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Population based data on urinary excretion of calcium, magnesium, oxalate, phosphate and uric acid in children from Cimitile (southern Italy)

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Abstract. Population based data on 24-h urinary excretion of calcium, oxalate, magnesium, phosphate, uric acid and creatinine were collected from 220 children (aged 3–16 years) living in Cimitile, Campania, southern Italy. Mean excretion rates for 7 days were correlated with age, body weight, body mass index and height. The prevalence of hypercalciuria (>4 mg/kg body weight) and of hyperoxaluria (>60 mg/day) were 9.1% and 1.8%, respectively. The same 20 children were also identified as hypercalciuric when a calcium/creatinine ratio of greater than 0.15 was considered. No significant differences between boys and girls were found in the urinary excretion of the five constituents implicated in urolithiasis. The study data provide additional childhood reference values for urinary excretion of compounds related to stone formation.

Key words: Urinary excretion – Age – Body weight – Height – Body mass index – Hypercalciuria – Hyperoxaluria

Introduction

There is a need to collect population-based data from children on the daily excretion of urinary constituents related to urolithiasis. Specific metabolic disturbances associated with an abnormality of urinary mineral or electrolyte excretion account for slightly more than 60% of the cases of nephrolithiasis in children [1]. The most common metabolic abnormality present in children with nephrolithiasis is hypercalciuria [2], and the most common cause of the excessive urinary calcium excretion is idiopathic hypercalciuria [3]. Other important metabolic causes of stone disease in children include: primary and secondary disorders of oxalate metabolism, primary and secondary disorders of uric acid metabolism, and less commonly, combinations of several metabolic disturbances in which excess urinary calcium, oxalate and uric acid may be seen. The specific therapy employed for the treatment of nephrolithiasis in children is wholly dependent upon an accurate assessment of the aetiology. It is therefore essential to have reliable data on the urinary excretion of relevant minerals and electrolytes in normal children in order to properly diagnose and treat children with nephrolithiasis.

Until recently, studies of urinary calcium excretion have involved ill-defined groups of normal children [4, 5], or children hospitalized for medical and surgical reasons unrelated to the intestinal, renal or skeletal systems [6, 7], or children visiting a paediatric acute care clinic [8]. Diagnostic guidelines for children have also been derived from experience with adults [9, 10]. The same applies to data on oxalate excretion in normal children. In two frequently quoted papers [11, 12], it was reported that urinary oxalate attains adult values at age 12–14 years, but the studies were performed on few children who were not well defined. In a study of uric acid excretion [13], normal children aged 2–15 years were evaluated during a clinic visit in two American cities (Kansas City and Philadelphia). To our knowledge, there is only one study on phosphate excretion in childhood [6]. The aim of the present study was to obtain reference values for urinary excretion of constituents associated with renal stone formation in a population-based sample of apparently healthy children in southern Italy.

Methods

Population and sampling. The study was performed in the ancient small town of Cimitile 20 km from Naples along the motorway to Avellino. The population of Cimitile numbered 6,719 (3,227 males, 3,492 females) including 1,706 children aged 3–16 years, of whom 220 (13%) completed the study. Of these 220 participants, 48 were pupils in nursery school, 65 in primary school, 50 in junior high school and 57 in high school. Children were enrolled in the study with informed parental consent. They were asked not to alter their usual food consumption during the 7-day study, which was begun on Sundays in April and May 1985. During these months in southern Italy, the intake of fresh vegetables is

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Table 1. Population of children in Cimitile – age, sex, number and percentage of children completing 7-day urine collections

Age (years)	Boys			Girls			All		
	Population[a]	Sample		Population[a]	Sample		Population[a]	Sample	
		(no.)	(%)		(no.)	(%)		(no.)	(%)
3	56	6	10.7	36	6	16.7	92	12	13.0
4	43	12	27.9	59	10	16.9	102	22	21.6
5	52	8	15.4	37	6	16.2	89	14	15.7
6	54	4	7.4	43	2	4.7	97	6	6.2
7	57	6	10.5	48	6	12.5	105	12	11.4
8	49	4	8.2	59	5	8.5	108	9	8.3
9	59	14	23.7	77	10	13.0	136	24	17.6
10	65	10	15.4	67	4	6.0	132	14	10.6
11	83	10	12.0	82	10	12.2	165	20	12.1
12	83	8	9.6	73	8	11.0	156	16	10.3
13	63	8	12.7	58	6	10.3	121	14	11.6
14	66	20	30.3	85	14	16.5	151	34	22.5
15	76	6	7.9	84	4	4.8	160	10	6.2
16	73	8	11.0	77	5	6.5	150	13	8.7
All	879	124	14.1	885	96	10.8	1,764	220	12.5

[a] Number of children

high, but little fresh fruit is yet available. Prior to the start of study recruitment, teachers of the nursery-elementary school in the Cimitile historical centre agreed to co-operate; they taught 611 of the 861 children aged 3–10 years. Initially a randomly selected 50% of each class were enrolled; 113 completed the 7-day study and only their urine specimens were analysed. Of 442 children aged 11–13 years attending the junior high school, a random 50% were requested to participate and 50 completed a 7-day urine collection. Of 246 Cimitile girls aged 14–16 years, 23 attending the high school in Pomigliano completed the study; of 215 boys aged 14–16 years, 34 seen at the public health facility of Cimitile completed the 7-day programme.

The data described here are from 24-h urine collections performed on 7 consecutive days, with the use in the statistical analyses of a 7-day average for each child. Children (and their mothers for those aged 3–10 years) were instructed on the procedure for 24-h urine collections. On the Saturday preceding the day the collections were to start, children were given four large-mouthed plastic bottles, two for the Sunday and two for the Monday. They were asked to collect each 24-h sample in two separate bottles, one for the night-time (all urine voided after going to bed at night plus the first morning void) and the other for the day-time (the remainder of the day) [14]. They were informed in detail exactly how to collect and to record the timing of these specimens. They were asked to discard the first voiding on Sunday morning, but to record the time (hours and minutes) and to begin collection of the Sunday day-time specimen from that point to the time of the last void before retiring. That time was also recorded and the the first void on the Monday morning completed the timed collection for the 1st day. They were asked to bring each day's collection to school separately. On each day, Monday to Friday, they received two additional bottles, i. e. a total of 14. All bottles contained 2 ml 10% hydrochloric acid as preservative. Children and parents were advised about the precautions for handling bottles containing acid. When the bottles were brought in, children were asked about the completeness of the collection and the accuracy of timing. Samples deemed to be incomplete or inaccurate in timing were discarded. For those completing the study, collaboration was assessed as excellent with respect to timed urine collection and record keeping.

Measurements. Height (Harpenden stadiometer) and body wt. (beam balance) were measured with the child in stocking feet and wearing only light indoor clothing. Urine samples were analysed for calcium with the *o*-creosol phthalein method [15], oxalate by the chromatropic acid reaction [16], magnesium by atomic absorption photometry, creatinine by the Jaffé reaction [17], phosphate by the molybdate method [18] and uric acid by the uricase method [19].

Statistical methods. Age-sex-specific mean 24-h excretions were computed with standard deviations. Correlations with age, body wt., body mass index (BMI) (kg/m^2) and height were calculated for calcium, oxalate, magnesium, phosphate and uric acid. In addition, the calcium/creatinine ratio was calculated and used in the analyses. Significance of excretory differences between the sexes was evaluated by Student's *t*-test, differences among age groups by analysis of variance.

Results

Study population and sample

Table 1 shows the sex and age of the population of children in Cimitile at the time of the study and the number completing the 7-day urine collection in each group – 12% overall, 14% of boys and 11% of girls.

Height, weight and BMI

Data on height, weight and BMI of the 220 children grouped according to sex and age are given in Table 2. In this and subsequent tables age groups 3–5, 6–8, 9–11, 12–14 and 15–16 years are considered in order to obtain larger groups and more meaningful results. BMI was significantly higher with age for both boys and girls, up to age 15–16 years. In pubertal and especially post-pubertal children, BMI was greater in boys than girls, reflecting the fact that at these ages the difference between boys and girls in weight was greater than in height.

Urinary excretion patterns

Creatinine. Group mean 24-h creatinine excretion was progressively higher with age in both sexes up to age 12–14 years (Table 3). It was similar in boys and girls up

Table 2. Weight, Height and body mass index (BMI) in relation to age and sex

Age (years)	Number		Weight (kg)			Height (cm)			BMI (kg/m²)*		
	Girls	Boys	Girls	Boys	All	Girls	Boys	all	Girls	Boys	All
3–5	22	26									
Mean			17.5	18.8	18.2	104.5	108.0	106.4	16.0	16.1	16.0
(SD)			(3.0)	(3.8)	(3.5)	(8.3)	(7.1)	(7.8)	(1.4)	(2.4)	(2.0)
6–8	13	14									
Mean			29.1	27.4	28.2	128.6	129.4	129.0	17.4	16.3	16.8
(SD)			(6.6)	(6.2)	(6.3)	(10.4)	(10.9)	(10.5)	(1.9)	(2.2)	(2.1)
9–11	24	34									
Mean			35.8	37.4	36.7	138.7	139.7	139.3	18.3	18.9	18.6
(SD)			(9.9)	(9.2)	(9.5)	(9.2)	(9.2)	(9.1)	(2.9)	(2.5)	(2.7)
12–14	28	36									
Mean			48.3	52.7	50.8	152.6	156.1	154.6	20.7	21.5	21.1
(SD)			(7.7)	(10.7)	(9.7)	(7.0)	(9.1)	(8.4)	(2.3)	(3.3)	(2.9)
15–16	9	14									
Mean			52.7	65.2	60.3	166.3	171.4	169.4	19.0	22.2	20.9
(SD)			(8.0)	(9.4)	(10.7)	(4.6)	(5.1)	(5.4)	(2.4)	(2.9)	(3.1)

* BMI significantly related to age for girls and boys ($P < 0.001$) (F test)

Table 3. Urinary excretion of creatinine in relation to age and sex

Age (years)	Number		Creatinine excretion (mg/kg)*			Creatinine excretion (mg/day)**		
	Girls	Boys	Girls	Boys	All	Girls	Boys	All
3–5	22	26						
Mean			40.6	40.5	40.5	702.6	738.9	722.3
(SD)			(14.2)	(10.9)	(12.4)	(229.1)	(160.8)	(193.8)
6–8	13	14						
Mean			34.8	35.3	35.1	989.8	951.3	969.9
(SD)			(6.4)	(7.0)	(6.6)	(182.3)	(225.5)	(202.8)
9–11	24	34						
Mean			34.3	29.3	31.4	1,181.5	1,061.6	1,111.2
(SD)			(16.9)	(8.3)	(12.7)	(507.3)	(275.0)	(388.8)
12–14	28	36						
Mean			32.4	31.1	31.7	1,528.2	1,568.5	1,550.9
(SD)			(9.0)	(10.5)	(9.8)	(341.5)	(369.3)	(355.2)
15–16	9	14						
Mean			24.2	23.9	24.1	1,231.4	1,501.8	1,396.0
(SD)			(11.2)	(10.6)	(10.6)	(502.2)	(554.1)	(539.8)

* Excretion (mg/kg) significantly related to age, $P < 0.05$ for girls, $P < 0.001$ for boys; ** excretion (mg/day) related to age, $P < 0.001$ for girls and boys (F test)

to 12–14 years, but higher in post-pubertal boys than girls, as found for BMI. Mean creatinine excretion (expressed as mg/kg body wt. per day) was highest for the youngest children and lowest for the oldest. It was significantly different for boys and girls across the age groups. Overall values for all 220 children were $1{,}166.7 \pm 464.1$ mg/day and 33.2 ± 11.9 mg/kg body wt. per day.

Calcium and calcium/creatinine ratio. Twenty-four-hour calcium excretion was 79.8 ± 54.3 mg/day for the group overall. It was similar for the two sexes and for the three younger age groups (Table 4), and higher for the two older age groups. None of the differences between the sexes was statistically significant. Mean calcium excretion was 2.3 ± 1.7 mg/kg body wt. per day. It was similar for boys and girls at every age, with highest values for the youngest children (3.5 and 4.0 mg/kg body wt. per day) and values in the range 1.7–2.3 mg/kg body wt. per day for other age groups. Differences between age groups were significant for both girls and boys ($P < 0.01$ and $P < 0.001$). When excretion was assessed as milligrams per day, differences between age groups were significant for boys ($P < 0.01$), for girls P was between 0.05 and 0.10. Of the 220 children, 20 (9.1%) – 15 boys and 5 girls (12.1% and 5.2%, respectively) – excreted more than 4 mg/kg body wt. per day. Scattergrams with linear regression and correlation analyses for the relationships of age, weight, height and BMI with 24-h calcium excretion are shown in Figs. 1–4. A sig-

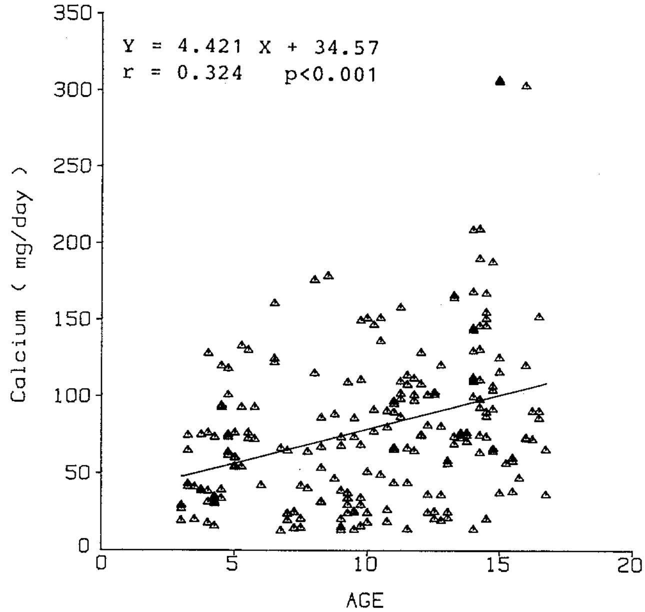

Fig. 1. Calcium excretion in relation to age

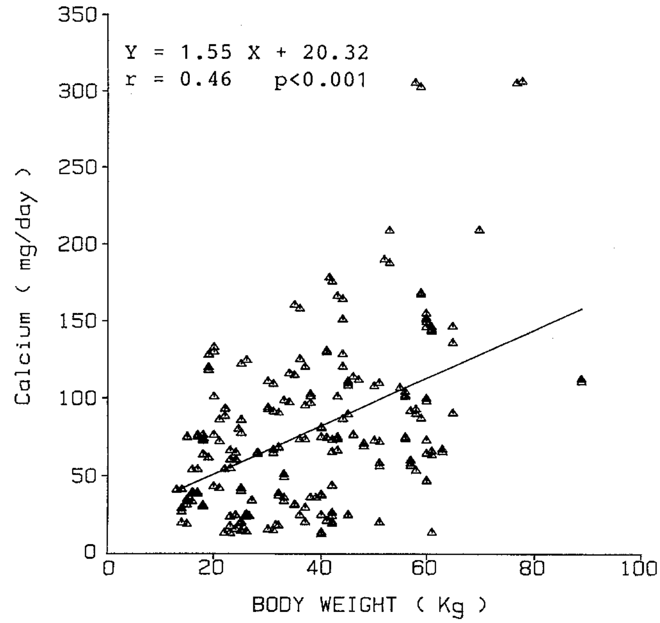

Fig. 2. Calcium excretion in relation to weight

nificant positive association was found between calcium and each of these variables ($P < 0.001$), with simple correlation coefficients of 0.324, 0.460, 0.390 and 0.396, respectively.

The mean urinary calcium/creatinine ratio was 0.076 ± 0.060 for all the 220 children. The mean ratio was highest at age 15–16 years for both sexes, and next highest at age 3–5 years, the P value for the differences between mean values of the five age groups was between 0.05 and 0.10 for both girls and boys (Table 5). Mean values were generally similar for the two sexes. In the 20 children with calcium excretion above 4 mg/kg body wt. per day, calcium/creatinine ratios were 0.615 for 2 boys, 0.170 for 3 boys, 0.175 for 1 boy and 3 girls, 0.190 for 4 boys and 1 girl, 0.195 for 2 boys and 1 girl, and 0.210 for 3 boys.

Oxalate. The mean oxalate excretion was 32.2 ± 16.8 mg/day and 1.0 ± 0.6 mg/kg body wt. per day for the 220 children. Mean levels of 24-h excretion were similar for boys and girls; for both sexes they tended to be higher with age, at least across the three younger age groups, but differences in mean values across the five age groups were not statistically significant (Table 6). When expressed as milligrams per kilogram body wt. per day excretion was

Table 4. Urinary excretion of calcium in relation to age and sex

Age (years)	Number		Calcium excretion (mg/kg)*			Calcium excretion (mg/day)**		
	Girls	Boys	Girls	Boys	All	Girls	Boys	All
3–5	22	26						
Mean			3.5	4.0	3.7	61.0	71.4	66.6
(SD)			(2.0)	(2.6)	(2.3)	(34.8)	(40.4)	(37.9)
6–8	13	14						
Mean			2.3	2.2	2.3	69.0	59.7	64.2
(SD)			(1.4)	(1.7)	(1.6)	(42.2)	(48.8)	(45.1)
9–11	24	34						
Mean			1.8	1.8	1.8	63.8	68.3	66.5
(SD)			(1.4)	(1.1)	(1.2)	(41.1)	(41.7)	(41.1)
12–14	28	36						
Mean			2.0	1.8	1.9	96.2	95.8	96.0
(SD)			(1.1)	(0.9)	(1.0)	(52.5)	(48.4)	(49.9)
15–16	9	14						
Mean			1.7	2.0	1.9	89.4	131.0	114.7
(SD)			(1.3)	(1.6)	(1.4)	(76.8)	(105.5)	(95.6)

* Excretion (mg/kg) significantly related to age, $P < 0.01$ for girls, $P < 0.001$ for boys; ** excretion (mg/day) significantly related to age for boys, $P > 0.01$, for girls $0.05 < P < 0.10$ (F test)

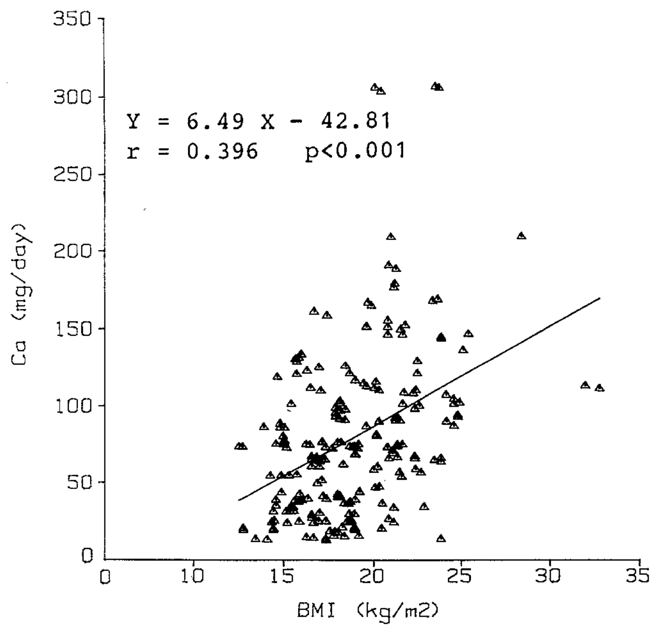

Fig. 3. Calcium excretion in relation to body mass index (*BMI*)

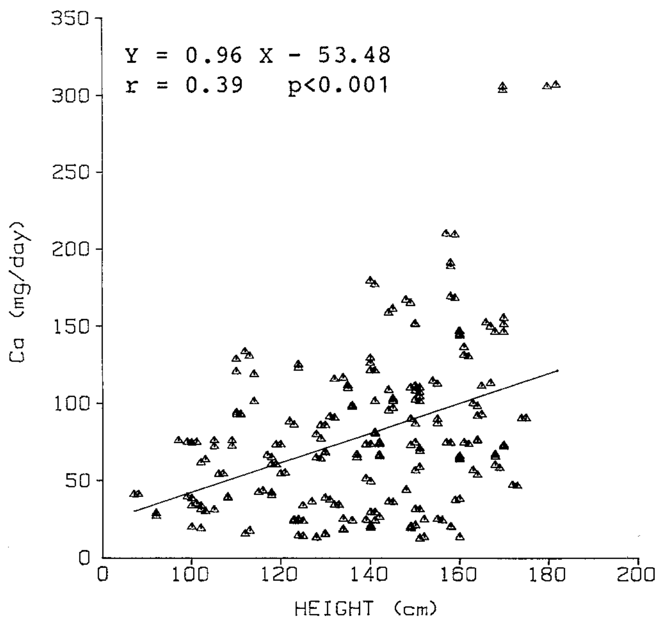

Fig. 4. Calcium excretion in relation to height

progressively lower with age for both sexes; the differences across the five age groups were significant (Table 6). Four children, all girls, excreted more than 60 mg/day. All other children excreted less than 50 mg/day; 6 excreted 45–49 mg/day, the remaining 210 less than 45 mg/day (range 8–44 mg/day). Total 24-h oxalate excretion was significantly related to age, height and BMI, but not to weight (Table 7)[1].

[1] For oxalate, magnesium, phosphate and uric acid, copies of scattergrams corresponding to Figs. 1–4 for calcium are available from the authors on request.

Table 5. Twenty-four-hour urinary calcium/cratinine ratio in relation to age and sex

Age (years)	Number		Calcium/creatinine ratio*		
	Girls	Boys	Girls	Boys	All
3–5	22	26			
Mean			0.091	0.098	0.094
(SD)			(0.046)	(0.057)	(0.052)
6–8	13	14			
Mean			0.070	0.073	0.072
(SD)			(0.044)	(0.077)	(0.062)
9–11	24	34			
Mean			0.055	0.069	0.063
(SD)			(0.036)	(0.046)	(0.042)
12–14	28	36			
Mean			0.064	0.064	0.064
(SD)			(0.034)	(0.034)	(0.033)
15–16	9	14			
Mean			0.076	0.123	0.104
(SD)			(0.053)	(0.153)	(0.124)

* For both girls and boys 0.05 <P <0.10 for relationship between age and ratio (F test)

Magnesium. For the 220 children, magnesium excretion averaged 73.0±34.0 mg/day, 2.06±0.78 mg/kg body wt. per day. Levels of excretion were similar for boys and girls (Table 8). For both sexes, 24-h excretion values were significantly higher with age, but expressed as milligrams per kilogram body wt. per day they were lower at 9–16 years than 3–8 years. Differences across the five age groups (in mg/kg body wt. per day) were significant for boys (P <0.001); for girls P was between 0.05 and 0.10. Total 24-h magnesium excretion was significantly related, not only to age (r = 0.550), but also weight (r = 0.570), height (r = 0.601) and BMI (r = 0.370) (Table 7).

Phosphate. Mean phosphate excretion was 759.6±311.8 mg/day, 22.7±11.3 mg/kg body wt. per day for the 220 children. Values were similar for boys and girls (Table 9). For both sexes, 24-h excretion was higher at 12–16 years than at 3–11 years, but expressed as milligrams per kilogram body wt. per day it was highest for the children aged 3–5 years. Differences in excretion among age groups were all significant (P <0.001). Four children excreted more than 60 mg/kg body wt. per day, i.e. an amount exceeding the group mean plus three standard deviations. Total phosphate excretion per day was significantly related not only to age, but also to weight, height and BMI (Table 7).

Uric acid. For the entire group, mean uric acid excretion was 347.1±192.6 mg/day, 10.4±7.0 mg/kg body wt. per day. For three of the five age groups, mean values tended to be higher for girls than boys, but the differences were not statistically significant (Table 10). For both boys and girls, mean 24-h excretion tended to be higher at 9–16 years than at 3–8 years. Differences in excretion among age groups were all significant (P <0.001). For 20 children, excretion greater was than 20 mg/kg body wt. per day. Uric

Table 6. Urinary excretion of oxalate in relation to age and sex

Age (years)	Number		Oxalate excretion (mg/kg)*			Oxalate excretion (mg/day)		
	Girls	Boys	Girls	Boys	All	Girls	Boys	All
3–5	22	26						
Mean			1.35	1.47	1.42	23.4	26.1	24.8
(SD)			(0.43)	(0.82)	(0.66)	(8.0)	(11.6)	(10.1)
6–8	13	14						
Mean			1.18	1.13	1.15	33.5	30.5	31.9
(SD)			(0.31)	(0.41)	(0.36)	(9.1)	(11.6)	(10.4)
9–11	24	34						
Mean			1.12	0.94	1.01	36.5	34.4	35.3
(SD)			(0.98)	(0.40)	(0.70)	(23.6)	(19.8)	(21.3)
12–14	28	36						
Mean			0.87	0.64	0.74	39.8	32.6	35.8
(SD)			(0.71)	(0.20)	(0.50)	(27.0)	(8.9)	(19.2)
15–16	9	14						
Mean			0.54	0.49	0.51	27.7	31.5	30.0
(SD)			(0.17)	(0.13)	(0.14)	(8.0)	(7.2)	(7.6)

* Excretion (mg/kg) significantly related to age, $P < 0.05$ for girls, $P < 0.001$ for boys; excretion (mg/day) not related to age $0.05 < P < 0.10$ for girls, $P > 0.10$ for boys (F test)

Table 7. Simple correlation and linear regression analyses: age, weight, height, BMI, and 24-h urinary excretion of calcium, oxalate, magnesium, phosphate and uric acid, all children[a]

24-h excretion (mg/day)	Age (years)			Weight (kg)			Height (cm)			BMI (kg/m²)		
	a	b	*r*	a	b	*r*	a	b	*r*	a	b	*r*
Calcium	+ 34.57	4.42	0.324*	+ 20.32	1.55	0.460*	–53.48	0.96	0.390*	– 42.81	6.49	0.396*
Oxalate	+ 9.27	1.11	0.370*	+ 17.07	0.09	0.126	–11.66	0.23	0.420*	– 4.05	1.31	0.360*
Magnesium	+ 25.43	4.70	0.550*	+ 27.20	1.20	0.570*	–56.43	0.93	0.601*	+ 1.91	3.78	0.370*
Phosphate	+485.94	24.48	0.396*	+423.27	8.69	0.450*	–41.51	5.74	0.403*	+247.53	12.65	0.211*
Uric acid	+247.53	12.65	0.211*	+233.00	3.75	0.255*	+22.75	2.55	0.235*	+ 44.36	17.61	0.244*

* $P < 0.001$

r, Simple correlation coefficient

[a] Simple linear regression equation: $y = a + bx$

Table 8. Urinary excretion of magnesium in relation to age and sex

Age (years)	Number		Magnesium excretion (mg/kg)*			Magnesium excretion (mg/day)**		
	Girls	Boys	Girls	Boys	All	Girls	Boys	All
3–5	22	26						
Mean			2.41	2.47	2.44	42.4	45.0	43.8
(SD)			(0.68)	(0.71)	(0.69)	(14.2)	(11.3)	(12.6)
6–8	13	14						
Mean			2.59	2.42	2.51	72.0	64.5	68.1
(SD)			(0.80)	(0.71)	(0.75)	(15.8)	(17.4)	(16.8)
9–11	24	34						
Mean			2.00	1.78	1.87	69.7	65.3	67.1
(SD)			(0.94)	(0.60)	(0.76)	(35.6)	(23.7)	(29.0)
12–14	28	36						
Mean			1.95	1.78	1.86	90.6	92.1	91.5
(SD)			(0.83)	(0.71)	(0.76)	(32.5)	(37.2)	(35.0)
15–16	9	14						
Mean			1.91	1.68	1.77	98.4	106.9	103.6
(SD)			(0.67)	(0.64)	(0.65)	(34.8)	(35.6)	(34.7)

* Excretion (mg/kg) significantly related to age for boys, $P < 0.001$, for girls $0.05 < P < 0.10$; ** excretion (mg/day) significantly related to age for both girls and boys, $P < 0.001$ (F test)

Table 9. Urinary excretion of phosphate in relation to age and sex

Age (years)	Number		Phosphate excretion (mg/kg)*			Phosphate excretion (mg/day)*		
	Girls	Boys	Girls	Boys	All	Girls	Boys	All
3–5	22	26						
Mean			37.1	37.4	37.3	644.3	690.5	669.3
(SD)			(12.6)	(10.2)	(11.3)	(214.0)	(182.0)	(196.5)
6–8	13	14						
Mean			24.3	22.3	23.2	699.1	614.2	655.0
(SD)			(12.1)	(7.9)	(10.0)	(414.7)	(260.6)	(339.4)
9–11	24	34						
Mean			17.1	17.2	17.1	580.9	611.0	598.6
(SD)			(6.2)	(6.3)	(6.2)	(163.2)	(162.5)	(162.0)
12–14	28	36						
Mean			19.7	17.1	18.2	939.7	886.4	909.7
(SD)			(6.1)	(4.7)	(5.5)	(271.6)	(250.9)	(259.4)
15–16	9	14						
Mean			17.1	19.0	18.2	874.8	1,178.1	1,059.4
(SD)			(6.9)	(9.4)	(8.4)	(327.8)	(531.8)	(478.6)

* Excretion significantly related to age for both girls and boys, $P < 0.001$ (F test)

Table 10. Urinary excretion of uric acid in relation to age and sex

Age (years)	Number		Uric acid excretion (mg/kg)*			Uric acid excretion (mg/day)*		
	Girls	Boys	Girls	Boys	All	Girls	Boys	All
3–5	22	26						
Mean			15.01	14.57	14.77	258.6	261.1	259.9
(SD)			(7.94)	(8.98)	(8.44)	(125.3)	(142.1)	(133.3)
6–8	13	14						
Mean			7.84	6.82	7.31	230.9	177.1	203.0
(SD)			(3.76)	(3.79)	(3.74)	(111.0)	(85.6)	(100.5)
9–11	24	34						
Mean			15.62	11.03	12.93	506.8	399.6	444.0
(SD)			(10.14)	(5.57)	(8.04)	(265.9)	(208.2)	(237.6)
12–14	28	36						
Mean			7.32	7.22	7.26	342.7	361.8	353.4
(SD)			(2.85)	(3.44)	(3.17)	(118.4)	(137.2)	(128.7)
15–16	9	14						
Mean			9.78	5.89	7.41	531.0	375.1	436.1
(SD)			(4.23)	(3.11)	(4.00)	(262.1)	(182.2)	(225.1)

* Excretion significantly related to age for both boys and girls, $P < 0.001$ (F test)

acid excretion was significantly related not only to age, but also to weight, height and BMI (Table 7).

Simple correlations. Excretions of most of the analytes were significantly related to each other. Of the 15 simple correlation coefficients for all 228 children, 10 had P values less than or equal to 0.05 (Table 11).

Discussion

The present study presents the mean 24-h excretion rates for 7 days in normal children of several chemicals related to urinary tract stone formation. It was undertaken because of current limitations in reported "normal" data due to limited characterization of the children enrolled in earlier studies [4–13, 20]. The present investigation involved 220 healthy boys and girls age 3–16 years living in a southern Italian town, Cimitile. They made up 12% of all children of that age in the community. They were studied in the spring of 1985 under conditions of uniform sun exposure, stable alimentation and usual activities. Pains were taken to maximize the accuracy and completeness of urine collections.

Group mean 24-h creatinine excretion levels of the Cimitile children were on average higher than those reported by Ghazali and Barratt [7] who estimated an excretion of 17 mg/kg for mid-childhood. They were also higher than the 15–16 mg/kg for the children aged 11–14 years studied by Cooper et al. [21–23]. For older children, they were in agreement with data reported by Bulusu et al. [20],

Table 11. Simple correlation between daily excretion of creatinine, calcium, oxalate, magnesium, phosphate and uric acid, all children (mg/day)

	Calcium	Oxalate	Magnesium	Phosphate	Uric acid	Creatinine
Calcium	1.000					
Oxalate	0.112	1.000				
Magnesium	0.217**	0.142*	1.000			
Phosphate	0.082	0.082	0.392***	1.000		
Uric acid	0.010	0.205**	0.160*	0.046	1.000	
Creatinine	0.187**	0.206**	0.473***	0.487***	0.239***	1.000

* $P<0.05$; ** $P<0.01$; *** $P<0.001$

but mean values for the younger Cimitile children were higher. As has been shown repeatedly in clinical and epidemiological studies, intra-individual variation in 24-h creatinine excretion is sizeable, as is also inter-individual variation, even after adjustment for age, sex and body mass [24–28]. One reason for this is the influence of the dietary protein intake. It is relevant to note that protein intake of the Cimitile children was high, above the Italian recommended daily allowance.

The 24-h calcium excretion in our study – a group mean of 2.3±1.7 mg/kg body wt. per day and 20 children (9%) excreting more than 4 mg/kg body wt. per day – is comparable with the findings of Ghazali and Barratt [7] in a group of English children, 75% of whom were studied during the first 24 h of hospitalization for elective minor surgery [7]. However, our data differ from those of Moore et al. [8] who reported a 2.9% prevalence of hypercalciuria (based on the calcium/creatinine ratio) in 273 American children (90% of whom were black) admitted to an acute paediatric emergency unit. Based on a study of 74 Swiss children age 0–18 years, whose characteristics were not fully described, Royer [4] found that 12% excreted more than 4 mg calcium/kg body wt. per day, a level similar to that found in Cimitile. Royer concluded that calciuria of less than 3 mg/kg body wt. per day should be considered normal, 3–6 mg/kg body wt. per day should be viewed with suspicion, and more than 6 mg/kg body wt. per day should be considered pathological. A mean value somewhat higher than that found in Cimitile was reported in another Swiss study of 38 hospitalized children aged 1 month to 14 years (3.6±2.4 mg/kg body wt. per day) [6]. This higher value may reflect a greater calcium intake of the Swiss children. A high sodium intake also enhances calciuria, and this too may be a factor influencing the Cimitile pattern.

The mean of 0.076 for the urinary calcium/creatinine ratio of the Cimitile children agrees closely with the value given by Moore et al. [8] for children from the United States, but is lower than that reported in the United Kingdom study of Ghazali and Barratt [7]. In a recent study of two groups of school children aged 6–17.9 years in Kiel, Federal Republic of Germany, Kruse et al. [29] also found that there were no age-sex differences in the group mean calcium/creatinine ratio. In that study, 24-h urine specimens were not collected, rather approximately 2-h post-absorptive samples from about 2. p.m. to 4. p.m. (fasting specimens from about 7. a.m. to 9. a.m. were also taken in the first group). The median value for the post-absorptive afternoon specimens of 236 children was 0.071, similar to the Cimitile value. In the second sample of 1,013 children, with the collection of two post-absorptive specimens from each individual on 2 consecutive days, 3.8% of children were designated hypercalciuric (21 girls, 18 boys) with girls predominating in the age group 12 years and over. These findings and those of the present study are concordant.

Furthermore the criteria used to define childhood hypercalciuria are important. Of the 220 children in the Cimitile study, 20 exhibited both a calcium excretion above 4 mg/kg and a calcium/creatinine ratio greater than 0.15, but for only 3 of these children was the ratio greater than 0.196, i.e. greater than two standard deviations above the group mean. Eight children (5 boys, 3 girls) had a calcium excretion greater than 5.7 mg/kg body wt. per day, i.e. greater than two standard deviations above the mean. As shown particularly by prospective epidemiological studies (e.g. of blood pressure and serum cholesterol), use of a statistical criterion, such as two standard deviations above the observed population mean, is not a valid basis for the establishment of cut-off points for biologically abnormal values for either children or adults. In fact, there are no data to support the assumption that 2.5% (>2 SD above the mean) of the population is "abnormal" for this or any other continuous variable, while everyone else is "normal". The levels of urinary calcium excretion that place people at greater risk of renal stone disease can be obtained only by cross-sectional and prospective studies addressing this issue directly, preferably with use of multiple measurements of 24-h calcium excretion. In the interim, cross-sectional population data on excretion levels permit formulation of clinical guidelines.

Only 4 Cimitile children excreted more than 65 mg/day oxalate. This finding supports the concept that absolute values of oxalate excretion are similar in children and adults and rarely exceed 65 mg/day. In fact, of the remaining 216 children in the Cimitile population sample, all excreted less than 50 mg/day and most less than 45 mg/day. The problems inherent in the use of statistical criteria for the identification of cut-off points for abnormal levels are well illustrated by the oxalate data. Thus, for girls aged 12–14 years the mean plus or minus two standard deviations was 39.8±54.0, yielding – if the two standard deviation cut-off point were applied – a level above 93.8 as the criterion for "abnormal", not recorded for any child. This finding is of course a reflection of skewing, i.e. a distribution that was not statistically normal. For boys of the same age, the mean plus or minus two standard deviations was 32.6 ± 17.8, yielding a criterion of above 50.4 for "abnormal". This approach is not satisfactory for the definition of abnormal levels.

Group mean magnesium excretion was lower than that found by Paunier et al. [6] and by Ghazali and Barratt [7]. Again the differences may relate to diet or may reflect a more reliable estimate based on the larger sample size in Cimitile than in the Swiss and United Kingdom studies. Mean phosphate excretion in the present study was in agreement with findings for 27 Swiss children aged 1–14 years [6]. Further study of the 4 Cimitile children excreting more than 60 mg/kg is indicated.

Group mean uric acid excretion of the Cimitile children was in agreement with data from Stapleton et al. [13], with the difference that in the Italian sample there was no clear-cut evidence of a decline with age in uric acid excretion (mg/kg body wt. per day). Twenty Cimitile children excreted 20 or more mg/kg body wt. per day uric acid, exceeding the limit of 18 mg/kg body wt. per day currently accepted as normal for this age group.

It may be useful to add a further comment about possible dietary influences on the several variables studied here. As noted earlier, fruits and vegetables are eaten in abundance in Cimitile. These are only in small part home grown; most are commercially produced in the Campania region or another part of southern Italy, by modern intensive agriculture with ample use of chemical fertilizers (types and quantities not known).

In conclusion, the data from this population-based study indicate normal levels for childhood excretion of stone-forming urinary constituents, and reinforce existing criteria for hypercalciuria, hyperoxaluria and hyperuricosuria. They also demonstrate that total 24-h urinary excretion by children of calcium, oxalate, magnesium, phosphate and uric acid correlate with age, body wt., height and BMI, with the exception that oxalate does not correlate with body wt.

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