Nutritional and household risk factors for xerophthalmia in Aceh, Indonesia: a case-control study¹⁻⁴

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ABSTRACT Risk factors for xerophthalmia were assessed in 466 subjects [38% with night blindness (XN), 60% with Bitot's spots (X1B), 2% with corneal xerophthalmia (X2 or X3)] under age 6 y and their village-age-sex-matched control subjects during a community trial. Socioeconomic status and hygiene standards were lowest for households of xerophthalmic children and highest for nonstudy households in the trial population, with values for control households lying in between (P < 0.001 by linear trend). Risk of xerophthalmia increased with less frequent consumption of dark green leaves, yellow fruits, or egg during weaning, adjusted for current intake and present age [odds ratio (OR) = ~3.5]. Exclusion of these same foods from the current diet (except for mango and papaya in older children) was associated with a two- to ninefold excess risk of xerophthalmia, adjusted for weaning influences. Xerophthalmic children aged < 3 y were generally at higher risk of dietary imbalance than were older children. Xerophthalmia is associated with a chronic, infrequent consumption of key vitamin A foods from weaning through early childhood. Am J Clin Nutr 1991;53:1460-5.

KEY WORDS Xerophthalmia, dietary risk factors, nutritional status, case-control study, Indonesia

Introduction

Xerophthalmia, due to vitamin A deficiency, is the leading cause of childhood blindness in developing regions of the world (1, 2). Evidence is mounting from epidemiologic investigations and controlled trials that vitamin A deficiency is more widespread (3, 4) than previously thought and that it appears to be an important underlying determinant of preschool-child morbidity (5–9) and mortality (10–14).

Vitamin A deficiency requires a basic dietary solution: increase the intake of preformed vitamin A and provitamin A carotenoids to meet normal requirements. This may be achieved in the short term by periodic delivery of large doses of vitamin A (15) and, in some situations, by food fortification (13, 16, 17) but, in most developing countries, long-term prevention must rely on efforts to improve the local diet.

For the development of appropriate dietary intervention, there is an urgent need to identify both the positive and the detrimental feeding patterns that most influence vitamin A status of preschool children. Studies in several countries have reported that children with xerophthalmia are weaned earlier from the breast and consume foods rich in preformed and provitamin A less frequently than do clinically normal children (1, 8, 18, 19).

A case-control substudy of nutritional and household risk factors for xerophthalmia was carried out during the baseline survey of the Aceh Study, a randomized community trial in Indonesia that assessed the impact of large-dose vitamin A supplementation on mortality (11, 12), xerophthalmia (20), and growth (21) in preschool children. The Province of Aceh in northern Sumatra was previously identified as an area of endemic vitamin A deficiency (1). The present study sought to clarify the relationships between xerophthalmia, poverty, and nutritional status and to test three hypotheses related to diet: that xerophthalmic children *I*) wean from the breast earlier, *2*) consume fewer vitamin Arich foods during weaning, and *3*) continue to eat a vitamin Adeficient diet once fully weaned.

Methods

Field procedures of the Aceh vitamin A trial were previously reported (11, 12, 20, 21). Children for the case-control study were enrolled from among ~29 000 children living in the 450 trial villages plus an added 15 villages (not previously reported)

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that had been surveyed but nonrandomly assigned to receive the Indonesian government's Family Nutrition Improvement Program (UPGK).

Villages were surveyed by two field teams between September 1982 and August 1983 (each including an ophthalmologist, dietary interviewer, and anthropometrist). Where children aged < 6 y lived, parents were questioned about selected demographic and socioeconomic characteristics of the household. Children were examined for xerophthalmia at a central site and standard clinical diagnostic criteria for staging xerophthalmia were used (22). A history of night blindness was obtained, which, in Indonesia, corresponds to serum concentrations of retinol (23).

A child with xerophthalmia [night blindness (XN), Bitot's spots (X1B), or corneal xerophthalmia (X2 or X3)] was defined as a case. A control child was the next child seen at the central site in the same village who was free of xerophthalmia and who was matched for sex and age of the case (±2 mo for cases aged < 1 y, ±4 mo for cases aged 1-2 y, and ±6 mo for cases aged 3-5 y). Dietary, anthropometric, and socioeconomic assessments were carried out by workers who were unaware of the clinical status of children.

The dietary questionnaire addressed three aspects of the preschool diet: duration of breast-feeding, foods routinely given to the child (every day or every other day) during the first 12 mo of weaning, and intake frequency of food sources of preformed vitamin A (egg) and provitamin A carotenoids (selected dark green leaves, papaya, and mango) within the past month (daily, 1–6 times/wk, 1–3 times/mo, or not eaten). Portion sizes were not ascertained.

Interworker agreement was investigated before the study. First one and then the other dietary interviewer questioned the same 15 mothers of young children 2 d apart at home. Kappa (K) scores, which quantify worker agreement adjusted for chance (24), were as follows: 1.00 for the age in months at which breastfeeding stopped, 0.59 for the age in months at which weaning began, and 0.56 (mean) for seven classes of foods given daily or every other day during the first 12 mo of weaning (on average, from 1 to 13 mo of age). A weighted K, K_w , was computed for each 4×4 matched-pair contingency table related to intake frequency during the previous month, where w=1.0 for diagonal and 0.5 for adjacent cells. The K_w for 17 foods (11 dark green leafy vegetables, 3 other vegetables, 2 yellow fruits, and egg) was 0.71 ± 0.32 ($\bar{x}\pm0.32$) (KP West, unpublished observations, 1983).

Methods for measuring recumbent length (< 2 y), standing height (≥ 2 y), weight, left midupper-arm circumference (MUAC), and left triceps skinfold thickness (TSF) were described previously (21). Weight, length/height, and age were used to derive a child's percent of the National Center for Health Statistics (NCHS) median (25) weight-for-height (%WH) and heightfor-age (%HA) as indicators of wasting and stunting, respectively.

Matched-pair contingency tables and differences in continuous data were evaluated by the chi-square and paired t tests, respectively (26). Linear trends in proportions were evaluated by the Z test (26). Crude estimates of relative risk [odds ratio (OR), or relative odds] were computed for matched-pair data (27). Adjusted ORs were derived by conditional-likelihood logistic-regression analyses (27, 28) with case-control status as the dependent variable and dietary and other factors modeled as independent variables. OR estimates were calculated from the logistic-regression coefficients and 95% confidence limits (95%)

CL), from the standard errors of the logistic-regression coefficients by published methods (27).

Study procedures were approved by a Steering Committee representing the Government of Indonesia's Department of Health, The Johns Hopkins University and Helen Keller International.

Results

Of a total of 30 685 children examined at baseline, 515 (1.7%) were diagnosed with active xerophthalmia. This rate is lower than the \sim 2% prevalence reported previously (11) because the added UPGK villages had less xerophthalmia than did those in the community trial. Four hundred sixty-six (90%) of these cases were matched to controls, 78% of whose paired records (n=365) were complete for dietary-risk-factor analysis. Dietary records were considered incomplete when, for either a case or control, an interview had not been carried out, a form was physically missing, or, later, baseline and follow-up forms could not be matched in the database because of missing or incomplete identifiers.

Ninety-eight percent of all cases were mildly xerophthalmic (38% with XN only and 60% with X1B) and 2% had X2 or X3 (Table 1). Ninety-six percent of all cases were ≥ 2 y due, in part, to an inability to identify correctly XN children aged < 2 y by a history from parents and a lower risk of xerophthalmia in children < 2 y of age (1). Ages of cases and controls were similar. Sixty percent of all xerophthalmic children were male and 40% were female. Cases of xerophthalmia without dietary data were practically identical to cases with dietary data in terms of age and severity of xerophthalmia (ie, 38% with XN, 61% with X1B, and 1% with X2 or X3).

There were consistent trends in levels of household hygiene (water source and type of latrine), socioeconomic status (house wall material, occupation of head of household, and level of maternal education), and demographic status (proportion of all mothers with a history of one or more child deaths) with child status. That is, households of xerophthalmic children were consistently worse than were households of control children, which in turn, were more disadvantaged than the remaining households that participated in the large community trial (**Table 2**). Each trend, except for head of household's occupation, was statistically significant (P < 0.001).

TABLE 1 Distribution of children by xerophthalmia status and age

Age (y)		Number xerophtha		Total	Number of control subjects	
	XN	XIB	X2 or X3			
<1	0	1	2	3 [0.6]†	3 [0.6]	
1	4	11	1	16 [3.4]	12 [2.6]	
2	37	38	1	76 [16.3]	79 [17.0]	
3	43	76	2	121 [26.0]	123 [26.4]	
4	47	58	-0	105 [22.5]	103 [22.1]	
5	48	95	2	145 [31.0]	146 [31.3]	
Total	179	279	8	466 [100.0]	466 [100.0]	

^{*} Classified by most severe stage of xerophthalmia: XN, night blindness; X1B, Bitot's spots; X2 or X3, corneal xerophthalmia (22).

[†] Percent in brackets.

TABLE 2 Household characteristics of xerophthalmia cases, controls, and the remaining Aceh Study population

Household characteristic	Cases (n = 466)*	Controls $(n = 466)$ *	Aceh Study households (n = 15 915)†
		%	
Unprotected water			
source	47.5	43.8	41.1‡
No private latrine	86.7	83.6	71.3‡
Bamboo house walls	47.1	33.5	31.6‡
Household head farms	57.3	55.5	53.4
Mother has < 6 y			
education	94.3	86.6	80.3‡
History of child death	12.1	9.7	7.5‡

^{*} There were 11-15 values missing for any one characteristic.

Age-specific paired comparisons in anthropometric status revealed decreased height (-1 %HA), MUAC (-2 mm), and TSF (-0.3 mm) measurements in mildly xerophthalmic children, which were most apparent in children < 2 y of age (**Table 3**). Mild wasting by %WH was also evident in children < 2 y of age, but at older ages (4-5 y) xerophthalmic children were heavier for their height compared with controls (+2 %WH).

Curves describing the duration of breast-feeding were constructed using previously described methods (19) and the curves were compared (Fig 1). No differences were observed between cases and controls; > 90% of children in both groups had been breast-fed through 12 mo of age, but < 5% were breast-fed by their 24th month. At the time of study 1.1% of all cases and 1.8% of all controls were still breast-feeding.

a rice-banana porridge (98%) and sugar-rice formula (60%) (both lacking in vitamin A), roughly one-third fewer cases were regularly given foods high in vitamin A (dark green leafy vegetables, yellow fruits and vegetables, egg, or milk) during weaning. Cases were also less likely to have had meat or fish in their weaning diet compared with control children. The relative odds of xerophthalmia were highest if children had not been regularly fed dark green leafy vegetables (OR 6.4; 95% CL 3.4, 12.2), and next highest for yellow fruits and vegetables (OR 4.6; 95% CL 2.7, 7.7). Infrequent consumption of egg, milk, or meat and fish

was associated with an OR of 2.2-2.7 with all lower 95% CL

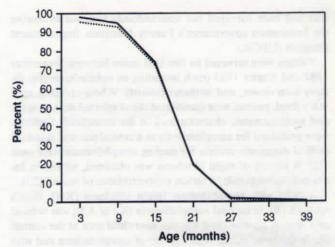


FIG 1. Duration of breast-feeding reported by xerophthalmic cases (n = 272, ---) and their village-age-sex matched controls (n = 275, ---).

Marked differences were observed in foods routinely given to children during the first 12 mo of weaning (Table 4). Whereas

equal proportions of children in both groups were regularly fed

TABLE 3
Matched-pair case-control differences in anthropometric status* by age

Age of cases	Number of pairs	% HA		%WH		MUAC		TSF	
		Control	D‡	Control	D‡	Control	D‡	Control	D‡
y									
<1	1	97.5	-6	96.4	-9	155	-30	8.2	-1
1	15	91.6	-3	87.3	-1	136	-8	7.3	-1
2	74	92.2	-1	90.9	0	144	-4	8.0	-1
3	118	91.7	-1	92.4	0	149	-4	8.3	-1
4	105	90.9	-1	92.6	2	152	-1	8.0	0
5	141	90.1	-1	92.4	2	153	-1	7.3	0
All ages	445	91.1 ± 4.9§	-1 ± 7	92.0 ± 6.4	1 ± 9	150 ± 10	-2 ± 1	7.8 ± 1.5	-1 ± 2
t (paired t test)			-3.57		2.26		-3.63		-2.80
$P\parallel$			< 0.001		< 0.03		< 0.001		< 0.01

values > 1.0 (Fig 2).

[†] There were ≤ 59 missing values for any one characteristic except mother's education, which is based on 15 208 maternal responses (706 missing).

[‡] Significant linear trend in proportions, P < 0.001.

^{*} Percent NCHS medians of height-for-age (% HA) and weight-for-height (% WH), midupper-arm circumference (MUAC) in mm, and triceps skinfold (TSF) in mm.

[†] Mean anthropometric status of control children.

[‡] Mean of paired differences (xerophthalmic case-control).

 $[\]delta \bar{x} \pm SD$

Indicates significance of the differences between the matched pairs.

TABLE 4
Foods regularly consumed by xerophthalmic cases and controls during the first 12 mo of weaning and the relative odds of xerophthalmia if not consumed

		Subjects cons		
Food	Number of pairs*	Cases	Controls	Odds ratio
Rice-banana mix	329	321 [97.6]†	324 [98.5]	1.7 (0.5, 6.0)‡
Sugar-rice formula	320	189 [59.1]	192 [60.0]	1.0 (0.7, 1.5)
Dark green leafy				
vegetables	327	42 [12.8]	102 [31.2]	6.4 (3.4, 12.2)
Yellow fruits and				
vegetables	321	105 [32.7]	166 [51.7]	4.6 (2.7, 7.7)
Egg	327	153 [46.8]	197 [60.2]	2.7 (1.7, 4.3)
Milk	327	65 [19.9]	114 [34.9]	2.2 (1.5, 3.3)
Meat and fish	326	112 [34.3]	150 [46.0]	2.4 (1.5, 3.8)

^{*} Excludes 36-45 pairs with missing values.

During the previous month, cases also reported less frequent consumption of egg, dark green leafy vegetables, and papaya or mango (**Table 5**). The difference in egg consumption was the largest, with 22% of cases vs 10% of controls not having consumed this food. The relative odds of xerophthalmia rose in a dose-response fashion with less frequent consumption of all three foods: children who, by history, ate neither egg nor dark green leafy vegetables were 2.2 times more likely to have xerophthalmia than were those who reported eating these foods 1–3 times/mo, and at 3.8 times greater risk than were children who reported eating them < 1 time/wk. The same effect estimates for papaya or mango were 1.3 and 2.2, respectively.

ORs were estimated separately for two age groups (< 3 y and 3-5 y) by logistic regression in a model that included an independent variable representing routine exclusion of queried vitamin A foods during weaning, plus variables for nonconsumption of egg, dark green leafy vegetables and papaya or mango during the previous month. In addition, the model was adjusted for indicators of household status (maternal education and history of child death, and house construction) and the child's age and nutritional status (%HA and %WH) (Table 6).

A weaning diet that had not routinely included key vitamin A foods was associated with an increase in the risk of xerophthalmia of ~ 3.5 times in both age groups. The current diet also appeared to affect risk after adjustment for the weaning diet. Younger children (< 3 y) who did not eat papaya or mango in the previous month were at a ninefold higher risk of xerophthalmia than were their peers who ate these yellow fruits. In contrast, yellow-fruit consumption had no effect on the risk of xerophthalmia among older children.

Exclusion of dark green leafy vegetables and egg was associated with an elevated risk of xerophthalmia in both younger (OR 6.1 and 3.6, respectively, with lower 95% CL < 1.0 for both) and older (OR 2.4 and 5.5, respectively) children.

Discussion

Three aspects of early-childhood feeding were investigated in relation to risk of xerophthalmia: duration of breast-feeding, weaning diet, and current intake frequency of food sources of vitamin A.

An apparent lack of effect of breast-feeding on risk of xerophthalmia, in light of strong evidence to the contrary (1, 8, 18, 19), may have been due, in part, to a much shorter duration of breast-feeding in this culture. Earlier cessation would contribute less to a build-up of hepatic vitamin A reserves than would later cessation; such reserves may protect children from xerophthalmia once weaned (19). Fewer than 5% of Acehnese children in this study were reportedly still breast-fed beyond their second year of life vs $\sim 30\%$ in the previous Indonesian national survey (1, 18) and $\sim 60\%$ in Bangladesh (Helen Keller International and Institute of Public Health Nutrition, unpublished observations, 1985) and Malawi (19), where a protective effect of breast-feeding was reported.

In this culture the weaning diet more strongly influenced the risk of xerophthalmia. Literally, mothers were asked which foods had been given to the child "daily or every other day during the first 12 mo of weaning" (on average, 1-13 mo of age). We interpreted positive responses to indicate foods that were routinely or regularly given to the child during the weaning period. Traditional rice-based mixes with little vitamin A food value had no effect on risk, a result that supports the validity of the dietaryassessment technique. However, routine inclusion of foods high in vitamin A (dark green leafy vegetables, yellow fruits and vegetables, and egg) during weaning were associated with a protective effect against xerophthalmia throughout the preschool period. This prolonged, adjusted effect may be a proxy for long-term, favorable dietary practices that have continued to the present but that were not assessed in the frequency questionnaire that was administered.

Consumption of animal-protein foods such as meat, fish, and milk (mostly powdered but vitamin A content unknown) was also protective, likely reflecting socioeconomic disparities between families with and without xerophthalmic children. This inference is supported by the poorer educational, demographic, and hygiene status of xerophthalmic households (Table 2). Clear differences in socioeconomic status related to xerophthalmia were not apparent in the previous national survey in Indonesia (1) but were reported elsewhere (29, 30).

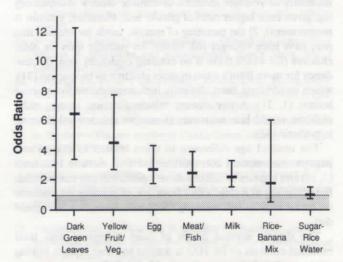


FIG 2. Estimated relative risk (by matched-pair odds ratio) of xerophthalmia in children by type of selected food not routinely given during the first 12 mo of weaning. Data were collected retrospectively by history (n = 320-329 matched pairs for any one food).

[†] Percent in brackets

^{‡ 95%} confidence limit in parentheses.

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TABLE 5
Frequencies with which cases and controls consumed selected food sources of vitamin A during the previous month*

	E	gg	Dark green leafy vegetables		Mango and papaya	
Frequency	Cases	Controls	Cases	Controls	Cases	Controls
			n	[%]		
One or more times/wk One to three times/	76 [20.9]	127 [34.9]	60 [16.4]	101 [27.7]	33 [9.0]	55 [15.1]
mo	209 [56.6]	201 [55.2]	241 [66.0]	236 [64.7]	251 [68.8]	249 [68.2]
Never	82 [22.5]	36 [9.9]	64 [17.5]	28 [7.7]	81 [22.2]	61 [16.7]
X^2	30.8		24.6		8.3	
P	< 0.001		< 0.001		< 0.02	

^{*} n = 365 per group, except for egg consumption, when n = 364 per group.

While the intake-frequency assessment literally addressed intake during "the past month," we interpret the time bounds more broadly to reflect a child's current, usual diet. Exclusion of dark green leafy vegetables and egg from the current diet was associated with an increased risk of xerophthalmia after adjustment for other measured influences. The dose-response gradient observed between frequency of consumption and relative odds of xerophthalmia suggests a causal relationship. A similar dose-response association for egg consumption was reported from the Indonesian national survey (18).

ORs were adjusted for age, diet during the other feeding period (weaning or current), and other potentially confounding factors through age stratification and logistic-regression analysis. For both age groups, infrequent consumption of key food sources of vitamin A during weaning increased their risk of xerophthalmia after adjustment for current intake. The finding that exclusion of any egg from the current diet increased the risk of xerophthalmia regardless of age is consistent with other studies in Indonesia (1, 18) and Bangladesh (8; Helen Keller International and Institute of Public Health Nutrition, unpublished observations, 1985).

Age differences in dietary effect existed, with higher ORs seen in children aged < 3 y vs older children (except for current egg consumption). This may be reflecting, in part, I) a greater vulnerability of younger children to chronic dietary insufficiency (eg, given their higher rates of growth and, therefore, vitamin A requirement), 2) the targeting of specific foods for inquiry that may have been stronger risk factors for younger than for older children (for which there is no external evidence), and 3) a tendency for more Bitot's spots in older children to be inactive (31), which would have been clinically indistinguishable from active lesions (1, 31). Active disease misclassification among older children would bias estimates of relative risk toward the null hypothesis (32).

The marked age difference in effect related to mango and papaya consumption corroborates previous work in Indonesia (1, 18) and appears to reflect a dietary pattern of risk that parallels the transition of a child's diet from one of primary dependence on breast milk to soft weaning foods and, later, to a household diet.

The slightly stunted height of cases compared with their matched controls (-1% HA) is similar to other reports linking mild xerophthalmia to stunting (1, 33, 34). Differences in wasting were minor and inconsistent by different indicators (ie, weightfor-height vs upper-arm indicators), except in the small number of pairs < 2 y of age. At this early age, mildly xerophthalmic

children were both more wasted and more stunted. Although this observation is consistent with data from the national survey (1), relatively low weight-for-height among weanlings with mild xerophthalmia is not widely recognized.

Comparisons of household factors revealed a consistent gradient of improved socioeconomic status moving from households of cases to those of controls who lived in the same villages as cases to all other households in the Aceh trial population. Previously, it was shown that in Aceh, xerophthalmia clustered at the village level (35). Similarly, nonxerophthalmic neighborhood controls in West Java, Indonesia, had serum retinol concentrations that were above those of xerophthalmic children but below those of clinically normal children randomly sampled from the surrounding population (1). The data from this study suggest that household socioeconomic risk factors for xerophthalmia also cluster at the village level, because control households were

TABLE 6
Estimated relative risks, by age, of xerophthalmia when selected foods were not consumed during weaning or within the past month

Foods	Unadjusted odds ratio	Adjusted odds ratio	
Age < 3 y $(n = 65 \text{ pairs})$ †	Date in A. The	the best replies on	
Not in weaning diet:			
vitamin A foods‡	6.5	3.6 (0.7, 19.0)§	
Not eaten in previous month		Mary To to the state of	
Papaya or mango	4.0	9.4 (1.6, 55.9)	
Dark green leafy vegetables	6.0	6.1 (0.9, 42.9)	
Egg	4.0	3.6 (0.7, 19.0)	
Age $3-5 \text{ y } (n = 238 \text{ pairs}) \dagger$			
Not in weaning diet:			
vitamin A foods‡	3.4	3.3 (1.7, 6.2)	
Not eaten in previous month		THE PARTY OF	
Papaya or mango	1.4	1.2 (0.7, 2.3)	
Dark green leafy vegetables	3.0	2.4 (1.0, 5.8)	
Egg	5.4	5.5 (2.2, 13.8)	

^{*} By logistic regression adjusted for other foods plus maternal education, history of child deaths in the household, quality of house construction, and child age and nutritional status (% HA, % WH).

[†] Seventeen pairs aged < 3 y and 45 pairs aged 3-5 y were excluded from the 365 dietary case-control pairs (see text) because of missing values.

[‡] Includes egg, dark green leaves, and yellow fruits and vegetables.

^{§ 95%} confidence limits in parentheses.

better off than those of case households but worse off than other study households.

Whereas many studies have reported an association between current diet and xerophthalmia (1, 8, 18, 36, 37), this study attempted to reconstruct and combine period-specific dietary influences throughout early childhood on risk of xerophthalmia. The findings implicate a diet chronically deficient in vitamin A, from the time weaning begins through the fully weaned preschool years, as an important risk factor for xerophthalmia. Although area variation in the magnitude and strength of dietary risk factors must be expected (dictated by local causes), as seen in the lack of an association with duration of breast-feeding, these findings emphasize the protective value of ripened yellow fruits and dark green leafy vegetables (perhaps in that temporal order) and egg in the weanling and preschool-child diet. Chronic relative poverty, typified by the poor maternal education, high rates of previous child mortality, and inadequate hygiene in this population, provides the milieu in which vitamin A deficiency per-

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