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1 **Are intestinal parasitic infections associations with obesity in Mexican children and**
2 **adolescents ?**

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11 Running title: Parasitic infection and obesity

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22 **1. INTRODUCTION**

23 Obesity and associated morbidities are rapidly growing public health challenges that
24 many low and middle income countries are facing [1, 2]. Often in these countries, infections are
25 common as well, especially in children [3, 4]. Recent studies have shown that certain viral and
26 bacterial infections are associated with obesity (described as “infectobesity”) [5-8]. However,
27 studies on the association between parasite infections and obesity are still scarce [9-11].

28 We hypothesize that intestinal parasites may be associated with obesity by two plausible
29 mechanisms. The first possibility is that both obesity and parasitic infections are positively
30 associated with poverty, as reported previously in different low and middle income countries [12,
31 13]. However, a second alternative may be that intestinal parasites have an effect on the
32 metabolism by the alteration of the gut microbiome composition.

33 It is assumed that “stress factors” or “insults” such as infectious diseases and under-
34 nutrition presented during a “critical window” of development (i.e. childhood or puberty) can
35 lead to changes in the gut microbiome composition [14-16]. These changes may be reflected as
36 alterations in metabolism and may lead to fat deposition over time [17-20]. For instance,
37 modified gut microbiota can increase caloric uptake from the diet and can modulate host genes
38 that affect energy deposition in adipocytes and thereby increase the risk of diet-induced obesity
39 [19].

40 According to the last health and nutrition survey of Mexico (ENSANUT 2012) Mexico has
41 a combined prevalence of overweight and obesity of approximately 70% in adults and 30% in
42 children [21, 22]. Approximately 50% of the total population is infected with one or more species
43 of intestinal parasites [23, 24] with *A. lumbricoides* being the most common intestinal helminth

44 infection, and *E. coli* the most prevalent intestinal protozoan infection [11, 25]. In a previous
45 study, we found intestinal protozoa infection, particularly *Entamoeba coli* (*E. coli*) infection was
46 associated with a higher percentage of body fat and food intake, while *Ascaris lumbricoides* (*A.*
47 *lumbricoides*) infection was associated with a lower food intake in children [11]. The objective of
48 this ecological study is to test if children living in states with high (reported) incidence of intestinal
49 parasitic infection have higher BMIz and higher BMIz later in life.

50 **2. Materials and methods**

51 *2.1 Datasets:*

52 We used individual and state-wide data (32 states) collected by three different federal
53 organizations of Mexico. Individual level data on height, weight and age was obtained from the
54 2012 National Health and Nutrition Survey (ENSANUT 2012). This survey of over 50,000
55 households is representative for the Mexican population at national and state level. The data is
56 available at <http://ensanut.insp.mx> and the methodology is described elsewhere [26]. Statewide
57 data on intestinal helminths and protozoa in 2012, 2006 and 2000 was obtained from the
58 National System for Epidemiological Surveillance (SINAVE) [27]. The data is available at:
59 <http://www.epidemiologia.salud.gob.mx/anuario/html/anuarios.html> Finally we used state-
60 wide data on demographic and socioeconomic variables from the National Institute of Statistics
61 and Geography (INEGI) 2012 report, available at <http://www.inegi.org.mx/> [28].

62 *2.2 Dependent Variable: BMI for age z-score*

63 Using data from ENSANUT 2012, we calculated the BMI for age z-score (BMIz) for all
64 individuals. BMIz for individuals above 19 years was calculated using the last available point of

65 the WHO grow charts for children (228 months). The calculations were made using the World
66 Health Organization (WHO) SPSS anthroplus macro for children 5-19 years (WHO, Geneva,
67 Switzerland). The macro is publicly available at <http://www.who.int/childgrowth/software/en/>.

68 *2.3 Independent variables: infection with intestinal parasites*

69 Information on intestinal helminths and protozoa was extracted from SINAVE, which is
70 the only publicly available data source on intestinal parasite infection across the county. In this
71 system, data is reported annually as the incidence per 100 000 person-years in different age
72 groups (i.e. less than 1y, 1-5y, 6-10y, 11-19y) following the same procedures in each of the 32
73 states of Mexico [27]. *A. lumbricoides* infection, the most common helminth infection in Mexico,
74 is reported as the incidence of *A. lumbricoides* infection. For protozoa infection the only available
75 data was on “intestinal protozoa infection”: that is calculated by SINAVE as the grouped incidence
76 of *Balantidium coli*, *Cryptosporidium* and *unspecified intestinal protozoa infection*.

77 We used the SINAVE incidence data as a proxy for the probability of infection, in function
78 of the state and the age of the subject at a particular time point. For instance, the probability of
79 infection in 2012 of an individual of 15 years old was approximated by the incidence of the
80 intestinal parasite infection in his/her state of residence in 2012 for his/her corresponding age
81 group. In addition, the same individual’s probability of infection in 2006 and in 2000, was
82 determined by the incidence of each intestinal parasitic infection in his/her state and for his/her
83 age group at that given year.

84 2.4 Additional covariates

85 We included both individual-level covariates from the ENSANUT 2012 survey and state-
86 level covariates from the INEGI survey in 2012. The individual-level covariates used in the analysis
87 were: sex (male/female), age (years), place of residence (rural/urban) and “marginality”
88 (marginalized/not-marginalized). Marginality indicates whether a child is from a marginalized
89 socioeconomic status or not based on indicators such as parents education level, access to
90 sanitation facilities, access to drinking water, income and population size of the community, as
91 described in detail elsewhere [26]. State-level covariates were: population with health coverage
92 (%), education level of adults (mean number of years in school), households without sanitation
93 facilities (%) and the poverty rate (population living in poverty). The poverty rate was determined
94 by the “poverty index”, which indicates whether a household is poor or not. In addition to
95 income, the poverty index also takes into consideration access to healthcare, social security,
96 material of the roof, floor and walls of the household, access to basic services and food, according
97 to standard procedures which are described elsewhere [29].

98 2.5 Statistical analysis

99 As shown in figure 1 the population was stratified into three age groups depending on the
100 age of individuals in 2000, 2006 and 2012. For the cross sectional analysis on the association
101 between infection and obesity in 2012 we extracted data on individuals aged 1-5y (n=8,927), 6-
102 10y (n=16,347) and 11-19y (n=13,992) in 2012. For the analysis on the association between
103 infection in 2006 and obesity in 2012 we selected those individuals from the ENSANUT survey of
104 2012 who were aged 1-5y (n=9,523), 6-10y (n=13,025), and 11-19y (n=7,845) in 2006. Likewise

105 for the analysis concerning infection in 2000 we selected those individuals from the ENSANUT
106 survey of 2012 who were aged 1-5y (n=6,625), 6-10y (n=7,580), and 11-19y (n=5,623) in 2000.

107 Linear regression models were used to determine the association between the probability
108 of infection (2000, 2006 and 2012) with BMIz or in 2012. Associations were estimated for *A.*
109 *lumbricoides* and intestinal protozoa for each of the three age groups separately. In order to
110 facilitate interpretation of the results, the incidence of infection (proximate probability of
111 infection) for the regression analysis was transformed from new cases in 100 000 person-years
112 to new cases per 100 person-years. Findings bellow p value of 0.05 were considered significant.

113 Poverty rate and sex were explored as a possible effect modifiers [30]. For this purpose
114 we performed the same analyses as described above, including an interaction term between sex
115 or poverty rate and the probability of infection in each model. Models with statistically significant
116 interaction terms ($p < 0.05$) were stratified in two groups, one above and one below the median
117 of poverty rate.

118 In order to have a visual overview of the combined prevalence of overweight and
119 obesity and the incidence of each parasitic infection in 2012, we mapped each variable stratified
120 in quintiles. The unit of mapping was “the state” the largest administrative unit of Mexico, and
121 the maps were generated using Arc GIS V10.1 (Redlands, CA).

122 **3. Results**

123 In 2012, the combined prevalence of overweight and obesity in Mexico was 10% for
124 children aged 1-5y, 35% for children aged 6-10y, 36% for the age group of 11-19y (Figure 2). In
125 total, 47% percent of the population lived in poverty. The health coverage was 62% and the rate

126 of households without sanitation facilities was 12% (Table 1). The incidence of *A. lumbricoides*
127 and intestinal protozoan infection decreased from 2000 to 2006 and from 2006 to 2012 for all
128 age groups (Table 1).

129 3.1 *Ascaris lumbricoides*

130 Table 2 shows a positive association between the probability of *A. lumbricoides* infection
131 in 2000 and 2006 with BMIz in 2012. In the adjusted model, an increase of 1% in the probability
132 of infection in 2006 was associated with an increase of 0.13 in the BMIz in 2012 for age group 1-
133 5y, 0.27 for age group 6-10y and 0.50 in BMIz for age group 11-19y. Furthermore, an increase of
134 1% in the probability of infection with *A. lumbricoides* in 2000 was associated with an increase of
135 0.10 in the BMIz in 2012 for age group 1-5y, 0.11 for age group 6-10y, and 0.25 for the 11-19y
136 age group. In contrast table 3 shows that a higher probability of being infected with *A.*
137 *lumbricoides* in 2012 was associated with a decrease of 0.32 in the BMIz for age group 1-5y and
138 a decrease of 0.21 for age group 6-10y.

139 Table 4 shows the results stratified by poverty rate. In the states with low poverty rates
140 in 2012, *A. lumbricoides* infection was associated with an increased BMIz in 2012 in all age
141 groups. In states with high poverty rates *A. lumbricoides* infection differed between age strata;
142 the probability of infection with *A. lumbricoides* was associated with a lower BMIz for age group
143 1-5y, no association in BMIz for age group 6-10y and a higher BMIz for age group 11-19y. Neither
144 sex nor poverty rate were modifiers for the associations between the probability of *A.*
145 *lumbricoides* infection in 2006 or 2000 with BMIz in 2012 for any of the age groups. Therefore no
146 stratified analysis were performed for these years.

147 3.2 Intestinal Protozoa

148 Table 2 shows the associations between the probability of infection with intestinal
149 protozoa in 2000 and 2006 and BMIz in 2012 across the three studied age groups. The probability
150 of infection with protozoa in 2006 was associated with a higher BMIz in 2012 in the 6-10y and
151 11-19y age groups. An increase of 1% in the probability of infection in 2000 was associated with
152 an increase in the BMIz in 2012 of 0.47 for age group 1-5y, 0.61 for age group 6-10y and 0.99 for
153 age group 11-19y.

154 Table 3 shows the associations between the proximate probability of intestinal protozoan
155 infection in 2012 and BMIz in 2012 for every age group. In the adjusted model an increase of 1%
156 in the probability of protozoan infection was associated with an increase of 0.6 in the BMIz for
157 age group 6-10y and an increase of 0.9 for age group 11-19y

158 Neither sex nor poverty rate were effect modifiers for the associations between the
159 probability of protozoan infection in 2012, 2006 or 2000 with BMIz in 2012 for any of the age
160 groups. Therefore no stratified analysis were performed.

161

162 **4. Discussion**

163 Our results indicate that children with a higher probability of *A. lumbricoides* or intestinal
164 protozoan infection (*Balantidium coli*, *Cryptosporidium*, *unspecified intestinal protozoa infection*)
165 are more likely to have a higher BMIz in the same year, 6, and 12 years later in life. This finding is
166 consistent with other studies showing early child “insults” including infections to be associated

167 to later overweight and obesity [31-33]. This finding could be related to changes in the gut
168 microbiota and inflammatory reactions due to parasitic infection that may lead to changes in
169 appetite, food intake and thereby BMIz [34-36]. In line with this hypothesis, we recently found
170 that *E. coli* infection was associated with a higher percentage of body fat and food intake in
171 children [11, 37]. Similarly Schilder et al., in a firefly model, observed that an intestinal protozoa
172 common in insects caused fat deposition in the thorax which is comparable to obesity in
173 mammals [9, 10]. Longitudinal studies are needed to assess the temporal association of intestinal
174 parasites on obesity over time.

175 While a higher probability of intestinal protozoan infection in 2012 was associated with a
176 higher BMIz in the same year, we found the opposite for *A. lumbricoides* infection. If the
177 associations would have been explained purely by poverty, the same trend and direction on the
178 associations would have been observed for both parasitic infection incidence, which was not the
179 case either in the crude or adjusted model. We also found an association between BMIz and *A.*
180 *lumbricoides* for the age groups 1-5y and 6-10y, and not for the oldest age group (11-19y). The
181 difference between age groups might be explained by the fact that *A. lumbricoides* infection-
182 related symptoms are more common in younger children [38]. Children infected with *A.*
183 *lumbricoides* may experience abdominal pain, nausea and discomfort, which may lead to a lower
184 food intake and therefore lower BMIz [39]. The results of our previous study in Mexican
185 schoolchildren supports this hypothesis, as we found a negative association between *A.*
186 *lumbricoides* infection and food intake[37].

187 We found opposite associations between BMIz and *A. lumbricoides* incidence in states
188 with high and low poverty rates. These differences may be explained with previous studies, as

189 shown in a review by Guerrant et. al [33] in which children living in poverty were more likely to
190 be malnourished, but also more likely to have stronger symptoms when infected.

191 Our findings should be interpreted in the context of this being an ecological analysis and
192 not an estimate on any causal effect of parasitic infection on obesity at individual level (ecological
193 fallacy). However, we intended to minimize this issue using individual level data on BMIz and
194 specific covariates. Although we adjusted for potential confounders, we cannot control for
195 unknown or unmeasured factors such as food availability, diet, and physical activity, therefore
196 the outcomes of this study should be interpreted with caution. In addition, it was not possible to
197 take changes in the state of residence over the years in consideration, but according to INEGI,
198 migration between states was relatively low. In the year 2000: 3,584 957 persons migrated
199 between states, representing 3.6% of the population and in 2006: 2,406 454 persons migrated,
200 corresponding to 2.3% of the population at that time [40]. We used incidence data of the studied
201 parasites as a measure for the probability of infection [41], and the true prevalence of parasitic
202 infection is most likely underestimated. A major strength of our study is that ENSANUT and INEGI
203 surveys are representative of the Mexican population at national and state level. In addition the
204 parasite infection data of the SINAVE is collected following the same procedures nationwide and
205 is therefore a good measuring tool for comparison purposes.

206

207 **5. Conclusions**

208 Our results suggest that children living in states with a higher probability of infection with
209 intestinal parasites have a higher BMIz later in life. The association between current intestinal

210 parasite infection and BMI is less straightforward, and seems to be opposite for *A. lumbricoides*
211 and intestinal protozoa. Further research is needed to confirm these ecological associations and
212 study possible mechanisms underlying the short-term and long-term consequences of intestinal
213 parasite infections on health. These findings may have important implications for Mexico, given
214 the context of a high prevalence of parasitic infection and obesity.

215

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219 **Disclosure statement**

220 the authors report no conflicts of interest

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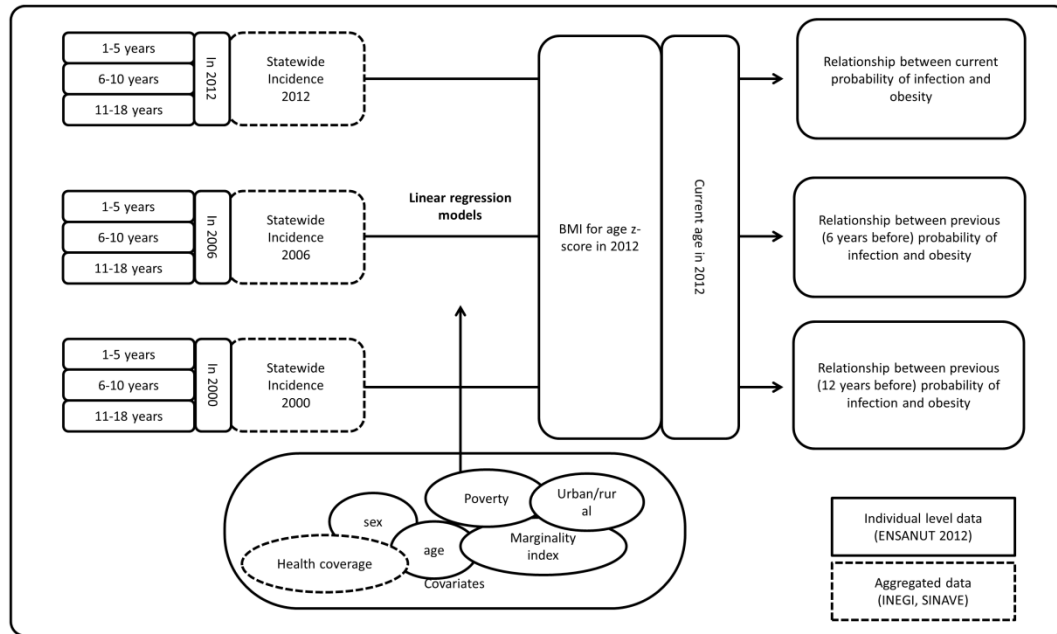
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Figure1. Diagram of the study design



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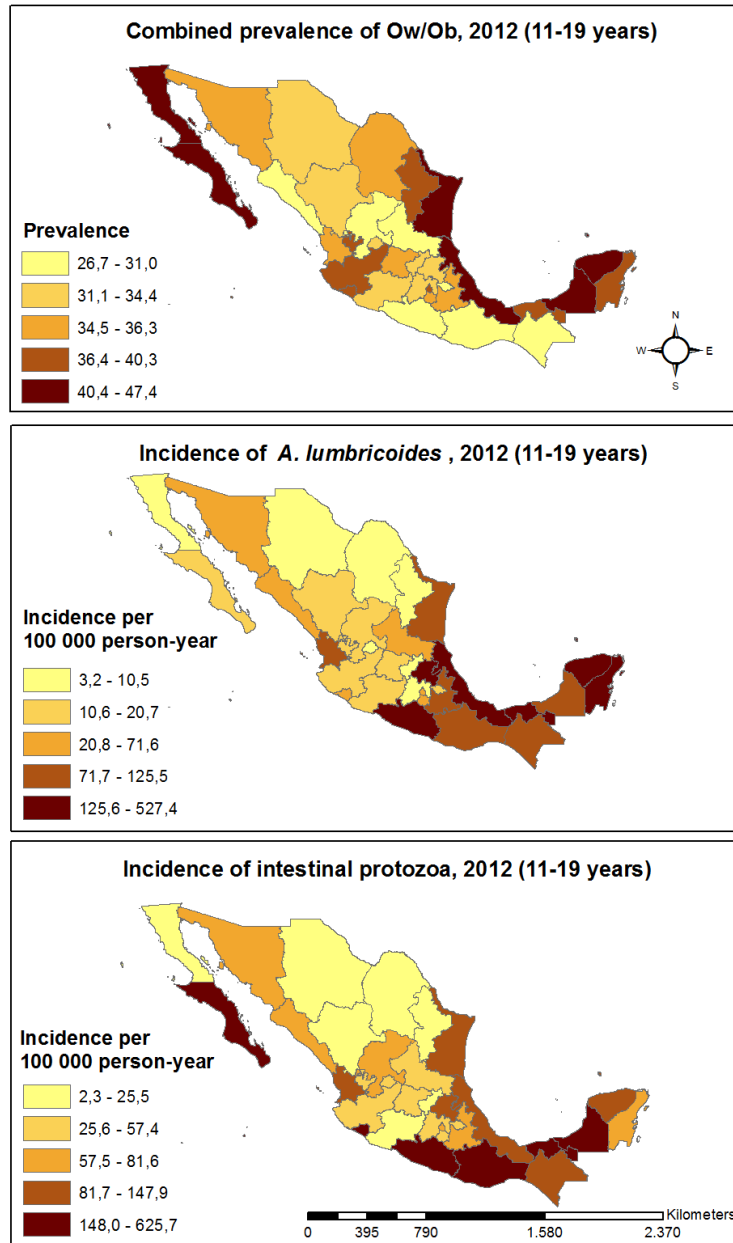
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342 **Figure 2.** Map of combined prevalence of overweight and obesity and the incidence of *Ascaris lumbricoides* and
343 protozoa in Mexico, 2012



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Table 1. General Characteristics of the population

	Mean	S.D.	Minimum	Maximum	Source
<i>A. lumbricoides</i> 1 to 5 years					
Incidence in 2012	94 ±	129.3	3	625	SINAVE 2012
Incidence in 2006	404 ±	461.1	5	1925	SINAVE 2006
Incidence in 2000	1177 ±	1151.2	99	4559	SINAVE 2000
<i>A. lumbricoides</i> 6 to 10 years					
Incidence in 2012	67 ±	108.2	0	526	SINAVE 2012
Incidence in 2006	212 ±	301.8	3	1822	SINAVE 2006
Incidence in 2000	907 ±	999.8	45	3990	SINAVE 2000
<i>A. lumbricoides</i> 11 to 18 years					
Incidence in 2012	27 ±	42.7	0	219	SINAVE 2012
Incidence in 2006	90 ±	140.0	1	757	SINAVE 2006
Incidence in 2000	367 ±	421.5	18	1711	SINAVE 2000
Protozoa 1 to 5 years					
Incidence in 2012	93 ±	104.0	2	545	SINAVE 2012
Incidence in 2006	239 ±	275.2	9	1498	SINAVE 2006
Incidence in 2000	351 ±	215.5	73	905	SINAVE 2000
Protozoa 6 to 10 years					
Incidence in 2012	78 ±	93.7	1	568	SINAVE 2012
Incidence in 2006	150 ±	200.7	4	1590	SINAVE 2006
Incidence in 2000	212 ±	154.8	43	731	SINAVE 2000
Protozoa 11 to 18 years					
Incidence in 2012	48 ±	65.4	0	354	SINAVE 2012
Incidence in 2006	78 ±	97.5	2	902	SINAVE 2006
Incidence in 2000	113 ±	88.0	23	420	SINAVE 2000
Prevalence of ow/ob (1-5 y) 2012	10.14 ±	2.6	4.91	14.83	ENSANUT 2012
Prevalence of ow/ob (6-10 y) 2012	34.54 ±	6.3	22.52	51.53	ENSANUT 2012
Prevalence of ow/obs (11-18 y) 2012	35.96 ±	5.0	27.80	47.38	ENSANUT 2012
Females (%)	53.4	2.2	50.6	56	ENSANUT 2012
High marginality (%)	42.5	5.3	36.2	43.5	ENSANUT 2012
Poverty (%)	46.6 ±	13.3	21.0	78.5	INEGI. 2012
Extreme Poverty (%)	11.2 ±	8.7	1.8	38.3	INEGI. 2012
Years in school	8.6 ±	0.9	6.3	10.6	INEGI. 2012
Health coverage (%)	62.4 ±	10.9	39.9	81.0	INEGI. 2012

ow/ob: overweight/obesity

Table 2. Linear regression model between the proximate probability of infection in 2012 with BMI for age z-score in 2012

Incidence in 2012	<i>Ascaris lumbricoides</i>						Protozoa					
	Crude model			Adjusted model			Crude model			Adjusted model		
	β	95% C.I.	p	β	95% C.I.	p	β	95% C.I.	p	β	95% C.I.	p
1 to 5 years (n=8927)	-0.17	(-0.18 - -0.16)	<0.01	-0.32	(-0.33 - 0.31)	<0.01	0.02	(0.01 - 0.03)	0.74	0.08	(0.06 - 0.10)	0.34
6 to 10 years (n=16347)	-0.15	(-0.16 - -0.14)	<0.01	-0.21	(-0.22 - 0.19)	0.01	0.19	(0.18 - 0.21)	0.02	0.61	(0.59 - 0.63)	<0.01
11 to 18 years (n=13992)	0.17	(0.16 - 0.19)	0.05	0.16	(0.13 - 0.18)	0.23	0.43	(0.42 - 0.45)	0.00	0.85	(0.83 - 0.88)	<0.01

Adjusted by: urban/rural strata, age, sex, marginality, poverty, health-coverage. Incidence per 100 person-year.

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Table 3. Linear regression model between the proximate probability of infection in 2000 and 2006 with BMI for age z-score in 2012

	<i>Ascaris lumbricoides</i>						protozoa					
	β	95% C.I.		p	β	95% C.I.		p	β	95% C.I.		p
Incidence in 2006	Crude model			Adjusted model			Crude model			Adjusted model		
1 to 5 years (n=9523)	-0.03	(-0.04 - -0.03)	0.16	0.13	(0.12 - 0.13)	<0.01	0.00	(0.00 - 0.01)	0.79	0.00	(0.00 - 0.01)	0.93
6 to 10 years (n=13025)	0.04	(0.04 - 0.05)	0.14	0.27	(0.26 - 0.28)	<0.01	0.07	(0.06 - 0.08)	0.14	0.13	(0.12 - 0.13)	0.01
11 to 18 years (n=7845)	0.33	(0.32 - 0.34)	<0.01	0.50	(0.49 - 0.52)	<0.01	0.24	(0.23 - 0.26)	0.00	0.16	(0.15 - 0.18)	0.03
Incidence in 2000												
1 to 5 years (n=6625)	0.04	(0.04 - 0.05)	<0.01	0.10	(0.09 - 0.10)	<0.01	0.29	(0.28 - 0.30)	0.00	0.47	(0.46 - 0.48)	<0.01
6 to 10 years (n=7580)	0.08	(0.08 - 0.09)	<0.01	0.11	(0.11 - 0.11)	<0.01	0.58	(0.56 - 0.60)	0.00	0.61	(0.59 - 0.63)	<0.01
11 to 18 years (n=5623)	0.19	(0.18 - 0.19)	<0.01	0.25	(0.24 - 0.26)	<0.01	0.88	(0.85 - 0.90)	0.00	0.99	(0.96 - 1.02)	<0.01

Adjusted by: urban/rural strata, age, sex, marginality, poverty, health-coverage. Incidence per 100 person-year.

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Table 4. Linear regression model between the proximate probability of infection with *A. lumbricoides* in 2012 with BMI for age z-score in 2012 according to statewide poverty rates

	Low Poverty			β	High Poverty		
	B	95% C.I.	p		95% C.I.	p	
<i>A. lumbricoides</i> Incidence in 2012							
1 to 5 years	0.33	(0.31 - 0.35)	<0.01	0.28	(0.29 - 0.27)	<0.01	
6 to 10 years	0.51	(0.48 - 0.53)	<0.01	0.05	(0.07 - 0.04)	0.42	
11 to 18 years	1.14	(1.11 - 1.17)	<0.01	0.34	(0.31 - 0.36)	0.01	

Adjusted by: urban/rural strata, age, sex, marginality, poverty and health-coverage. Incidence per 100 person-year.