to 1.46)	0.335	1.71 (1.19 to 2.46)	0.004	0.19 (-0.30 to 0.67)	0.450	0.20 (-1.89 to 2.29)	0.852
50-75%	0.59 (0.29 to 1.21)	0.153	0.95 (0.64 to 1.41)	0.795	1.13 (0.87 to 1.45)	0.362	1.65 (1.17 to 2.32)	0.004	0.35 (-0.13 to 0.83)	0.154	-1.76 (-3.89 to 0.36)	0.104
75-100%	1.17 (0.45 to 3.00)	0.747	0.99 (0.56 to 1.74)	0.976	1.77 (1.20 to 2.60)	0.004	1.92 (1.13 to 3.25)	0.016	0.44 (-0.28 to 1.16)	0.232	-0.90 (-3.87 to 2.07)	0.552
Overall p-value	0.580#		0.932#		0.028#		0.004#		0.127#		0.126#	
p- interaction	0.58		0.24		0.19		0.51		0.88		0.85	

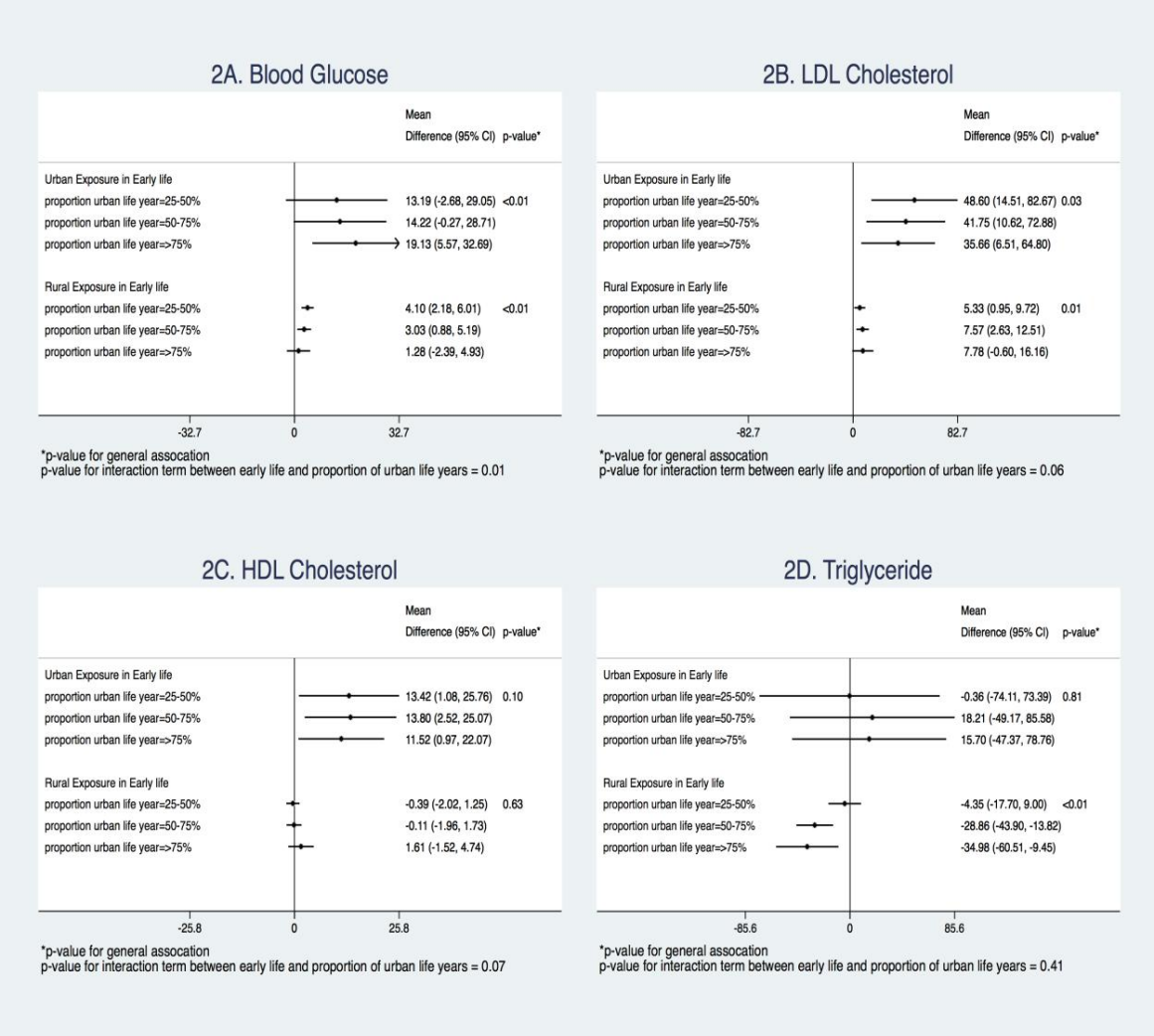
Each exposure is modeled together adjusting for age and sex; analysis performed separately for each NCD risk factors using logistic regression for behavioral risk factors and linear regression for physiological risk factors; * p-overall association, #p-trend; ## data only from Chiang Mai University Hospital (n=3,194)

For three of the four biological risk factors (glucose, LDL, and HDL), there was some evidence for interactions between early life exposure and the proportion of urban life years (Figure 2). For those spending their early life in an urban area, there was a strong positive relationship between increasing proportions of urban life years and blood glucose, and for those who had a rural childhood there was evidence of an inverse trend. For those who had an urban exposure in early life, there was a more pronounced association with LDL levels than seen for those with a rural upbringing. There was some weak evidence that increasing proportion of urban life years was associated with higher HDL only among those who spent their early life in an urban area. Although the point estimates for the people with urban upbringing were more extreme for proportion of urban life years spent, the confidence intervals were wide.

Sensitivity analysis

For all analyses, there was no evidence for interaction by sex. Some power was lost in the restricted analysis (Appendix 2 and 3), however the findings from the full and restricted analysis did not materially differ for all four behavioral risk factors and BMI. The only exception was for blood pressure, thus only observations from CMU hospital were used for analysis. There was good agreement between the biological risk factor laboratory results between Fang and CMU hospital (Appendix 4).

Figure 2 Associations between proportion of urban life year and biological risk factors for NCDs stratified by early life urban exposure



All results adjusted for age and sex. For each risk factor, the first group of results was restricted to those spending early life in urban area, the second group of results was restricted to those spending early life in rural area. The reference group for all analysis was 'proportion of urban life year <25%'. LDL-low density lipoprotein; HDL-high density lipoprotein; Units for all risk factors are in mg/dL.

Discussion

There was consistent evidence to support that both measures of urbanicity were independently associated with increases in all behavioral and physiological risk factors for NCDs. However, urban residence may not be associated with increases in all types of biological risk factors. For some biological risk factors, there was evidence that the association between proportion of urban life years and risk factors for NCDS may differ, depending on whether there was early life urban exposure.

Increases in distal behavioral and physiological risk factors may not translate directly to higher proximal biological risk factors such as high triglycerides and low HDL in Thailand. Dietary patterns may help explain such findings. Consumption of calories from dietary carbohydrates, such as sticky rice, may be higher in rural or less developed areas in Thailand (Kosulwat, 2002, Kedjarune et al., 1997). These dietary carbohydrates are be associated with high triglyceride and low HDL blood levels (McKeown et al., 2009). Urbanization may also be associated with lower biological risk factors through better awareness, availability of laboratory testing, and medical control (Porapakkham et al., 2008, Aekplakorn et al., 2011a). Data from the 2009 Thai National Health Examination Survey also demonstrated that not all biological risk factors were higher in urban areas (Aekplakorn et al., 2011b).

By modeling both exposures together, our study attempted to disentangle the life course mechanisms driving such associations. Our results suggest that for the all four behavioral risk factors, BMI and blood pressure, both the early life critical/sensitive period model and the cumulative risk model were possible. Heavy drinking and blood pressure may be predominantly driven by an early life critical/sensitive period model, while inadequate physical activity and inadequate fruit and vegetable intake may be predominantly driven by a cumulative risk model. Life course socioeconomic status (SES), a key mediator between urbanization and health, may help to explain such findings. Childhood SES, which is often measured through parental SES, has been linked to adult behavioral risk factors such as smoking and drinking (van de Mheen et al., 1998, Bowes et al., 2013). However, for other behavioral risk factors such as physical activity, early life SES is less important than later life influences on the risk of NCDs (Tammelin et al., 2003, Kuh and Cooper, 1992).

Distal behavioral and physiological risk factors are likely to be mediated through proximal biological risk factors. For these biological risk factors, our evidence suggests that living in an urban environment early in life interacts with urban life years. For example, people spending their early lives in urban areas may be more susceptible to developing diabetes

as a result of additional cumulative years of urban exposure than people who spent their early lives in a rural environment. It may be possible that some early life exposures have prolonged influences in health behavior and physiological factors as previously mentioned. It may also be possible that the rate of urbanization or changes in environmental influences are greater in areas already considered more urban (World Health Organization, 2011). It is however unlikely that these NCD risk factors in Thailand were predetermined outcomes of influences in early life but rather a complex interaction between both long term accumulation of exposure and early life exposures.

The study had several limitations. Due to the cross sectional study design we could only assume temporal relationships between increasing proportions of urban life years and increases in NCD risk factors. Data suggested that men could be underrepresented in the study population but the study population represented the source population well in terms of age and education level. The differences in methods of data collection between the two hospitals represented potential for information bias. However, restricted analysis did not materially change the conclusions for most of the outcomes. The results for biological outcomes were less likely to be affected by information bias as there was good agreement between the two hospitals. Our method of classifying urban versus rural exposure based solely on location may be prone to misclassification. We could not take into consideration the fact that some locations may have become urbanized over time. However, since few locations were considered as urban in our study, rural exposure is more likely to be misclassified. If recent changes in the degree of urbanicity have accelerated in recent years, especially for areas already considered urban, the associations seen, particularly for early life urban exposure, are likely underestimates. Due to the relationship between the two exposures and shared mediating factors, it may not be possible to empirically provide proof of one life course mechanism over the other (Hallqvist et al., 2004). Not all life course models, such as the social mobility model (in essence urban migration or rapid urbanization) could be assessed. Due to limited heterogeneity of exposure in this occupational cohort we were unable to explore the role of other critical periods, such as adolescence."

Our early life exposure also cannot distinguish between the critical period effect and the sensitive period effect. Our study did not focus on potential mediators between life course urban exposure and NCD risk factors (such social capital, parental and individual SES), which should be explored in future studies. The study of health care workers in the Northern region means that the results seen may not be generalizable to the Thai population. Nonetheless, the results should provide meaningful evidence as the rest on the county becomes more developed.

Policy Implications

Despite its limitations, our study offers evidence towards understanding how urbanization may drive NCDs in a developing country such as Thailand. Our findings are in line with other finding from developing countries (Miranda et al., 2008). Urban life years was associated with many risk factors for NCDs such as obesity and higher blood pressure in India (Kinra et al., 2011) . Both life time urban exposure and percentage of life time urban exposure was associated with obesity and diabetes in Cameroon (Sobngwi et al., 2004). These findings support evidence for targeting public health interventions during early life and throughout adulthood. For Thailand, targeting children in urban areas may be useful for behavioral and physiological risk factors as early life urban exposure (compared to early life rural exposure) was associated with increase odds of heavy alcohol drinking (OR 2.20, 95% CI 1.34 to 3.59) and higher systolic blood pressure (2.53 mmHg, 95% CI 0.16 to 4.90) in adulthood despite adjusting for proportion of urban life years. Trials have shown that childhood interventions can be effective measures to prevent and combat substance use, obesity and elevated blood pressure (van Lier et al., 2009, Cai et al., 2014, Flynn et al., 2006).

To effectively decrease biological risk factors, it may be important to integrate public health interventions in adulthood. Those who spent their early childhoods in an urban area and more than 75% of their life in an urban residence had a much higher LDL cholesterol level than those who also spent their childhoods in urban areas but have spent less than 25% of their lives in an urban residence, an effect size of similar magnitude to the effect of statins in lowering LDL cholesterol (Law et al., 2003). Incorporating individual and population level interventions focusing on population shifts in distributions of risk factors (Rose, 2001), such as the one conducted in Sweden that focused on adults from age 30 (Weinehall et al., 1999, Long et al., 2014), could be a cost-effective public health policy to prevent NCDs in developing countries such as Thailand.

Declaration of Interest: All authors have no competing interests

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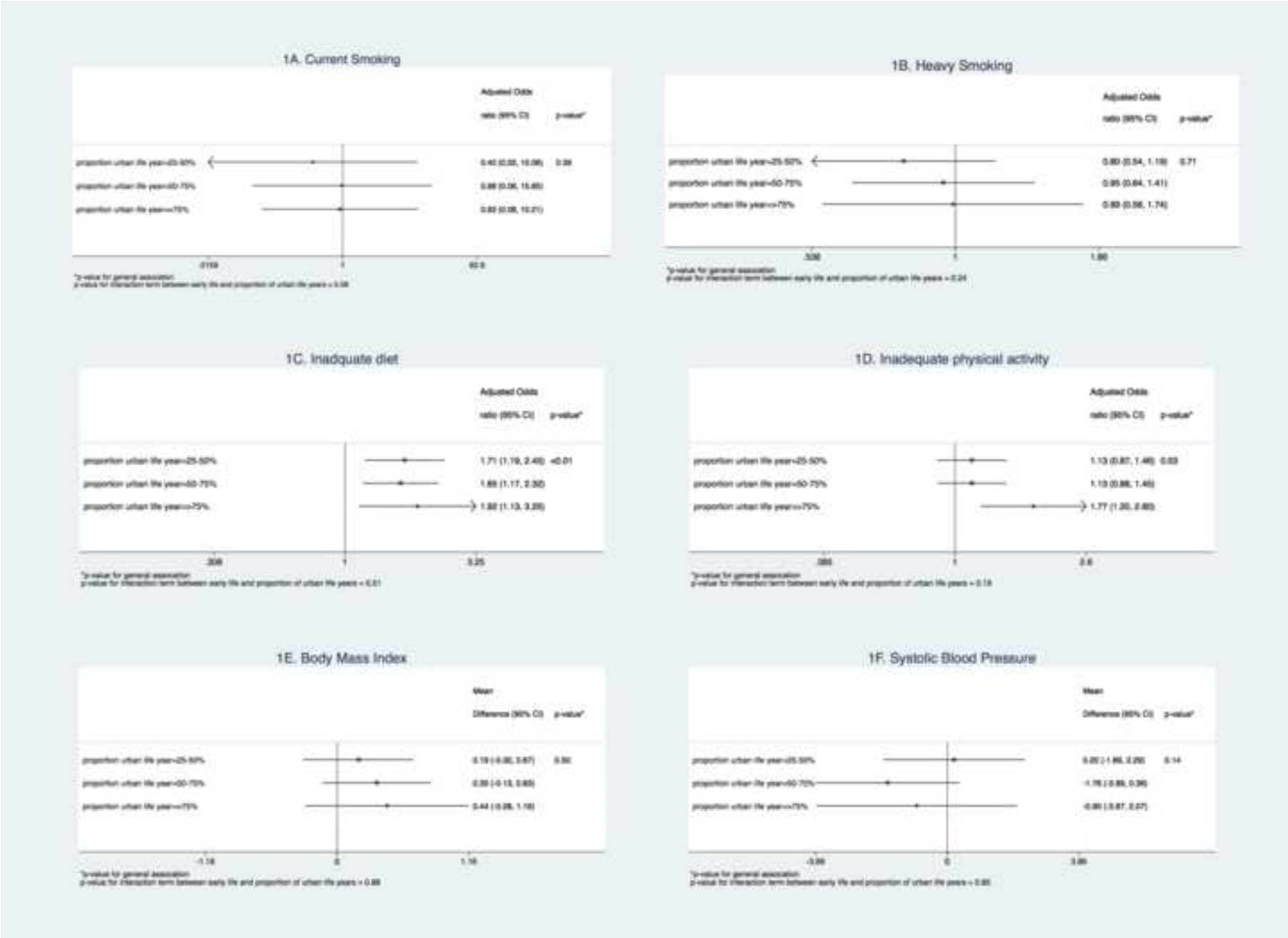

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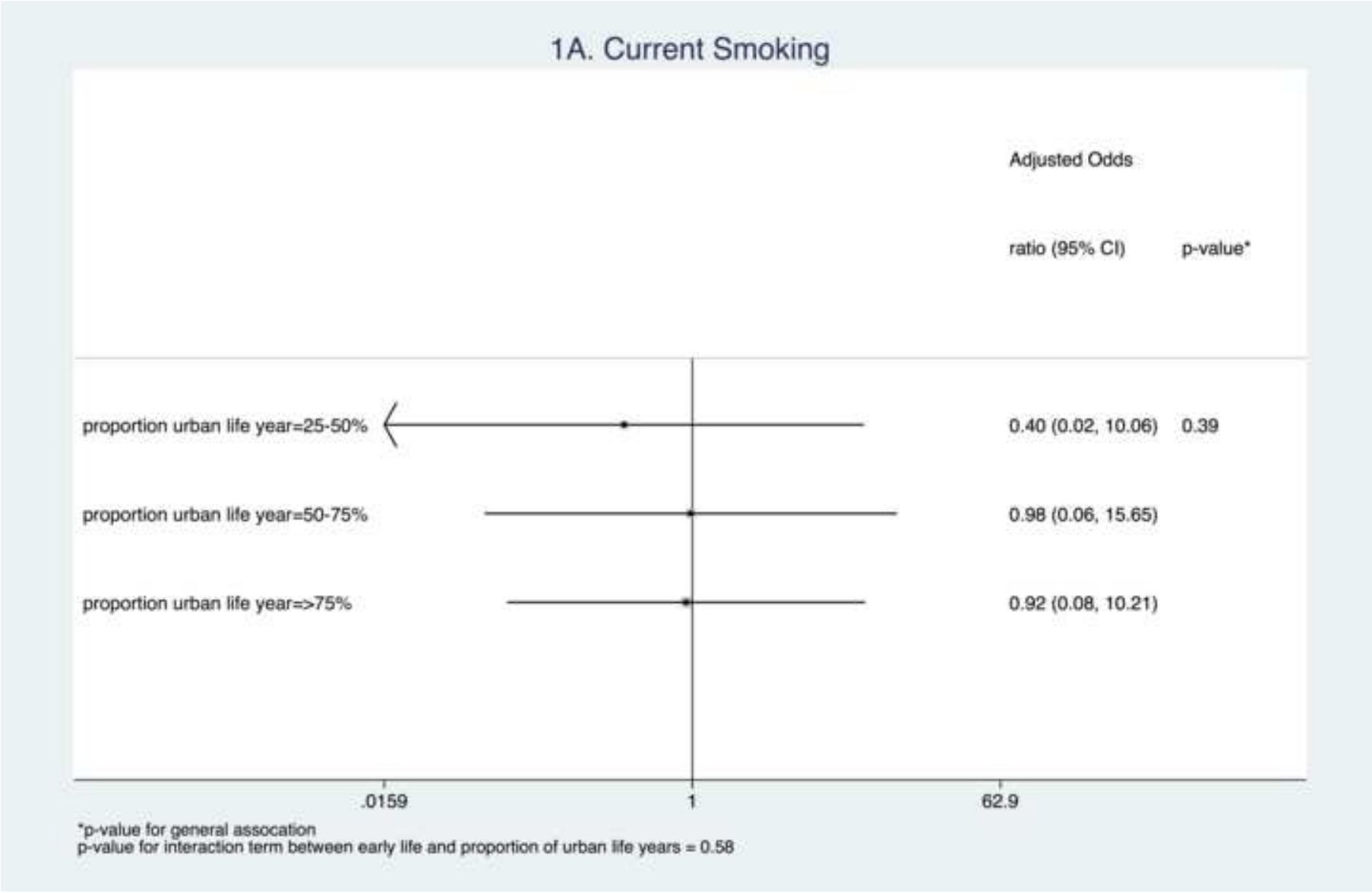

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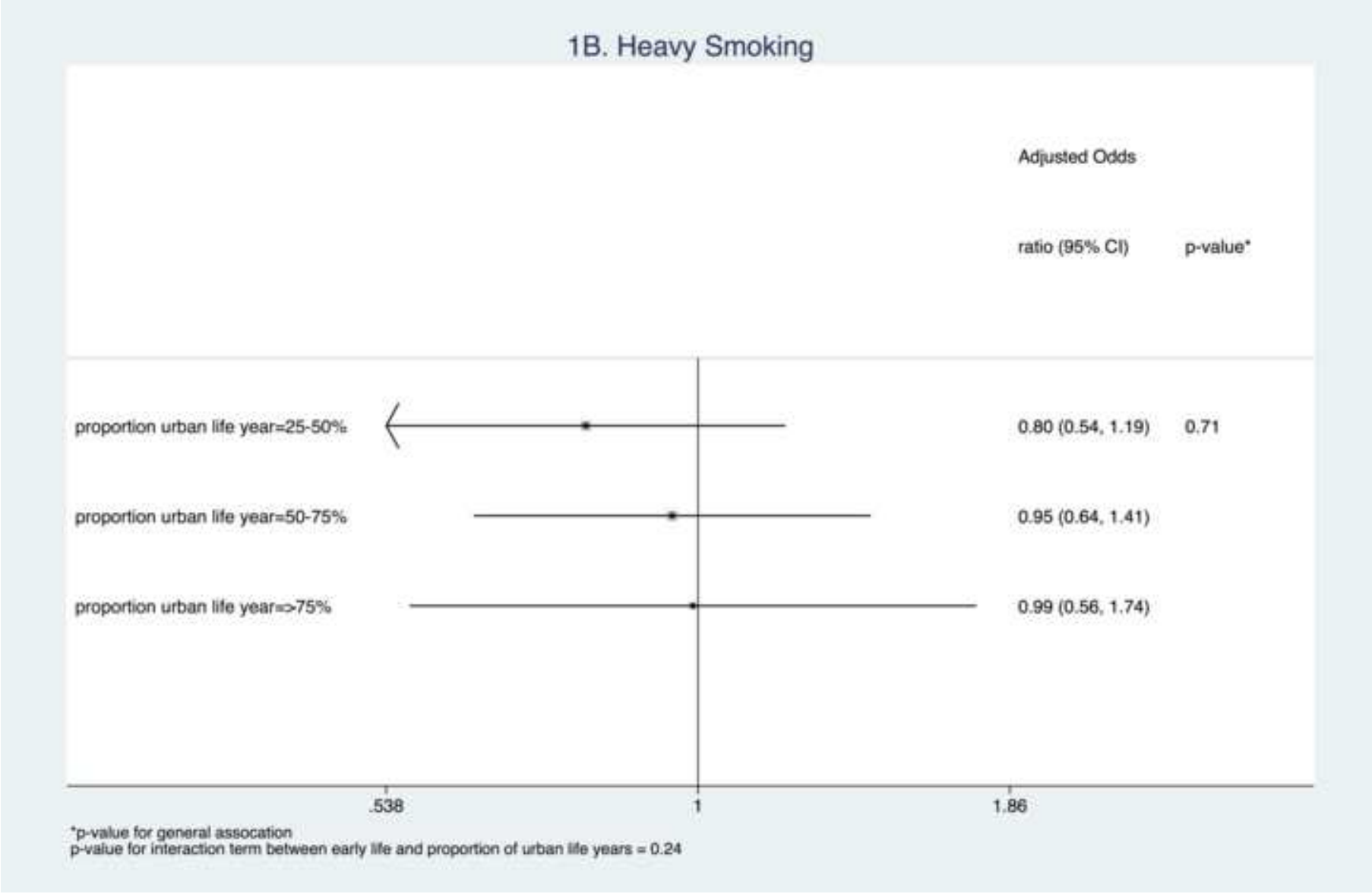

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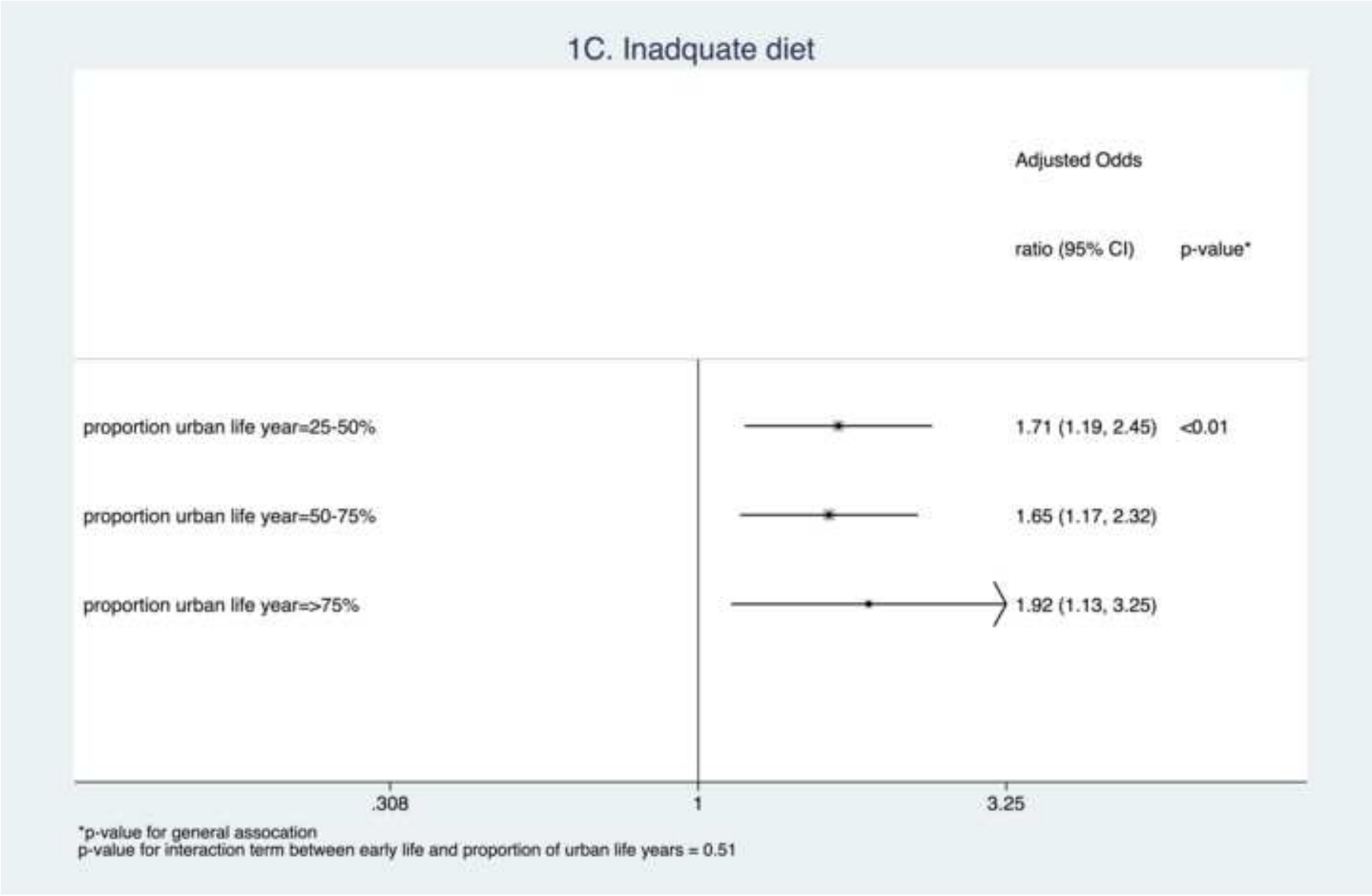

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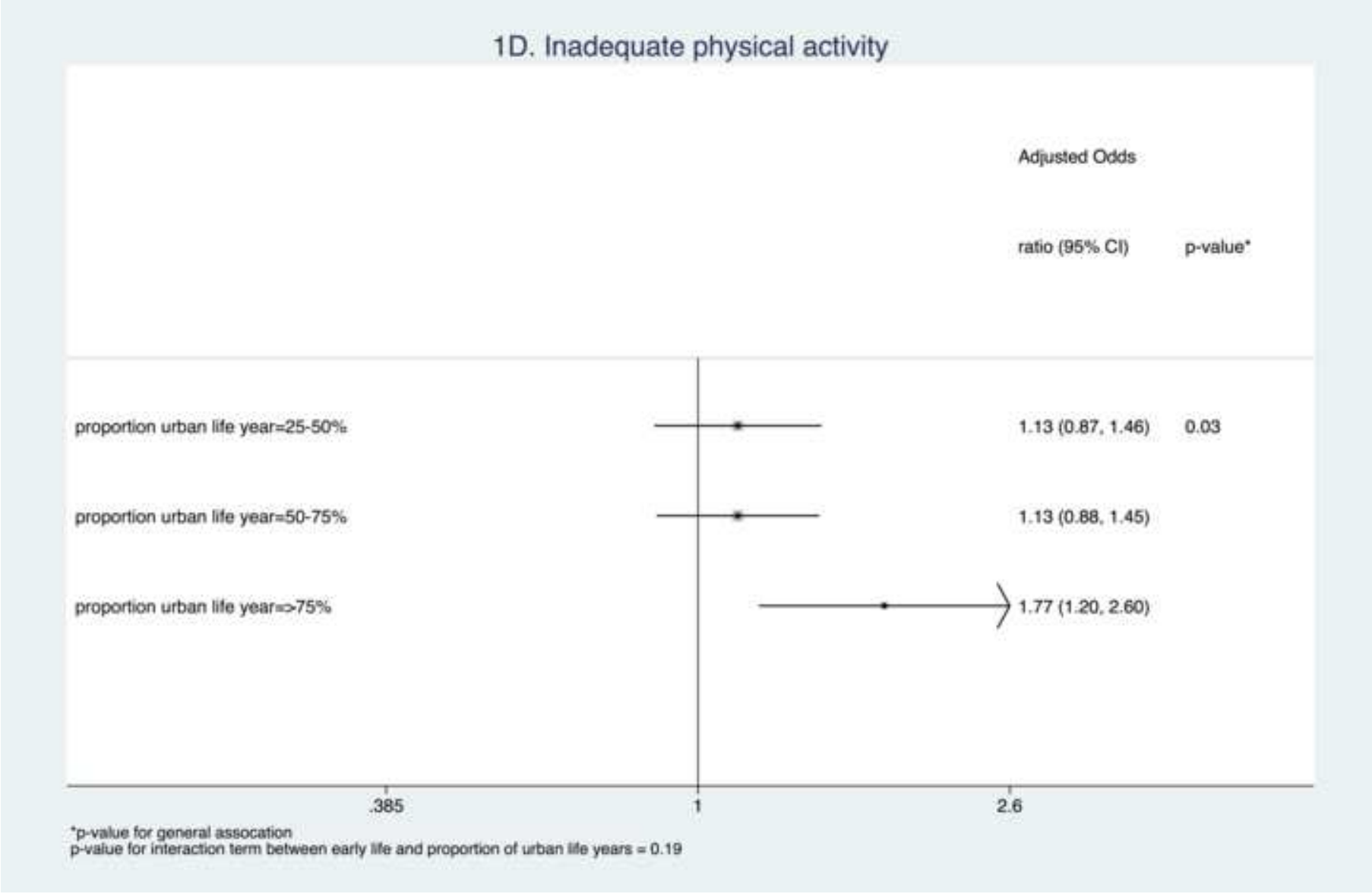

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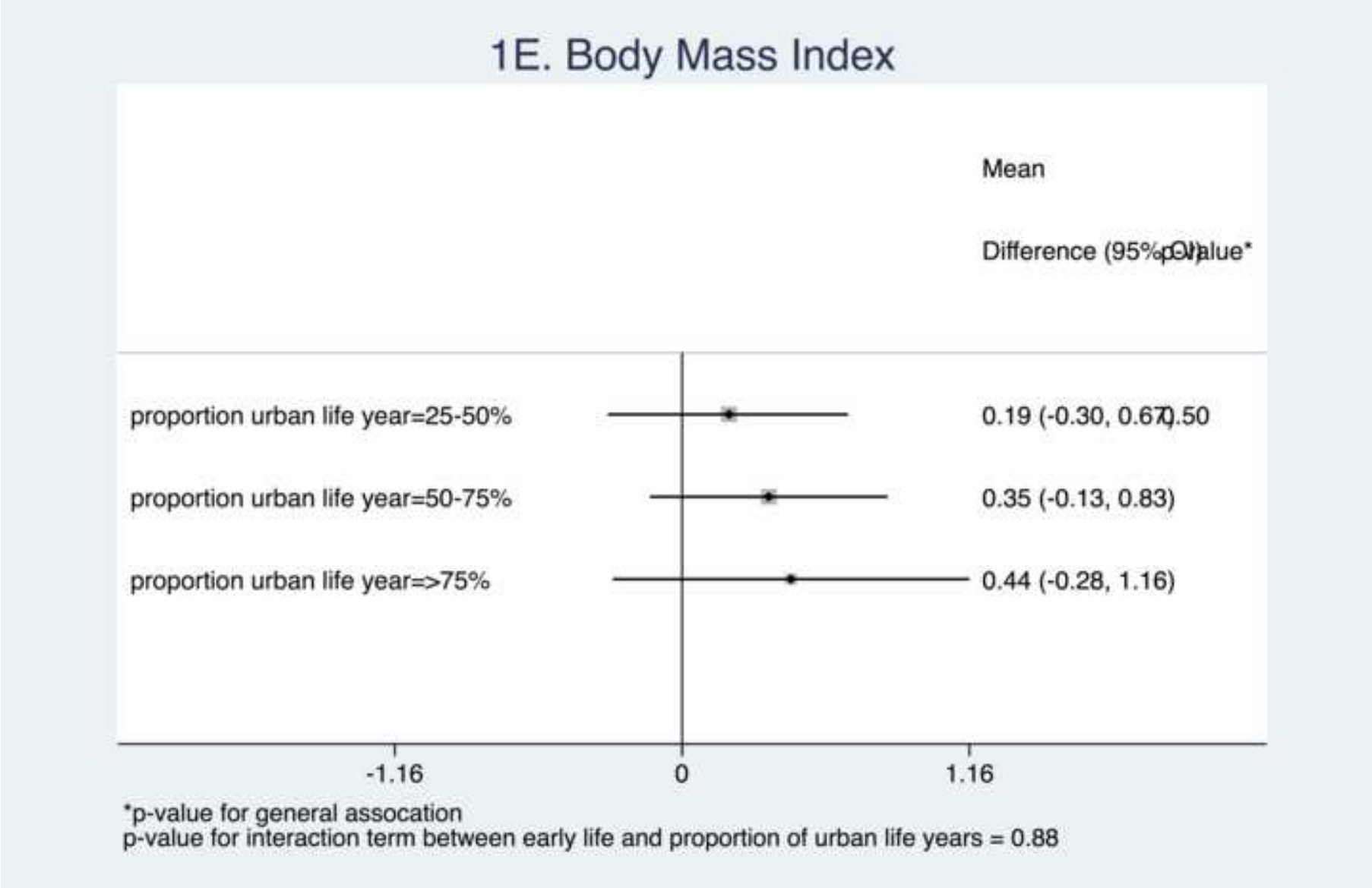

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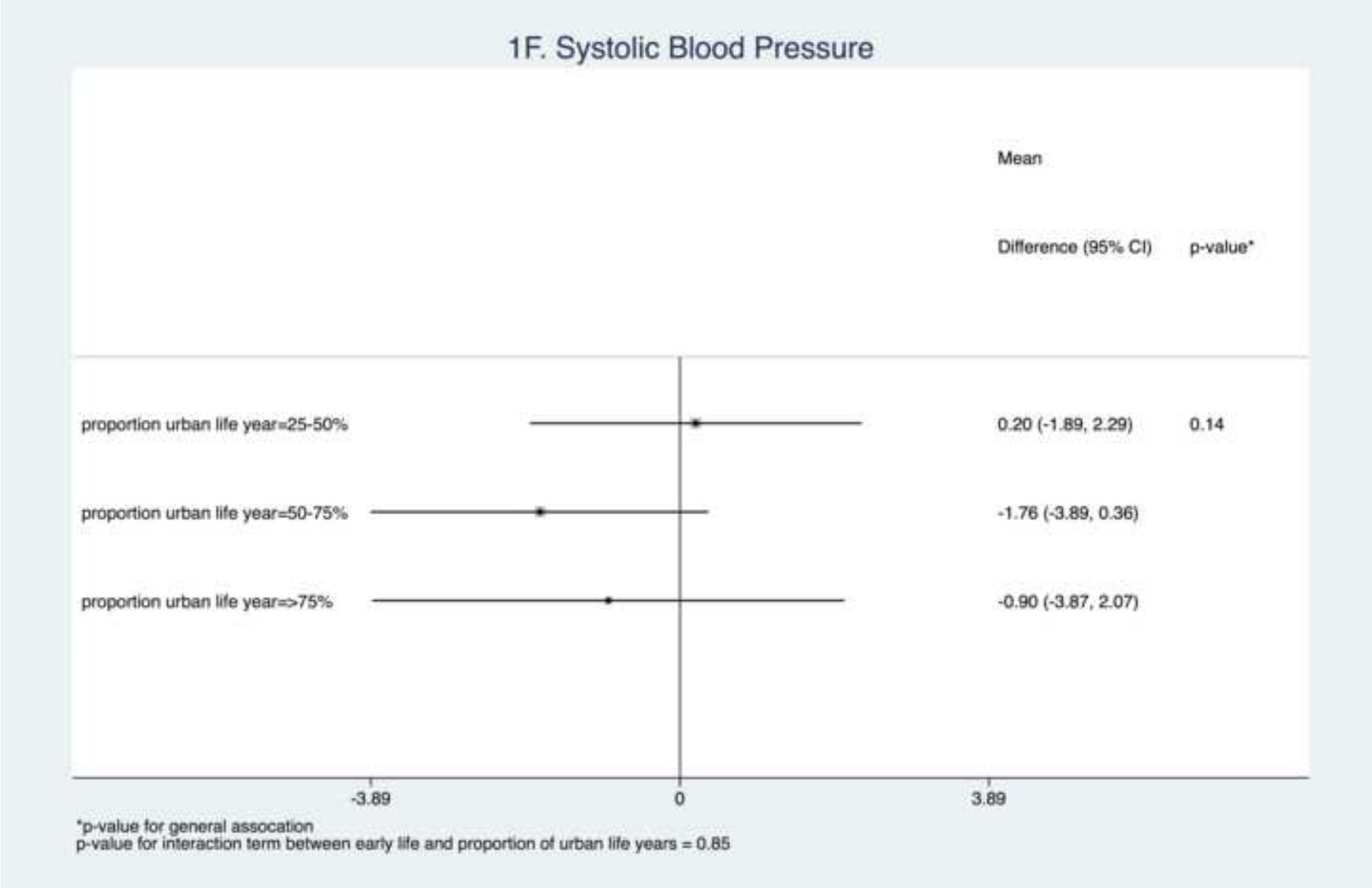

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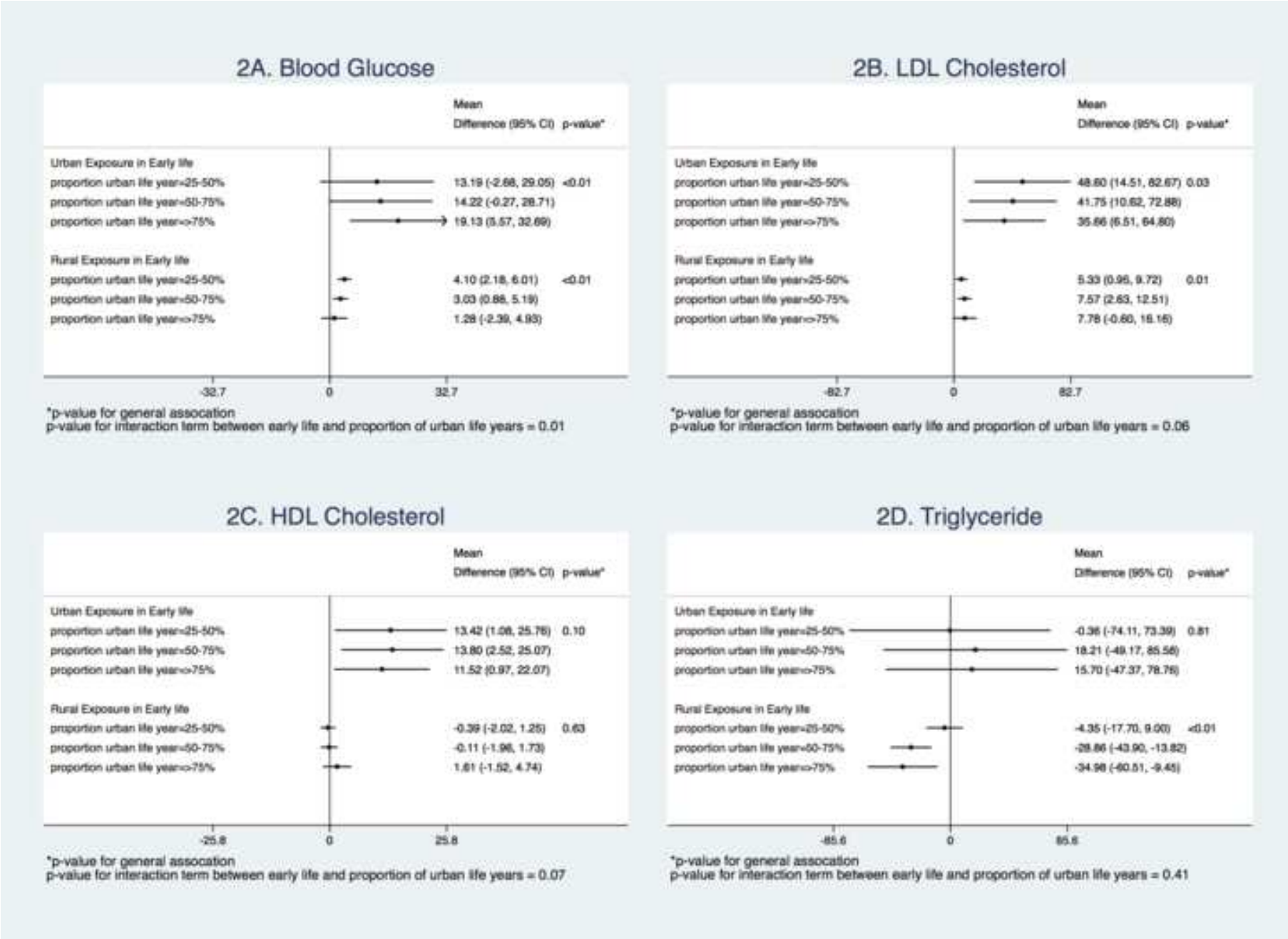

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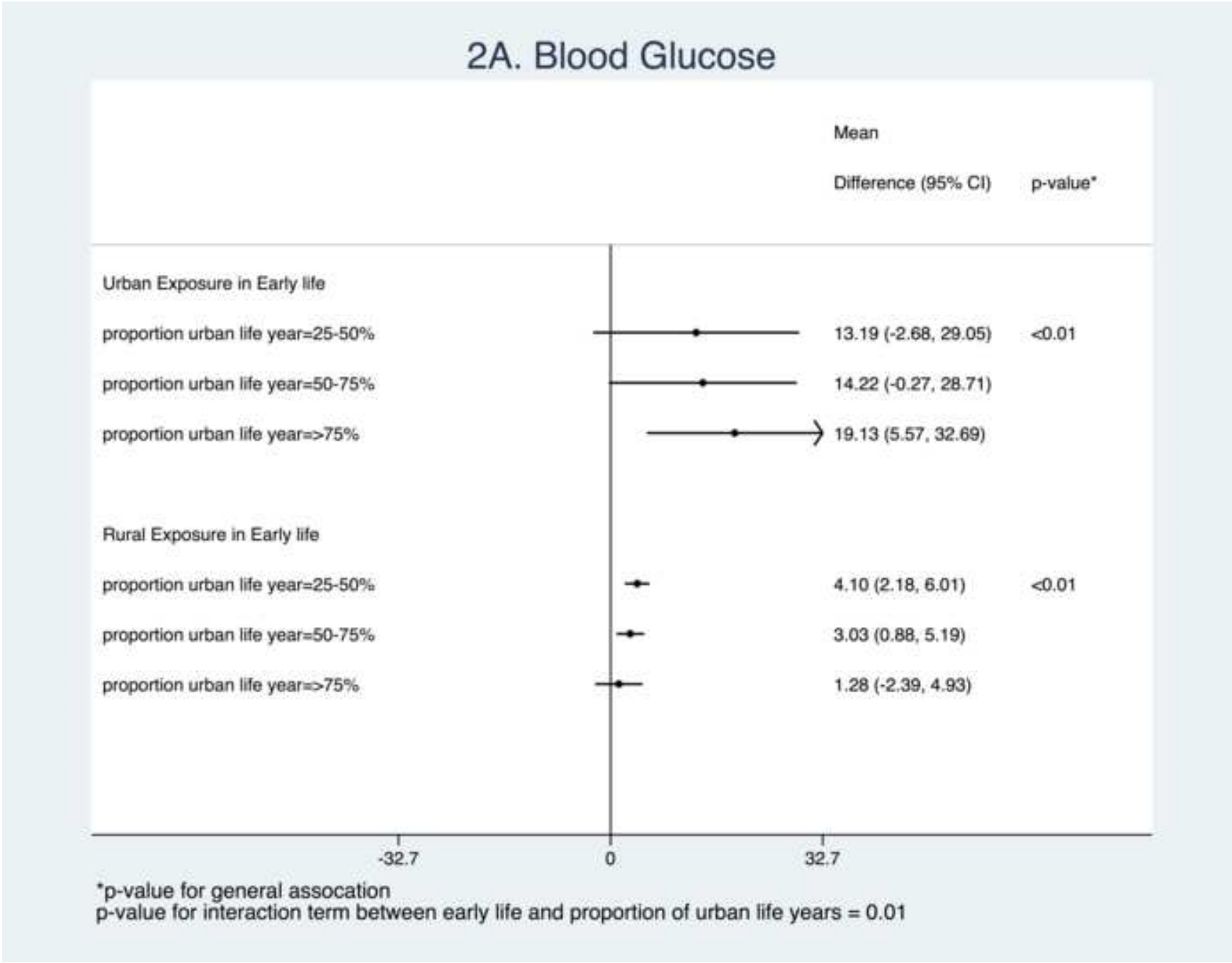

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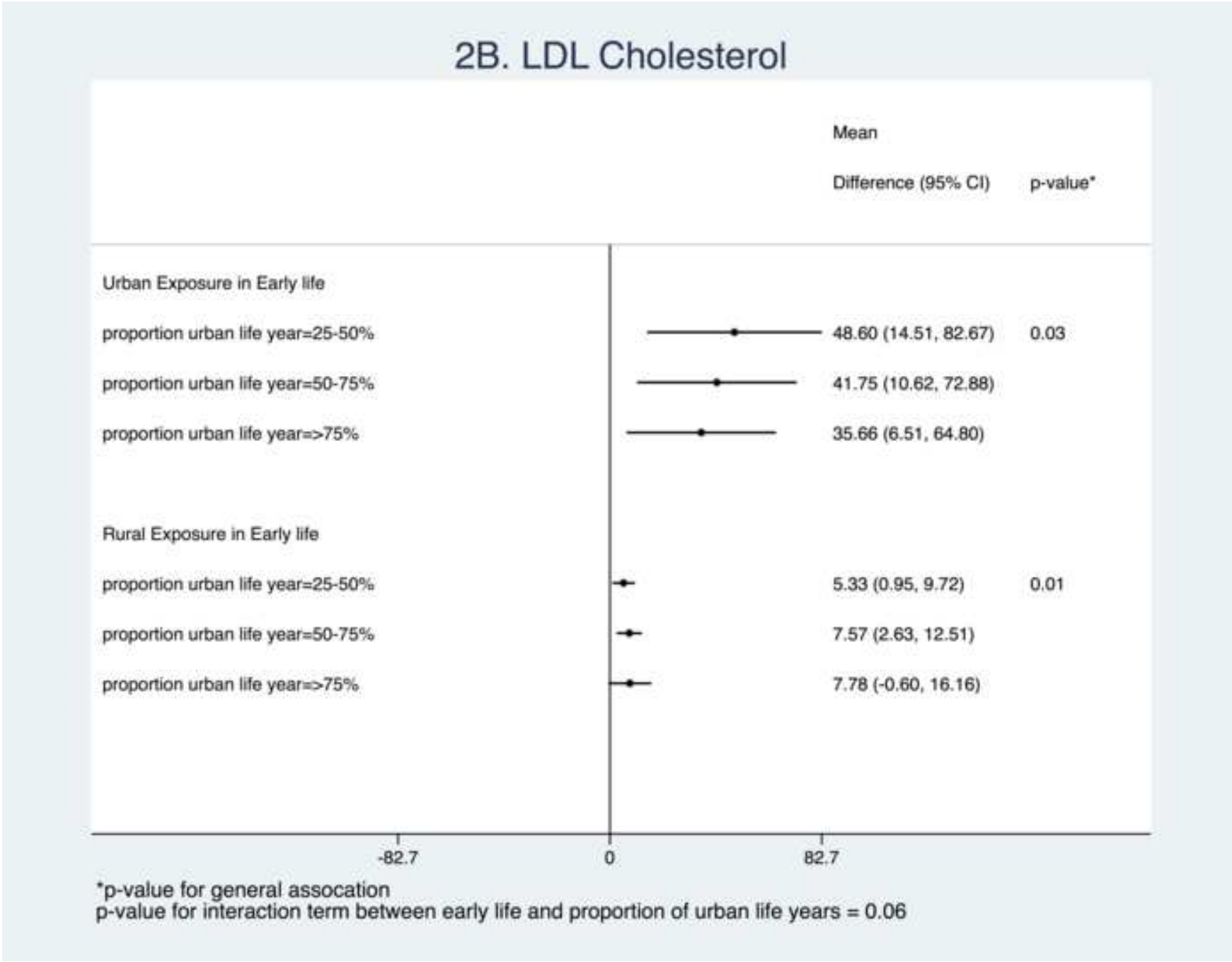

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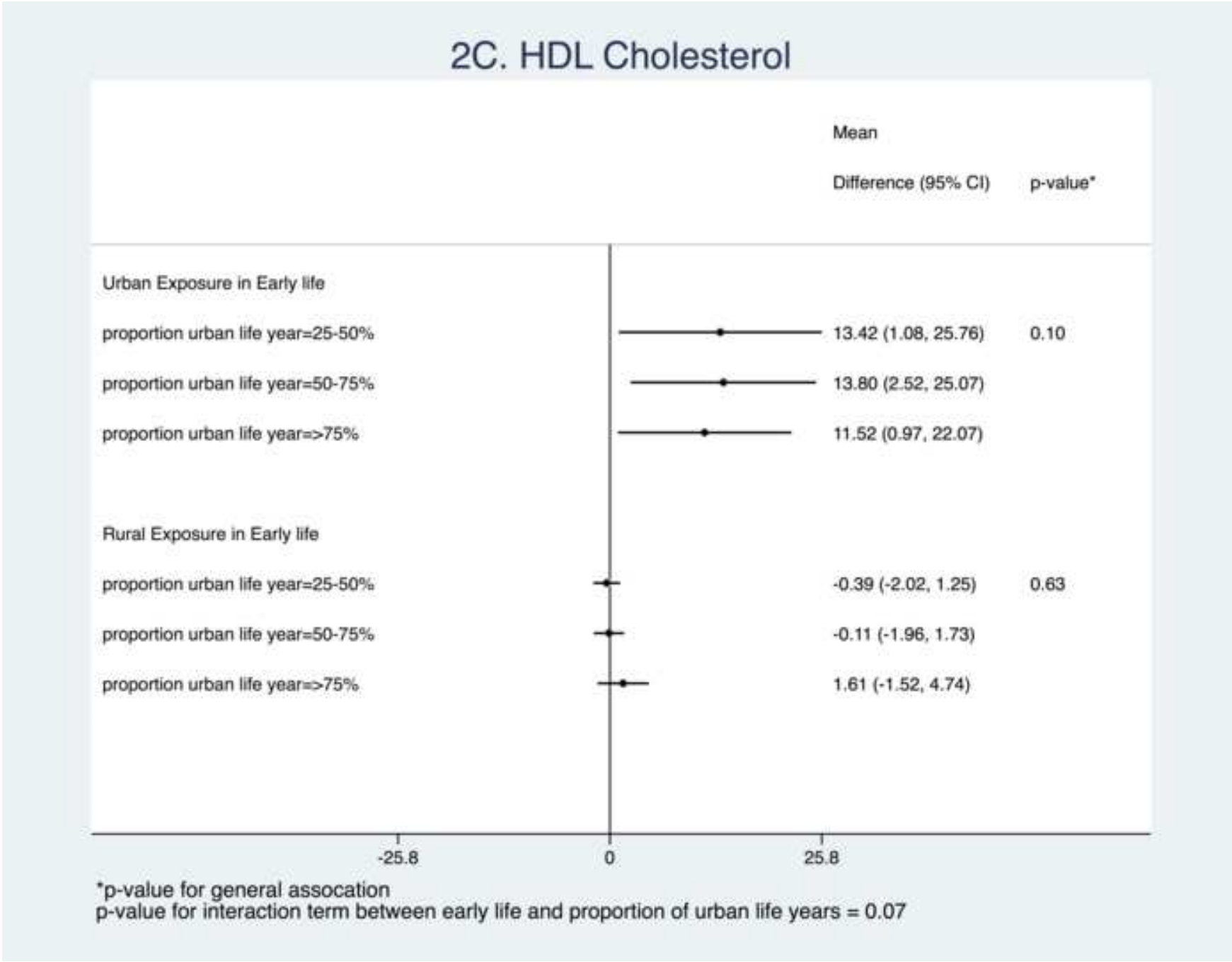

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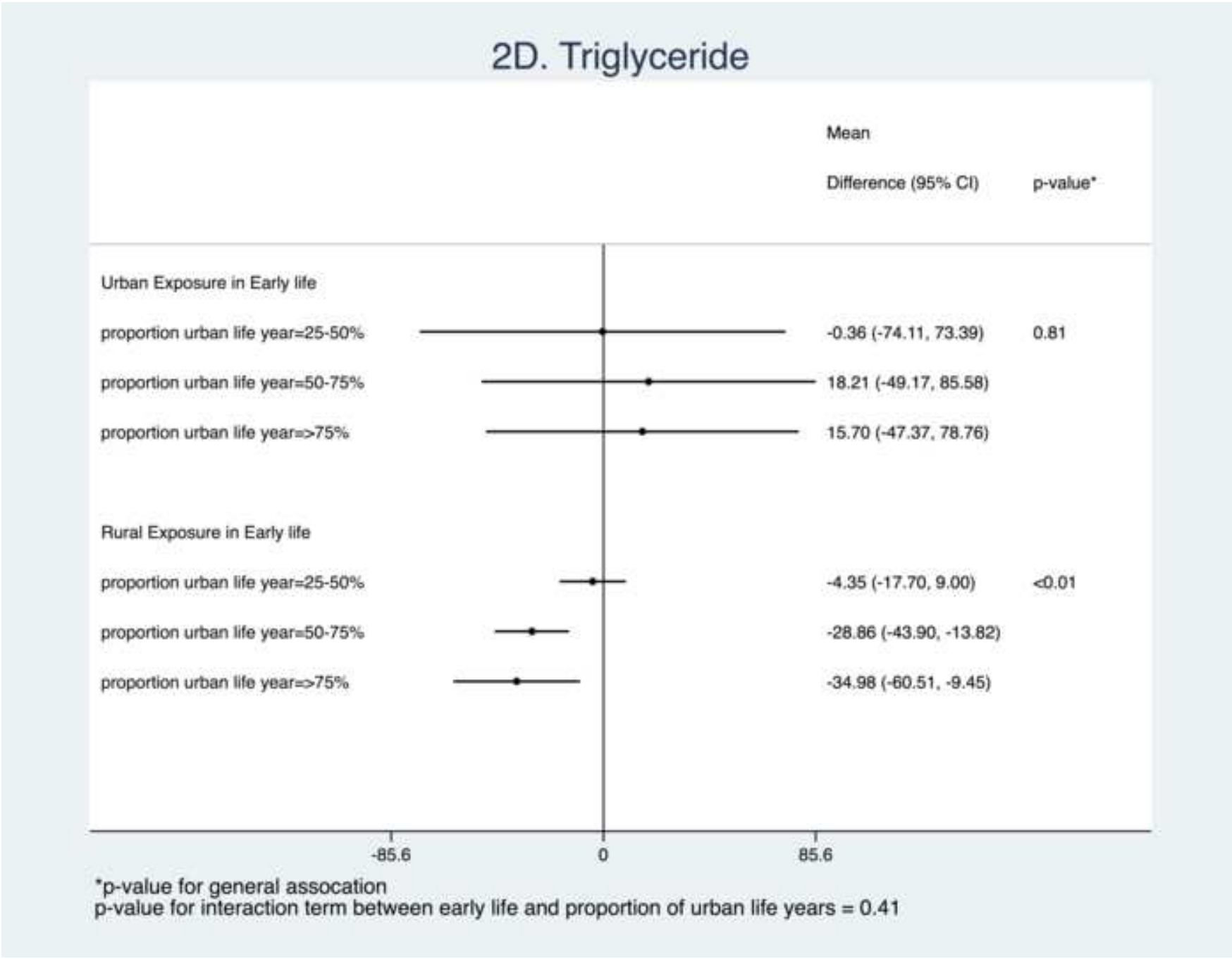


Appendix 1

Appendix 1 Distribution of demographic factors in sample and total population by hospitals

	Fang Hospital		Maharaj Nakorn Chiang Mai Hospital (Chiang Mai University Hospital)	
	Sample population	Total Population	Sample population	Total population
Number	312	459	3188*	5,364
% Female	75.0	74.5	77.3	68.8
Mean age (sd)	33.4 (10.6)	34.1 (10.8)	39.7 (10.7)	40.5 (11.0)
Age Distribution (%)				
< 25	23.1	21.1	10.7	8.8
25-30	21.8	20.9	13.6	14.3
30-35	16.9	18.6	13.5	12.7
35-40	12.7	13.4	14.0	12.6
40-45	6.5	5.7	11.7	10.9
45-50	5.4	6.4	16.2	15.4
50-55	9.4	9.0	12.0	13.9
55-60	3.3	4.4	8.3	10.5
> 60	0.6	1.0	0.5	0.6
Job Position#				
Special Advisor	--	--	0.0	<0.1
Instructor (MD)	--	--	1.8	6.4
Instructor (non-MD)	--	--	1.2	1.9
Doctor/Dentist	5.8	7.4	0.7	5.8
Pharmacist	1.3	3.0	2.1	2.2
Nurse	22.4	24.8	38.7	31.1
Nurse aide	--	--	13.2	12.2
Other health professionals	10.9	9.4	2.8	3.0
Non-health professionals	4.2	4.6	7.1	6.4
Administrative staff	2.9	2.6	4.1	3.9
Non-skill worker	15.7	14.2	12.5	12.1
Skill worker	36.9	34.0	15.7	14.8
Highest education				
Elementary school	3.2	Not available	4.0	4.3
Early secondary school	5.8		6.3	6.4
Late secondary school	37.0		13.6	12.9
Bachelor's degree	48.9		66.5	62.0
Higher than Bachelor's degree	5.1		9.5	14.3

*16 additional participants are in the study population but were no longer in the hospital database by July 2014 when demographic characteristics of the source population were obtain from official hospital personnel records.

Due to difference in how job positions are classified between the two hospitals, the job positions are broadly grouped by similar potential for earnings and educational requirements or training. Other health professionals included pharmacists, physiotherapist, laboratory technicians. Non-health professionals include positions such as accountants, lawyers, social workers.

Appendix 2

Appendix 2 Sensitivity analysis of associations between Early life urban exposure (Age 0-5) and Proportion of urban life years with Behavioral and Physiological Risk factors for NCDs using only results from Chiang Mai University

Exposure	Behavioral Risk Factors								Physiological Risk factors			
	Current Smoking		Heavy alcohol drinking		Inadequate physical activity		Inadequate fruit and vegetable intake		BMI (kg/m^2)		Systolic blood pressure[##] (mmHg)	
	Odds Ratio and p-value		Odds Ratio and p-value		Odds Ratio and p-value		Odds Ratio and p-value		Difference (Urban-Rural) and p-value		Difference (Urban-Rural) and p-value	
Early Childhood (0-5) Urban exposure	1.92 (1.31 to 2.82)	0.01	2.27 (1.84 to 2.80)	<0.001	1.14 (0.99 to 1.32)	0.067	1.14 (0.93 to 1.40)	0.213	0.58 (0.40 to 0.96)	<0.001	1.41 (0.49 to 2.33)	0.003
Proportion of urban life years		0.005*		<0.001*		0.009#		0.377#		<0.001 #		<0.001 *
0-25%	Reference		Reference		Reference		Reference		Reference		Reference	
25-50%	0.88 (0.38 to 2.02)	0.761	0.58 (0.37 to 0.92)	0.021	1.17 (0.85 to 1.60)	0.331	0.99 (0.61 to 1.60)	0.978	0.17 (-0.43 to 0.78)	0.575	-2.87 (-4.55 to -1.17)	0.001
50-75%	0.54 (0.22 to 1.30)	0.169	0.77 (0.49 to 1.20)	0.249	1.12 (0.82 to 1.55)	0.472	0.93 (0.58 to 1.50)	0.782	0.45 (-0.16 to 1.07)	0.150	-5.07 (-6.75 to -3.39)	<0.001
75-100%	1.45 (0.73 to 2.88)	0.288	1.60 (1.10 to 2.33)	0.014	1.37 (1.02 to 1.82)	0.035	1.09 (0.70 to 1.69)	0.696	0.95 (0.40 to 1.51)	0.001	-1.91 (-3.33 to -0.49)	0.008

Each exposure is modeled separately adjusting for age and sex; analysis performed separately for each NCD risk factors using logistic regression for behavioural risk factors and linear regression for physiological risk factors; * p-overall association, #p-trend; ## data only from both hospital (n=3504)

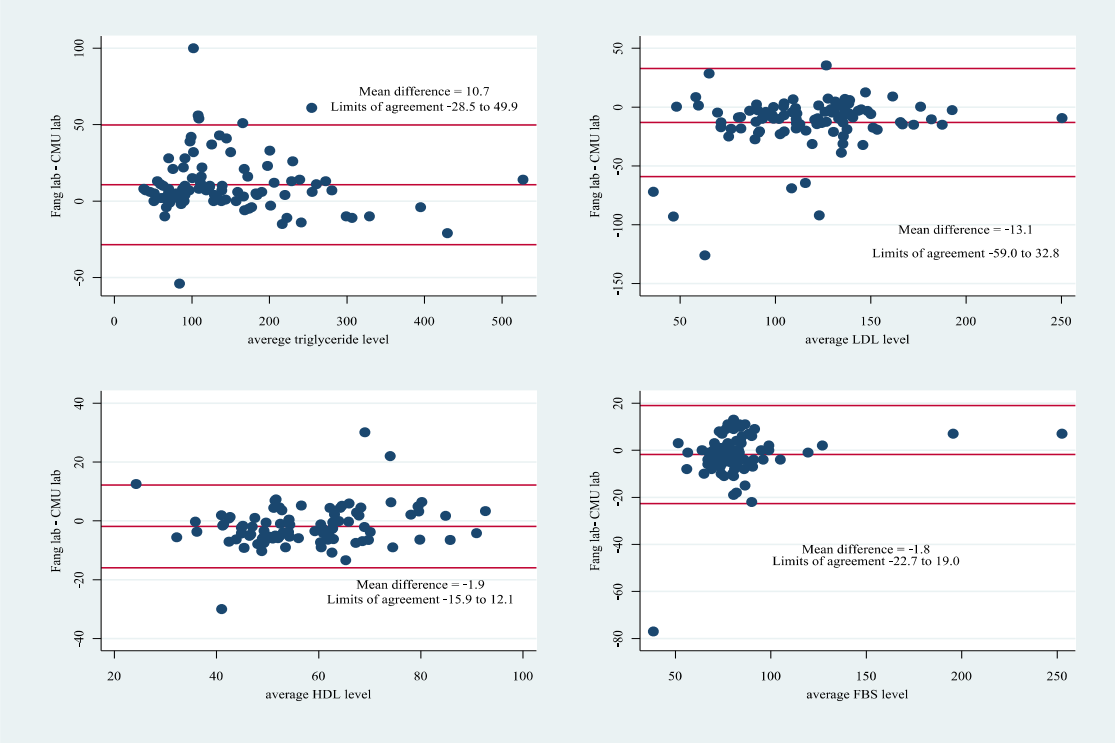
Appendix 3

Appendix 3 Sensitivity analysis of associations between Early life urban exposure (Age 0-5) and Proportion of urban life years with Behavioral and Physiological Risk factors for NCDs using only Chiang Mai University data

Exposure	Behavioral Risk Factors								Physiological Risk factors			
	Current Smoking		Heavy alcohol drinking		Inadequate physical activity		Inadequate fruit and vegetable intake		BMI (kg/m^2)		Systolic blood pressure## (mmHg)	
	Odds Ratio and p-value		Odds Ratio and p-value		Odds Ratio and p-value		Odds Ratio and p-value		Difference (Urban-Rural) and p-value		Difference (Urban-Rural) and p-value	
Early Childhood (0-5) Urban exposure	1.33 (0.53 to 3.33)	0.537	2.22 (1.29 to 3.83)	0.004	0.75 (0.52 to 1.07)	0.115	1.06 (0.64 to 1.73)	0.828	0.52 (-0.17 to 1.21)	0.141	2.28 (0.09 to 4.47)	0.041
Proportion of urban life years		0.583#		0.364#		0.055#		0.919#		0.163#		<0.001#
0-25%	Reference		Reference		Reference		Reference		Reference		Reference	
25-50%	0.88 (0.38 to 2.03)	0.765	0.58 (0.37 to 0.91)	0.018	1.17 (0.86 to 1.61)	0.318	0.99 (0.61 to 1.60)	0.976	0.17 (-0.44 to 0.78)	0.591	-2.92 (-4.61 to -1.22)	0.001
50-75%	0.54 (0.22 to 1.29)	0.164	0.72 (0.46 to 1.14)	0.162	1.14 (0.93 to 1.58)	0.409	0.93 (0.58 to 1.50)	0.772	0.42 (-0.20 to 1.04)	0.180	-5.23 (-6.92 to 3.55)	<0.001
75-100%	1.11 (0.37 to 3.29)	0.849	0.74 (0.39 to 1.42)	0.364	1.81 (0.15 to 2.85)	0.010	1.04 (0.54 to 1.97)	0.914	0.46 (-0.41 to 1.32)	0.301	-4.09 (-6.62 to -1.57)	0.001
p- interaction		0.81		0.33		0.49		0.60				0.20

Each exposure is modeled together adjusting for age and sex; analysis performed separately for each NCD risk factors using logistic regression for behavioural risk factors and linear regression for physiological risk factors; * p-overall association, #p-trend; ## data only from both hospitals (n=3,504)

Appendix 4 Bland-Altman Plots and 95% limits of agreement for Biological Risk factors between the two hospitals



Y-axis represents differences in laboratory results in the same individual

[Fang Hospital – Chiang Mai University Hospital]

X-axis represents the mean values of the laboratory result in the same individual

[Fang Hospital+ Chiang Mai University Hospital)/2]

All Units are in mg/dL