Original Article

Multiple micronutrient deficiencies persist during early childhood in Mongolia

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Data on the prevalence of micronutrient deficiencies in children in Mongolia is limited. We therefore determined the prevalence of anaemia, iron deficiency anaemia (IDA), and deficiencies of iron, folate, vitamin A, zinc, selenium, and vitamin D among young Mongolian children. Anthropometry and non-fasting morning blood samples were collected from 243 children aged 6–36 months from 4 districts in Ulaanbaatar and 4 rural capitols for haemoglobin (Hb), serum ferritin, folate, retinol, zinc, selenium, and 25-hydroxyvitamin D (25-OHD) assays. Children with α-1-glycoprotein ≥1.2mg/L (n=27) indicative of chronic infection were excluded, except for folate, selenium, and 25-hydroxyvitamin D assays. Of the children 14.5% were stunted and none were wasted. Zn deficiency (serum Zn<9.9 µmol/L) had the highest prevalence (74%), followed by vitamin D deficiency 61% (serum 25-OHD<25 nmol/L). The prevalence of anaemia (24%) and iron deficiency anaemia (IDA) (16%) was lower, with the oldest children (24-36 mos) at lowest risk. Twenty one percent of the children had low iron stores, and 33% had vitamin A deficiencies (serum retinol < 0.70 µmol/L), even though two thirds had received vitamin A supplements. Serum selenium values were low, perhaps associated with low soil selenium concentrations. In contrast, no children in Ulaanbaatar and only 4% in the provincial capitols had low serum folate values (<6.8 nmol/L). Regional differences ($p<0.05$) existed for anaemia, deficiencies of vitamin A, folate, and selenium, but not for zinc or IDA. Of the children, 78% were at risk of ≥ two coexisting micronutrient deficiencies emphasizing the need for multimicronutrient interventions in Mongolia.

Key Words: Mongolia, children, deficiencies, anaemia, zinc, selenium

INTRODUCTION

The high rate of malnutrition in young Mongolian children is a serious issue. Anaemia, stunting, and rickets have all been identified as significant problems.[1,2] At present, intervention strategies aimed to rectify this situation have only succeeded in markedly reducing anaemia, with levels falling from 46% to 25% in children aged 6 to 35 months in some regions.[2] Even so, anaemia levels are still unacceptably high, especially among infants aged 6 to 12 months in whom the level (i.e., 48%) remains that of severe public health significance.[3]

Whether the reduction in anaemia during childhood can be attributed solely to a response to iron is uncertain, given that folate and vitamin A are also included in some of the micronutrient intervention programmes targeted at infants and young children in Mongolia. Both folate and vitamin A are also required for normal hematopoiesis,[4] and low levels in serum, especially for folate, have been reported among some young children in two surveys in Mongolia,[5,6] although neither were population-based studies. Besides micronutrient deficiencies, chronic inflammatory disorders and parasitic infections may also play a role in the etiology of anaemia among Mongolian children, but their relative contribution is uncertain.

Zinc is a growth-limiting micronutrient that may contribute to the persistent stunting in young Mongolian children. The traditional rice and wheat-based complementary foods used for young child feeding are likely to be inadequate in zinc, as reported for cereal-based complementary diets in other low income countries.[5,8] Certainly, according to the International Zinc Nutrition Collaborative Group,[9] the overall prevalence of stunting in Mongolia (i.e., 20%) is suggestive of substantial risk of zinc deficiency. It is possible that co-existing low selenium status, induced by low soil selenium levels in Mongolia, as reported for Northeast China[10], may exacerbate zinc deficiency, because selenium compounds regulate the delivery of zinc from metallothioneine to zinc enzymes.[11] To date, however, there have been no studies on the selenium status of the Mongolian population.

In contrast to anaemia, the prevalence of rickets in Mongolia is at the same level as that reported in 1999 across the country,[12] despite efforts to combat vitamin D deficiency through supplementation,[13] home fortification targeted at young children, social marketing and community nutrition education.[2] Such high levels of rickets have

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been attributed to low intakes of vitamin D, limited exposure to sunlight, the northern latitude of Mongolia, and the practice of swaddling young infants.[14]

Therefore, in this cross-sectional survey we have investigated the prevalence of biochemical deficiencies of iron, folate, vitamin A, zinc, selenium and vitamin D among children aged 6 to 36 months in Mongolia, all micronutrient deficiencies that may contribute to the relatively high rates of anaemia and/or stunting that persist among this age group. In addition, we have also examined the risk of co-existing micronutrient deficiencies in view of their potential negative impact on the efficacy of single micronutrient intervention programmes. Anaemia is defined here by a low haemoglobin concentration and iron deficiency anaemia by a low haemoglobin and serum ferritin <12µg/L in the absence of infection. Deficiencies of iron, folate, vitamin A, zinc, selenium, and vitamin D were assessed by measuring ferritin, folate, retinol, zinc, selenium, and 25-hydroxyvitamin D concentrations, respectively in serum.

SUBJECTS AND METHODS

This cross-sectional study was conducted in November 2006 in four districts in Ulaanbaatar, the capital city of Mongolia, and in four capital towns of the provinces of Bulgan, Bayanhongor, Dornod and Khovd, located in the northern, southern, eastern, and western parts of the country, respectively. Eligible children were identified through official lists obtained from district hospitals in conjunction with the local governor's office. Inclusion criteria were apparently healthy children aged 6 to 36 months with no evidence of infection within the previous 7 days, and whose primary caregivers were willing to allow them to participate in the study. The age of each child was obtained by maternal self-reports and confirmed through immunization cards. Eligible children were stratified by age and gender, and then every fourth child was selected from a randomized list of each stratum. Of the 243 children recruited, 122 were male and 121 were female, with a mean (±SD) age of 20.0±8.5 months. This sample size (n=243) allowed estimation of the prevalence of micronutrient deficiencies in the children to within 10 percentage points of the true value with a confidence level of 95%. Ethical approval of the study protocol was obtained from the Human Ethics Committee of the Mongolian Ministry of Health. Verbal and written informed consent was obtained from the parents or guardians of each child in the survey.

Socio-demographic, health, and anthropometric status assessment

A pre-tested socio-demographic questionnaire was administered to the parent or caregiver of each child by trained Mongolian research assistants. Socio-demographic variables assessed included: household size, income, and level of education of mother and father or guardian. Use of vitamin and/or mineral supplements (including the last mega-vitamin A dose) and breastfeeding status was also determined.

Anthropometric measurements, including weight and length or height, were taken by trained research assistants using standardized techniques and calibrated equipment.[15] Supine length was measured in children less than 24 months of age and standing height in those 24–36 months of age, using a portable adult/infant length/stature measuring board (Perspective Enterprises, MI, USA). Each anthropometric measurement was taken in duplicate. A third measurement was taken if the difference between the first two measurements was outside the allowable difference for that measure.[16] Z-scores for length/height-for-age (HAZ), weight-for-age (WAZ), weight-for-length (WLZ) or weight-for-height (WHZ), and body mass index-for-age (BAZ) were calculated from the WHO 2006 multicenter growth-reference data using the computer program WHO Anthro 2005.[17] None of the children had unacceptably extreme anthropometric values (WHO, 1995).[18]

Biochemical assessment

Morning, non-fasting peripheral venipuncture blood samples were taken with subjects in a sitting position, held by a parent or caregiver. A topical local vasodilator anesthetic amethocaine (Ametop™) was applied to the venipuncture site to reduce any discomfort, and the blood drawn into a trace-element-(TE)-free evacuated tube (Becton Dickinson, Franklin Lakes, NJ, USA) in accordance with the IZiNCG [9] procedures for serum zinc. All blood samples were refrigerated immediately after collection,[19] protected from ultra-violet light, and the serum separated within two hours using TE-free techniques. Aliquots of serum were stored in trace-element free polyethylene vials and frozen immediately, initially at –20°C and later at –70°C. Frozen serum samples were hand-carried to the Trace Element Laboratory of the Department of Human Nutrition, University of Otago, New Zealand for analysis.

In Ulaanbaatar, an additional blood sample (~2ml) was taken from each child in an evacuated tube containing EDTA as an anticoagulant (Becton Dickinson, Franklin Lakes, NJ) for complete blood count (CBC) performed in a laboratory in Ulaanbaatar using an electronic coulter counter. In the four provincial capitols haemoglobin (Hb) analysis was performed on site using a haemoglobinometer (Hemocue AB, Ångelholm, Sweden) because electronic coulter counters were not available in these centers. Serum ferritin was analyzed by the IMx system that uses Microparticle Enzyme Immunoassays technology sera (Abbott Laboratories, IL, USA), and serum retinol by high-pressure liquid chromatography.[20] Serum zinc was analyzed by flame atomic absorption spectrophotometry (AAS) (Perkin Elmer 2690, Ebos Group Ltd., Auckland, New Zealand), and serum selenium via graphite furnace AAS. Analysis of serum folate was performed by using the microtiter technique described by O'Broin and Kelleher[21] with chloramphenicol-resistant *Lactobacillus casei* as the test microorganism. An external whole-blood standard (National Institute for Biological Standards and Control, South Mimms, United Kingdom) with a certified folate concentration of 29.4 nmol/L was used to generate the standard curve. Serum 25-hydroxyvitamin D was performed by using a 2-step radioimmuno assay procedure using commercial kits (DiaSorin, Stillwater, MN) which quantitatively recovers[22] both 25(OH)D_2 and 25(OH)D_3. Chronic infection or inflammation was based on serum α-1- glycoprotein concentrations ≥1.2mg/L,[23,24] assayed using an immunoturbidimetric assay on an automated analyser system (Cobas Mira II).

The precision of all the biochemical assays was checked using a pooled serum sample and their accuracy established using certified reference materials or appropriate manufacturers' controls. The between-assay coefficient of variation (CV as %) for the pooled serum for serum ferritin, zinc, retinol, folate, serum 25-hydroxyvitamin D, and α-1 glycoprotein were 5.5, 4.7, 4.8, 9.0, 12.9, and 2.8 %, respectively. Values for the certified reference materials or manufacturer's controls fell within the certified ranges for serum ferritin, zinc, 25-hydroxyvitamin D, and serum α-1- glycoprotein.

Anaemia was defined as a haemoglobin <110 g/L,[7] adjusted for the altitude for each location in Mongolia.[3] For storage iron depletion in the absence of anaemia, the commonly used cutoff for serum ferritin of <12 µg/L was used. Iron deficiency anaemia (IDA) was defined as iron deficiency concurrent with anaemia. The following interpretive criteria were used to define other micronutrient deficiencies in serum: zinc < 9.9 µmol/L,[25] retinol < 0.70 µmol/L,[26] selenium ≤ 0.82 µmol/L,[27] and 25-hydroxyvitamin D < 25nmol/L.[22] There are no pediatric interpretive values for serum folate so the cutoff value for "at risk" adults was used (i.e., <6.8nmol/L).[28]

Statistical analysis

All variables were tested for normality by using the Kolmogorov-Smirnov test, and log transformed to conform to a normal distribution, where necessary (i.e., serum ferritin and retinol). Differences in socio-demographic, health, and breast feeding status between Ulaanbaatar and the provincial capitols were examined using Fisher's exact test or the Mann-Whitney-*U* test, where appropriate. Two-way analysis of variance (ANOVA) was used to examine age-group and sex differences in the anthropometric Z-scores. Two-way analysis of variance was also used to assess whether the hematological variables for the children in Ulaanbaatar differed by age group and/or sex. Post hoc analysis (Tukey's honestly significant difference) was used to establish which means for each hematological variable were significantly different by age group. Differences between sexes for each age group were not examined because of the small number of subjects in each age-sex group. Analysis of covariance (ANCOVA) was used to investigate whether haemoglobin, serum ferritin (Table 4) or micronutrient indices (Table 6) were dependent on sex, age group, or setting (Ulaanbaatar or provincial capitols), adjusting for infection as a covariate, where appropriate. Differences in the prevalence of low biochemical indices by age group and setting were assessed using cross-tabulation and Fisher's exact test or chi-square test for these categorical variables, with children with serum α-1- glycoprotein concentrations ≥1.2 mg/L excluded, except for serum folate, selenium, and 25-hydroxyvitamin D. Correlations between biochemical indices were examined using Spearman's Rank correlation tests. A *p*-value <0.05 indicated statistical significance. Statistical analyses were carried out using SPSS version 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Socio-demographic and breastfeeding status

The socio-demographic status was similar for the children from Ulaanbaatar and the provincial capitols: in both settings, the median household size was four, and the median family income was about 75,000 Mongolian Tugriks or US$65.00 per month (Table 1). The proportion of fathers with at least a high school level of education was also similar in both settings, but for the mothers, significantly more (p=0.001) from Ulaanbaatar had a high school level of education or above, compared to those from the provincial capitols. The prevalence of chronic infection (α-1-glycoprotein concentration ≥1.2 mg/L) was significantly higher (p=0.001) for the children aged 24 to 36 months from the provincial capitols compared to Ulaanbaatar. More than two thirds of the children in Ulaanbaatar, and nearly 90% in the provincial capitols had received a vitamin A supplement within the past 200 days, based on self-reports by mothers or caregivers.

Table 1. Selected socio-demographic, health, and breastfeeding status of children from Ulaanbaatar and the four provincial capitol towns

	Age Group (month)	Ulaanbaatar	Provincial Capitols	Fisher's exact test(2 sided significance)
Number and percentage of male subjects	6 – 11.99	16/30 (53%)	13/28 (46%)	0.793
	12 – 23.99	30/50 (60%)	24/51 (47%)	0.233
	24 – 36	19/40 (48%)	24/44 (55%)	0.662
Breastfed at time of survey	6 – 11.99	29/30 (97%)	27/28 (96%)	1.000
	12 – 23.99	43/50 (86%)	34/51 (67%)	0.034
	24 – 36	15/40 (38%)	21/44 (48%)	0.383
Median household size (IQR), n = 243	6 – 36	4 (4, 5)	4 (3, 5)	0.603*
Median household income US $ (IQR), n = 236	6 – 36	69 (43, 111)	60 (43, 86)	0.101*
Number and proportion of mothers educated at high school and above	6 – 36	95/120 (79%)	69/117 (59%)	0.001
Number and proportion of fathers educated at high school and above	6 – 36	68/85 (80%)	70/93 (75%)	0.477
Infection (AGP ≥1.2 mg/L)	6 – 11.99	1/30 (3%)	2/28 (7%)	0.605
	12 – 23.99.	7/50 (14%)	7/50 (14%)	1.000
	24 – 36	0/39 (0%)	10/44 (23%)	0.001
Child given an iron supplement within 200days	6 – 36	2/120 (2%)	3/123 (2%)	1.000
Child given a vitamin A supplement within 200days	6 – 36	81/120 (68%)	109/123 (89%)	0.000

* Asymptotic significance of difference from Mann-Whitney U test.

Table 2. Mean (SD) anthropometric measures and Z-scores by age-group and sex for all the children.

Index	Age Group (month)	n	Females	n	Males
Weight	6 – 11.99	29	9.1 (1.2)	29	9.3 (0.9)
(kg)	12 – 23.99	47	10.7 (1.6)	54	10.8 (1.2)
	24 – 35.99	41	12.5 (1.8)	43	13.3 (1.4)
Length /	6 – 11.99	29	70.3 (3.5)	29	71.9 (3.3)
Height	12 – 23.99	46	78.8 (4.5)	54	79.3 (3.4)
(cm)	24 – 35.99	41	86.0 (4.5)	43	88.8 (4.9)
WLZ†	6 – 11.99	29	1.01 (0.94)	29	0.65 (0.80)
WLZ	12 – 23.99.	46	0.80 (1.01)	54	0.54 (0.99)
WHZ	24 – 35.99	41	0.65 (1.04)	43	0.62 (0.88)
LAZ†	6 – 11.99	29	0.26 (1.33)	29	–0.49 (1.16)
LAZ	12 – 23.99.	46	–0.71 (1.04)	54	–1.00 (1.05)
HAZ	24 – 35.99	41	–1.38 (1.22)	43	–0.78 (1.21)
WAZ†	6 – 11.99	29	0.83 (0.93)	29	0.20 (0.90)
	12 – 23.99	47	0.23 (1.02)	54	–0.08 (0.98)
	24 – 35.99	41	–0.28 (1.07)	43	0.03 (0.84)
BAZ†	6 – 11.99	29	0.94 (0.94)	29	0.67 (0.81)
	12 – 23.99	46	0.95 (1.00)	54	0.74 (0.99)
	24 – 35.99	41	0.86 (1.08)	43	0.75 (0.94)

†Z-Score differences distinguishing the age groups and sexes are not significant except for HAZ (for AgeGroup p= 0.000, Sex*AgeGroup = 0.002) and WAZ (for AgeGroup p= 0.001, Sex*AgeGroup p= 0.012).

Almost all of the infants aged 6 to 12 months in both settings, and at least two thirds or more aged 12 to 24 months were still being breastfed, especially in Ulaanbaatar (p=0.034). Even at 24 to 36 months of age, more than a third of the children in Ulaanbaatar and nearly half in the provincial capitols were still being breastfed. Indeed, only 30.5% (n=74) of the mothers had discontinued breastfeeding at the time of the study, after breastfeeding for a median duration of 14 months.

Anthropometry

There were no significant differences in the mean anthropometric indices for the children in Ulaanbaatar compared with the provincial capitols, in the districts within Ulaanbaatar, or across the four provincial capitols. Therefore, the anthropometric variables for the children from the eight geographical regions were combined (n=242), as shown in Table 2. Mean LAZ (or HAZ) scores were negative for both males and females for each age group, with the exception of females aged 6 to 12 months. In contrast, the mean WLZ/WHZ and BAZ scores were positive, and the mean WAZ scores either positive or approximately zero for both males and females in all three age groups. Two-way ANOVA, with sex and age-group as independent variables, shows age-related differences for the mean LAZ (or HAZ) and mean WAZ scores; values were lower in the two older age groups, especially for females aged 24 to 36 months.

Overall, the prevalence of stunting (i.e., LAZ or HAZ <–2.0 SD) was 14.5% (n=35), and independent of sex. Only 4% (n=9) of the children were underweight (i.e., WAZ <–2.0 SD) and none were wasted (WLZ or WHZ <–2.0 SD). Stunted children tended to have lower WLZ or WHZ scores than their non-stunted counterparts, although the difference was not significant.

Anaemia, iron deficiency anaemia, and low iron stores

There were no significant differences in the mean (SD) hematologic variables across the four districts in Ulaanbaatar so these hematologic data have been combined. The overall means (±SD) of the hematological variables by sex for the three age groups are shown in Table 3. None of the hematologic variables in Ulaanbaatar were affected by infection/inflammation. Two-way ANOVA with age-group and sex as independent variables shows that age-group differences were significant (p<0.003) for all variables except red blood cell count (p=0.143). Sex-related differences also existed for haemoglobin (p=0.029), mean cell volume (MCV) (p=0.006), and red cell distribution width (RDW) (p=0.029). Post-hoc analysis revealed that the difference between the older children (sexes combined) and each of the two younger age groups in Ulaanbaatar were significant (p<0.008) for all the hematological variables, except RBC count and white blood cell count. The oldest children aged 24 to 36 months had the highest mean values for haemoglobin and haematocrit but the lowest mean RBC count and RDW.

Based on a MCV < 77 fL,[29] almost half (i.e., 48%) of the anaemia in Ulaanbaatar was microcytic anaemia; there were no cases of an elevated MCV (i.e. > 98 fL) indicative of macrocytic anaemia. Of the children in Ulaanbaatar, 27.5% (30/109) had an elevated RDW (i.e., >14%).[30]

Table 4 compares the mean (95th CI) haemoglobin and geometric mean serum ferritin concentrations for the three age groups of children from Ulaanbaatar and the four provincial capitols combined. Both haemoglobin and serum ferritin concentrations were significantly affected by chronic infection/inflammation, so the values presented have been adjusted during ANCOVA and calculated at AGP = 0.85 mg/L. Sex-related differences in mean haemoglobin were not apparent for the children in the provincial capitols (data not shown) unlike the children from Ulaanbaatar. Age-related trends (p<0.001) in mean haemoglobin and geometric mean serum ferritin concentrations in the provincial capitols were comparable to those reported for Ulaanbaatar. Again, the oldest children (i.e., 24 to 36 months) had the highest values for both haemoglobin and serum ferritin, although the mean values for haemoglobin and ferritin were higher and lower respectively than their counterparts in Ulaanbaatar, and these differences were significant (p<0.05). There was no significant interaction between age-group and setting (age group * urban_rural) for haemoglobin or serum ferritin.

Overall, after excluding the children with α-1-glycoprotein ≥ 1.2 mg/L, 24.4% (n=49/201) of the children were anaemic. None of the children had severe anaemia (i.e., haemoglobin < 70 g/L). Anaemia prevlence

Table 3. Mean (SD) values for hematological variables by sex and age group for all the children in Ulaanbaatar.

Index	Age Group (month)	n	Females	n	Males		Males + Females
Haemoglobin	6 – 11.99	13	120.0 (8.9)	12	119.1 (9.2)	25	119.5 (8.9)
(g/L)	12 – 23.99	19	124.0 (11.1)	28	113.8 (14.8)	47	117.9 (14.2)
	24 – 35.99	19	131.3 (9.2)	18	127.4 (9.8)	37	129.4 (9.6)
Haematocrit	6 – 11.99	13	36.4 (2.5)	12	36.7 (2.5)	25	36.6 (2.5)
(%)	12 – 23.99	19	37.8 (2.8)	28	35.6 (3.6)	47	36.4 (3.4)
	24 – 35.99	19	39.7 (2.7)	18	38.4 (2.8)	37	39.1 (2.8)
Mean cell volume	6 – 11.99	13	73.8 (4.7)	12	70.9 (6.0)	25	72.4 (5.4)
(fL)	12 – 23.99	19	75.0 (6.2)	28	69.7 (8.2)	47	71.8 (7.8)
	24 – 35.99	19	81.0 (4.3)	18	78.6 (6.1)	37	79.8 (5.3)
Red blood cell count	6 – 11.99	13	4.95 (0.42)	12	5.19 (0.39)	25	5.06 (0.42)
(10^{12}/L)	12 – 23.99	19	5.04 (0.30)	28	5.15 (0.55)	47	5.11 (0.47)
	24 – 35.99	19	4.91 (0.39)	18	4.91 (0.45)	37	4.91 (0.41)
Red cell distribution	6 – 11.99	13	13.5 (0.8)	12	14.5 (1.6)	25	14.0 (1.3)
width (%)	12 – 23.99	19	14.4 (1.6)	28	15.6 (1.9)	47	15.1 (1.8)
	24 – 35.99	19	13.5 (1.0)	18	13.2 (1.5)	37	13.4 (1.3)
White blood cell count	6 – 11.99	13	11.9 (3.6)	12	12.0 (4.0)	25	11.9 (3.7)
(10^9/L)	12 – 23.99	19	11.4 (3.6)	28	9.7 (2.5)	47	10.4 (3.0)
	24 – 35.99	19	9.3 (2.6)	18	8.9 (2.6)	37	9.1 (2.6)

n=number of children
None of the hematological variables in the Ulaanbaatar sample are significantly affected by infection. Therefore no correction for α-1-glycoprotein levels has been applied. Age-Group differences are significant (p<0.003) for all the variables except red blood cell count (p=0.143). Differences between the sexes for all the children combined are smaller, but significant for haemoglobin (p=0.029), mean cell volume (p=0.006), and red cell distribution width (p=0.029). The interaction sex*AgeGroup is not significant for any of the variables.

Table 4. Haemoglobin (mean, 95th CI) and serum ferritin[1] (geometric mean, 95% CI) concentrations in children from Ulaanbaatar and the four provincial capitol towns.

	Age Group (month)	n	Ulaanbaatar	n	Provincial Capitols
Haemoglobin	6 – 11.99	25	119 (113, 125)	27	116 (110, 121)
(g/L)	12 – 23.99	47	118 (114, 122)	49	114 (110.118)
	24 – 35.99	36	129 (124, 134)	44	125 (121, 129)
Serum	6 – 11.99	30	12.3 (8.8, 17.2)	28	14.1 (10.0, 19.9)
ferritin†	12 – 23.99	50	9.7 (7.5, 12.6)	50	12.3 (9.5, 15.9)
(µg/L)	24 – 35.99	39	18.7 (13.9, 25.1)	44	30.1 (22.8, 40.0)

n=number of children
† Calculated from log-normal transformed values to improve the distribution
Note: Concentrations of both haemoglobin and serum ferritin are significantly (p<0.04) affected by infection and have been adjusted and calculated at α-1-glycoprotein = 0.85g/L. Age-group differences for the means are significant for both variables (p< 0.001). The differences between Ulaanbaatar and the provincial capitols are also significant for both variables (p<0.05). The interaction term (Agegroup * rural-urban) is non-significant in both cases.

was greater among the children in the provincial capitols than in Ulaanbaatar (31%, n=31/101 vs. 18%, n=18/100; p=0.048), but independent of sex (data not shown). The overall anaemia prevalence also differed by age group (p=0.002): the oldest children had a lower prevalence compared to the two younger age groups.

The prevalence of IDA was 16% (n=32/201) overall, and unlike anaemia, was independent of setting. Nevertheless, IDA did follow a significant age-related pattern (p=0.035) similar to that of anaemia, as shown in Table 5, with the oldest children aged 24 to 36 months having the lowest prevalence in both Ulaanbaatar and the provincial capitols. Overall, the prevalence of low iron stores (in the absence of anaemia) was 21% (43/201), and unlike iron deficiency anaemia, tended to be higher among the children in Ulaanbaatar than their counterparts in the provincial capitols (27%, n= 27/100 vs. 16%, n=16/101). The overall prevalence of low iron stores without anaemia also differed by age group (p=0.053): with the oldest

Table 5. Prevalence† of anaemia, iron-deficiency anaemia, and low iron stores by age group in children from Ulaanbaatar and the four provincial capitol towns.

	Age Group (month)	Ulaanbaatar	Provincial Capitols	Total
Prevalence of anaemia	6 – 11.99	6/24 (25%)	8/25 (32%)	14/49 (29%)
	12 – 23.99	12/40 (30%)	18/42 (43%)	30/82 (37%)
	24 – 35.99	0/36 (0%)	5/34 (15%)	5/70 (7%)
				p=0.002
Prevalence of iron-deficiency anaemia	6 – 11.99	5/24 (21%)	3/25 (12%)	8/49 (16%)
	12 – 23.99	11/40 (28%)	10/42 (24%)	21/82 (26%)
	24 – 35.99	0/36 (0%)	3/34 (9%)	3/70 (4%)
				p=0.035
Prevalence of low iron stores in the absence of anaemia	6 – 11.99	7/24 (29%)	6/25 (24%)	13/49 (27%)
	12 – 23.99	8/40 (20%)	9/42 (21%)	17/82 (21%)
	24 – 35.99	12/36 (33%)	1/34 (3%)	13/70 (19%)
				p=0.053

†Children with serum α-1-glycoprotein concentrations ≥1.2 mg/L were excluded.
Cutoffs used: Anaemia: haemoglobin < 110g/L; Iron deficiency anaemia: haemoglobin < 110g/L together with serum ferritin: <12µg/L; Low iron stores in the absence of anaemia: haemoglobin ≥ 110g/L together with serum ferritin: <12µg/L. The differences between the prevalence in Ulaanbaatar and the Provincial Capitols at each age group is only significant at 24-36 mo for anaemia ($p < 0.023$) and low iron stores in the absence of anaemia ($p < 0.001$) (Fisher's exact test).

Table 6. Mean (95% CI) serum folate, retinol, zinc, selenium, and 25-hydroxyvitamin D concentrations by age group in children from Ulaanbaatar and the four provincial capitol towns.

	Age Group (month)	n	Ulaanbaatar	n	Provincial Capitols
Serum folate† (nmol/L)	6 – 11.99	29	28.5 (25.5, 31.9)	26	16.7 (13.5, 20.7)
	12 – 23.99	45	22.8 (20.3, 25.7)	50	15.6 (13.8, 17.6)
	24 – 35.99	36	17.2 (14.7, 20.1)	44	12.0 (10.3, 14.1)
Serum retinol‡ (µmol/L)	6 – 11.99	24	0.73 (0.61, 0.85)	26	0.80 (0.68, 0.92)
	12 – 23.99	42	0.76 (0.67, 0.85)	43	0.77 (0.68, 0.86)
	24 – 35.99	29	0.86 (0.75, 0.97)	39	0.80 (0.70, 0.89)
Serum zinc‡ (µmol/L)	6 – 11.99	30	8.95 (8.44, 9.46)	28	8.52 (8.00, 9.05)
	12 – 23.99	50	9.11 (8.71, 9.50)	50	8.83 (8.44, 9.23)
	24 – 35.99	39	8.93 (8.48, 9.38)	44	8.99 (8.57, 9.42)
Serum Selenium (µmol/L)	6 – 11.99	30	0.72 (0.65, 0.78)	28	0.74 (0.69, 0.80)
	12 – 23.99	48	0.77 (0.73, 0.81)	51	0.80 (0.76, 0.84)
	24 – 35.99	39	0.78 (0.72, 0.84)	44	0.86 (0.81, 0.91)
Serum 25-hydroxy vitamin-D† (nmol/L)	6 – 11.99	15	16.1 (12.7, 20.5)	4	30.5 (15.3, 60.8)
	12 – 23.99	32	24.1 (18.6, 31.2)	12	23.0 (16.5, 32.0)
	24 – 35.99	24	25.9 (20.1, 33.4)	11	24.3 (18.0, 32.8)

† Log transformed prior to calculation of the mean and confidence interval.
‡ Evaluated at serum α-1-glycoprotein = 0.85 mg/L
Differences between Ulaanbaatar and the provincial capitol towns are significant for serum folate (p<0.001) and serum zinc (p<0.05).
Differences among the age groups are significant for serum folate (p<0.001) and serum zinc (p<0.01).

children again having the lowest prevalence of iron deficiency (Table 5).

Folate and vitamin A deficiency

The overall geometric mean serum folate concentration (n=230) was 17.65 nmol/L. Serum folate concentrations were independent of infection and sex, but two-way ANOVA showed they were significantly associated with age group (p<0.001) and setting(p<0.001). Concentrations decreased with age in both settings (Table 6), and the mean values in Ulaanbaatar were higher for each age group than those for the provincial capitols. There were no differences in mean serum folate values within the four districts of Ulaanbaatar, but the pattern across the provincial capitols (data not shown) varied significantly (p=0.000; r = 0.201); the mean value was lowest for Hovd (11.01 nmol/L; 95% CI:9.32, 13.02) and highest for Dornod (mean value 13.75 nmol/L; 95%CI: 11.13, 16.99).

Of the children overall, only 4% (9/230) (Table 8) had serum folate < 6.8 nmol/L indicative of risk of folate deficiency.[28,31] None of the children in Ulaanbaatar had low serum folate concentrations. In the provincial capitols, the oldest children had the highest prevalence (14%; 6/44) (Table 7) but this difference was not significant (p=0.093). There was no significant difference in the prevalence of anaemia for children with and without serum folate values <6.8nmol/L (i.e., 25 % (2/8) vs. 30.8%, 26/91).

Serum retinol concentrations were significantly lower in those children with elevated serum α-1-glycoprotein levels (n=23/203) indicative of chronic infection/ inflammation (i.e., ≥ 1.2 mg/L); mean serum retinol concentrations were 0.63 and 0.81 µmol/L (p=0.032) with

Table 7. Prevalence of low serum zinc, retinol, selenium, and 25-hydroxyvitamin-D concentrations according to age group and region.

	Age group (month)	Ulaanbaatar	Provincial Capitols	Total
Prevalence of low serum folate (<6.8 nmol/L)	6 – 11.99	0/29 (0%)	1/26 (4%)	1/55(2%)
	12 – 23.99	0/45 (0%)	2/50 (4%)	2/95(2%)
	24 – 35.99	0/36 (0%)	6/44 (14%)	6/80 (7%)
Prevalence of low serum retinol† (<0.70 μmol/L)	6 – 11.99	10/23 (43%)	9/24 (38%)	19/47 (40%)
	12 – 23.99	13/37 (35%)	11/38 (29%)	24/75 (32%)
	24 – 35.99	8/29 (28%)	9/29 (31%)	17/58 (29%)
Prevalence of low serum zinc† (<9.9 μmol/L)	6 – 11.99	25/29 (86%)	20/26 (77%)	45/55 (82%)
	12 – 23.99	28/43 (65%)	34/43 (79%)	62/86 (72%)
	24 – 35.99	27/39 (69%)	24/34 (71%)	51/73 (70%)
Prevalence of low serum selenium (<0.82μmol/L)	6 – 11.99	22/30 (73%)	16/28 (57%)	38/58 (66%)
	12 – 23.99	30/48 (62%)	28/51 (55%)	58/99 (59%)
	24 – 35.99	23/39 (59%)	17/44 (39%)	40/83 (48%)
Prevalence of low serum 25-hydroxy-vitamin-D (<25 nmol/L)	6 – 11.99	13/15 (87%)	1/4 (25%)	14/19 (73%)
	12 – 23.99	19/32 (59%)	7/12 (58%)	26/44 (59%)
	24 – 35.99	14/24 (58%)	6/11 (55%)	20/35 (57%)

†Children with serum α-1-glycoprotein concentrations ≥1.2 mg/L were excluded

Table 8. Overall prevalence of single and multi-micronutrient deficiencies among all the children†

Micronutrient indicator of deficiency	Overall prevalence
Anaemia (haemoglobin < 110g/L)	49/201 (24%)
Iron deficiency anaemia	32/201 (16%)
Low serum folate (<6.8 nmol/L)	9/230 (4%)
Low serum retinol (< 0.7μmol/L)	60/180 (33%)
Low serum zinc (<9.9 μmol//L)	158/214 (74%)
Low serum selenium (<0.82 μmol//L)	136/244 (56%)
Low serum 25-hydroxyvitamin D (<25 nmol/L)	60/98 (61%)
Two or more of the above	78%

† Children with serum α-1-glycoprotein concentrations ≥1.2 mg/L were excluded

and without infection/inflammation, respectively. Adjusted mean serum retinol concentrations were independent of sex (data not shown), setting (Ulaanbaatar versus provincial capitols), and age group (Table 6). No correlation was observed between serum retinol and either serum ferritin or haemoglobin concentrations.

Among the non-infected children, the overall prevalence of low serum retinol levels indicative of vitamin A deficiency (i.e., < 0.70 μmol/L)[26] was 33% (n=60/180) (Table 8), with no significant differences by setting or age group. Of the non-infected children, 8.9% (16/180) had severe vitamin A deficiency (i.e., serum retinol <0.35 μmol/L). Unlike serum zinc, the prevalence of low serum retinol concentrations differed across the four provincial capitols (data not shown, p=0.002), with Bayanhongor having the lowest (i.e., 11.1 %, 3/27) and Hovd the highest prevalence (71.4 %, 15/21).

Zinc, selenium, and vitamin D deficiency

As expected, children with elevated α-1-glycoprotein levels indicative of inflammation and infection (n=27) (ie., ≥ 1.2 mg/L;) had a significantly lower mean serum zinc (8.0 vs. 9.0 μmol/L, p=0.005) than those without inflammation or infection. The overall mean (SD) serum zinc concentration, after adjusting for infection, was 8.9 (1.4) μmol/L. Unlike serum ferritin, mean serum zinc concentrations were independent of sex (data not shown), setting, or age-group (Table 6). There was no significant difference in the prevalence of low serum zinc concentrations (<9.9 μmol/L)[25] between children living in Ulaanbaatar and the provincial capitols, or among the three age groups of children in either setting (Table 7). However, within Ulaanbaatar (but not across the four provincial capitols), the prevalence of low serum zinc differed significantly (p=0.022), ranging from 53.6 (15/28) to 92.3 % (24/26) across the four districts (data not shown). Overall, 74% (n=158/214) of the children had low serum zinc concentrations (<9.9 μmol/L) in the absence of infection or inflammation (Table 8).

In contrast, serum selenium concentrations were unaffected by infection. The overall mean serum selenium concentration (SD) was 0.77 μmol/L (95% CI 0.76, 0.80). Two-way ANOVA showed that values varied significantly with setting (p=0.043) and age (p=0.007): mean serum selenium concentrations were higher for children in the provincial capitols compared to Ulaanbaatar, and highest for the oldest children. There was a positive correlation between serum zinc and selenium (r=0.156; p=0.011) in non-infected children. The overall prevalence of serum selenium concentrations indicative of risk of deficiency was 56% (118/212) (Table 8), with no significant differences in the prevalence by setting or age-group (Table 7).

Serum 25-hydroxyvitamin D concentrations (n=98) were also independent of infection. The number of samples available from the provincial capitols for serum 25-hydroyvitamin D analyses (n=14) was very small so that no comparison between the Ulaanbaatar and the four capitol towns, or between the males and females could be made. Overall, 61% (60/98) (Table 8) of the children had serum 25-hydroxy-vitamin D concentrations <25nmol/L; infants aged 6 to 12 months in Ulaanbaatar had the highest prevalence of low values (Table 7).

DISCUSSION

This is the first study to present data on the zinc and selenium status of young Mongolian children, and highlights widespread deficiencies of these micronutrients in both Ulaanbaatar, the capital city, and the four provincial capitols of four rural provinces in Mongolia. Our findings also demonstrate that deficiencies of zinc, vitamin D, and selenium frequently co-exist with those of vitamin A and, to a lesser degree, IDA. Caution must be used, however, when interpreting these results, as they are not based on a nationally representative sample of Mongolian children aged 6 to 36 months of age. Further, the number of children in this study from each age group was small. Nevertheless, the overall prevalence of anaemia among young Mongolian children aged 6 to 23 mos based on the third Mongolian National Nutrition Survey[3] (i.e., 33.4%) in 2004 was very comparable to that reported here (i.e., 34%).

Zinc deficiency

The prevalence of zinc deficiency among these Mongolian children was much higher than that of anaemia or IDA, and more than three times the level set by IZiNCG as indicative of the need for a national zinc intervention programme.[9] This finding was unexpected, especially given that none of the children were wasted and only 14.5% were classified as stunted, a well-recognized feature of zinc deficiency during childhood.[9] Further, the stunted Mongolian children did not have significantly lower serum zinc concentrations than their non-stunted counterparts (data not shown). Also no sex-related differences were apparent among the children with low serum zinc concentrations, although some studies[32,33] have reported a higher prevalence of zinc deficiency among boys than girls.

Several factors may explain the lack of concordance between the prevalence of low serum zinc concentrations and stunting noted here. For example, it was not feasible to collect fasting blood samples from these young children; even though we were aware that serum zinc concentrations tend to increase after a recent meal.[9] Such meal-induced changes result in large variability in serum zinc concentrations both within and between subjects. We could not remove the within-subject variability statistically because it was not feasible to collect more than one blood sample from each child.[34] As a result, the variance of the distribution of serum zinc concentrations was likely to be large. There is also some uncertainty on the cutoff used to define low serum zinc concentrations among infants below 1 year of age.[35] The present cutoffs are based on data extrapolated from older children who participated in the US NHANES II survey.[25] However, there is some evidence that a lower cutoff value may be necessary for infants,[36] which could also be responsible in part for an overestimate for the prevalence of zinc deficiency among the infants studied here.

Two fortification interventions in Mongolia have included zinc. In a wheat flour fortification pilot programme, zinc (2.2 mg per 100 g flour as zinc oxide) is included as one of the fortificants in the pre-mix.[6] Zinc was also a component of a World Vision "Sprinkles" home-based micronutrient fortification programme (10 mg Zn as Zn gluconate together with iron, vitamin A, folic acid, and vitamin C) of complementary foods,[2,37] although based on maternal self-reports, none of the study children had been recipients of Sprinkles. Further, only one report of at least six studies that have included zinc as a fortificant in cereal-based complementary foods[38-41] has observed a significant increase in plasma zinc post-intervention compared to placebo.[42] In view of these negative findings, it is unlikely that zinc fortification had any impact on the serum zinc concentrations reported here.

Anaemia, iron deficiency anaemia, and deficiency of iron and folate

The lower prevalence of anaemia compared to zinc deficiency (27% vs. 76%) reported here was attributed to the success of several interventions designed to combat iron deficiency anaemia within Mongolia. Nevertheless, some iron deficiency anaemia still persisted: almost all (89%; 16/18) of the anaemia in Ulaanbaatar and about half (52%; 16/31) in the provincial capitols was attributed to iron deficiency, probably in part due to low coverage of supplemental iron to anemic children[2,12] and exclusion of children who had been recipients of Sprinkles (which contains 12.5 mg iron in microencapsulated ferrous fumarate).[37] Further, both the level and bioavailability of iron (5 mg/100 g as electrolytic iron) in the national wheat flour fortification programme in Mongolia, even if consumed, was unlikely to be adequate to impact on the iron status of the young children of this survey.

In general, the children aged 12 to 24 months appeared to be the most vulnerable to anaemia and IDA, irrespective of setting, a trend consistent with earlier surveys in Mongolia[5,12] and elsewhere.[29,43] This pattern is not unexpected. There is a gradual depletion of foetal iron stores in infants after six months of age, which are often not replaced by an adequate supply of readily available haem iron from non-milk transitional foods to support their rapid growth rate. After two years of age, however, children receive more haem iron-rich family foods such as meat, advocated by World Vision Mongolia in their social marketing and community nutrition education campaign.[2] Nevertheless, caution must be used when interpreting haemoglobin and ferritin concentrations during early infancy. Domellöf et al.[44] have defined alternative cutoffs for haemoglobin and serum ferritin for infants aged nine months of <100g/L and <5μg/L, respectively, based on –2SD for iron-replete infants.

It is of interest that in contrast to earlier Mongolian reports,[5,6] the prevalence of folate deficiency reported here was very low, especially among the younger breastfed children. Such an aged-related trend is not unexpected and is probably related to a protective effect of breastfeeding. Breast milk folate concentrations are maintained at the expense of maternal folate reserves.[45] Several other factors probably contributed to the low prevalence of folate deficiency noted here. First, the increasing availability and consumption of wheat flour fortified with folate (150 μg/100 g as folic acid), especially in Ulaanbaatar, may have been a factor. Certainly, results of a pilot survey in Mongolia reported a significant increase in mean plasma folate levels among children aged 2 to 15 years, six months after the introduction of the fortified wheat flour.[6] Similar improvements in folate status have been reported in other countries following the introduction of folic acid fortification of wheat flour,[46, 47] a trend attributed to the much higher bioavailability of the folic acid fortificant (i.e., 85%) than that of either the iron or the zinc fortificants in wheat flour. Second, differences in the analytical methods used for the folate assays may have been an additional factor. We used the microbiological assay whereas in the earlier reports, a radio-assay method was used; discrepancies between the two methods have been reported.[48]

Vitamin A deficiency

Despite maternal self-reports that more than two thirds of the children in Ulaanbaatar and 89% in the provincial capitols had received vitamin A supplements (Table 1), and the fortified wheat flour contained 180µg retinol/100 g, vitamin A deficiency appears to persist as a severe public health problem in Mongolia: the overall prevalence was 33.3% (60/180) based on serum retinol < 0.70 µmol/L,[26, 49] with 8.9% with severe vitamin A deficiency (i.e., serum retinol< 0.35 µmol/L). Such a high prevalence of vitamin A deficiency was not explicable on the basis of concomitant zinc deficiency, which is known to impair vitamin A metabolism.[50] There was no relationship between serum retinol and zinc concentrations. Instead, alternative explanations might involve poor absorption and/or retention of high doses of vitamin A, and/or failure to mobilize vitamin A for use by extra-hepatic tissue.[51] Certainly, in experimental studies, only small effects of large doses of retinol on serum retinol levels have been reported, with marked inter-individual variations in the response, which together have raised questions about the efficacy of high dose vitamin A supplements.[52]

Unlike folate, the prevalence of vitamin A deficiency was markedly higher than that reported earlier,[5] although there were some notable differences among the four provincial capitols. Such differences were not associated with use of vitamin A supplements, but may be related to household access and hence consumption of vitamin A-rich dairy products, as noted in an earlier study.[5]

Low selenium status

There are no well established pediatric cutoffs for serum selenium concentrations. We applied those of Thomson[27] that suggest that more than half of the younger children had levels below that required for optimal activity of iodothyronine 5'deiodinases. Certainly, the mean serum selenium concentrations reported here for each age group and setting were at the lower end of the range reported for breastfed infants and toddlers from the South Island of New Zealand,[53] a region with low soil selenium levels.[54] They are also among the lowest reported when compared to several other countries.[55, 56] Hence, the overall biochemical selenium status of the children in both Ulaanbaatar and the provincial capitol towns appears low.

Serum selenium concentrations are influenced by dietary selenium levels, which in turn are dependent on the local soil selenium content, as well as the form and distribution of selenium in foods; plant-based foods contain selenium in a more readily bioavailable form than animal-source foods.[57] Unfortunately, there are no data on levels of selenium in soil, breast milk, or foods in Mongolia, so the extent to which the dietary selenium intakes of the children are inadequate is unknown. The public health implications of suboptimal selenium status among these Mongolian children are uncertain, although suboptimal selenium status has been associated with impaired immune function,[58] and diseases such as asthma and cancer.[59-61]

Vitamin D deficiency

The high prevalence of low serum vitamin D concentrations is disappointing in light of the programmes that have been introduced in an effort to reduce vitamin D deficiency in Mongolia, as noted earlier.[2,5] Unfortunately, we have no information on the proportion of children who had received vitamin D supplements, but based on maternal reports, none had been recipients of Sprinkles, the home-based micronutrient fortificant that contained 10µg vitamin D per sachet (together with iron, zinc, vitamin A, folic acid, and vitamin C). Swaddling of young infants is a common practice in Mongolia[14] and this probably exacerbates, particularly in the younger children, an already low vitamin D status at birth caused by maternal vitamin D deficiency during pregnancy[5].

The much higher prevalence of serum 25-hydroxyvitamin D < 25 nmol/L observed here than that reported in 2003[5] is noteworthy. However, the earlier survey was conducted in June, a time when exposure to sunlight would be much greater than when our survey was conducted (i.e., November). Moreover in the 2003 survey, 30% of the children aged 6 to 23 months had reportedly received vitamin D supplements at least once in the six months prior to the survey. Clearly, there is a need to promote the expansion of the coverage of vitamin D supplements to include not only children aged 6 to 23 months of age, but also those aged 24 to 36 months, at least during the winter months.

In conclusion, of the Mongolian children studied here, 78% were at risk of two or more coexisting micronutrient deficiencies. At present, however, the majority of micronutrient interventions on-going in Mongolia emphasize single micronutrients. Clearly much more emphasis must be placed on alleviating co-existing micronutrient deficiencies. Based on our findings, a programme that supplies a combination of at least iron, folate, vitamin A, zinc, selenium, and vitamin D is needed to achieve optimal micronutrient status during childhood in Mongolia. The Sprinkles home-based fortification programme holds promise provided the efficacy of the fortificants to prevent anaemia and all the other micronutrient deficiencies is confirmed, and the sustainability of the programme is ensured.

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AUTHOR DISCLOSURES

Rebecca L Lander, Tserennadmid Enkhjargal, Jamiyan Batjargal, Karl B Bailey, Sarah Diouf, Timothy J Green, C Murray Skeaff, Rosalind S Gibson, no conflicts of interest.

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Original Article

Multiple micronutrient deficiencies persist during early childhood in Mongolia

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蒙古幼童持續多重微量營養素缺乏

蒙古兒童微量營養素缺乏盛行率的資料相當有限。因此我們評估蒙古幼童之貧血、鐵缺乏貧血(IDA)及鐵、葉酸、維生素 A、鋅、硒及維生素 D 缺乏的盛行率。收集來自烏蘭巴托 (Ulaanbaatar) 的 4 個行政區及 4 個鄉村城鎮的 243 名年齡為 6-36 個月大的兒童之體位資料及早上非禁食血液樣本，以進行血紅蛋白(Hb)、血清運鐵蛋白、葉酸、視網醇、鋅、硒及 25-烴化維生素 D(25-OHD)分析。除了葉酸、硒及 25 烴化維生素 D 分析外，兒童其 α-1-糖化蛋白質如果≥1.2mg/L (n=27)，表示有慢性感染，即將其值排除。14.5%的兒童有發育遲緩，但是沒有人是枯槁的。鋅缺乏(血清鋅<9.9µmol/L)的盛行率(74%)最高，維生素 D 缺乏 61%(血清 25-OHD<25 nmol/L)次之。貧血(24%)及鐵缺乏貧血(16%)的盛行率較低，年紀較大的兒童(24-36 個月)其危險性也較低。21%的兒童其鐵儲存量低，雖然有 2/3 的兒童接受維生素 A 補充劑，但仍有 33%有維生素 A 缺乏(血清視網醇<0.70 µmol/L)。血清硒的值是低的，可能與土壤硒濃度較低有關。相反的，在烏蘭巴托沒有兒童，而其他省的城鎮只有 4%的兒童有低血清葉酸值(<6.8 nmol/L)。貧血、維生素 A、葉酸及硒缺乏存在地區差異 (p<0.05)，鋅及 IDA 則沒有。這些兒童中，有 78%的人有≥2 種的微量營養素缺乏共存之現象，強調蒙古綜合微量營養素介入的需求。

關鍵字：蒙古、兒童、缺乏症、貧血、鋅、硒