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URINARY PORPHYRIN EXCRETION IN NORMAL CHILDREN AND ADOLESCENTS

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Abstract

Background—Urinary porphyrins are diagnostic of various metabolic disorders and xenobiotic exposures, but comprehensive normative data for urinary porphyrin concentrations in children are currently unavailable.

Methods—Subjects were participants in a prospective, randomized, controlled clinical trial of dental materials safety, 8 to 12 y at inception, who were followed longitudinally for 7 y after baseline with an extensive battery of neurobehavioral, neurological, renal function and urinary porphyrin assessments. Porphyrins were quantified by HPLC. Linear regression analyses were used to measure associations of porphyrin levels with age and gender.

Results—Mean concentrations, 95% confidence intervals, and 10th 50th, and 90th percentiles for all 5 typically excreted urinary porphyrins are presented by year of age and by gender. Unadjusted urinary concentrations ($\mu\text{g/l}$) of all 5 porphyrins remained relatively constant throughout the age range of 8–18 y for both males and females. In contrast, creatinine-adjusted urinary porphyrin concentrations ($\mu\text{g/g}$) declined significantly throughout this age range in both genders. Boys had significantly higher pentacarboxyl- and copro- porphyrin levels compared with girls both before and after creatinine adjustment.

Conclusions—Normative longitudinal data provided herein may facilitate the clinical assessment of pediatric metabolic disorders and may be of particular relevance in evaluating porphyrin changes as a biological indicator of disease or xenobiotic exposures among children and adolescents.

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Keywords

urine; porphyrins; children; adolescents

INTRODUCTION

Porphyrins are formed as intermediates in the biosynthesis of heme, a process that takes place in essentially all eukaryotic tissues. In humans and other mammals, porphyrins with 8,7,6,5, and 4 carboxylated side chains (uro-, heptacarboxyl-, hexacarboxyl-, pentacarboxyl-, and copro- porphyrins) are commonly formed in excess of that required for heme synthesis and are excreted in the urine and/or feces in established concentration ranges [1,2]. Urinary porphyrin excretion may be abnormally elevated in a number of disease states including the inherited porphyrias [3,4], certain liver and kidney diseases [5,6], and disorders of hemoglobin synthesis [7]. Abnormal porphyrin excretion has also been documented in response to a variety of drugs [8] and environmental chemical exposures, particularly, organochlorine compounds [9,10] and heavy metals such as lead [11], arsenic [12,13], and mercury [14,15]. In each case, the specific changes in porphyrin excretion patterns are potentially useful as diagnostic indicators of ensuing, existing or remitting disease or chemical toxicity [16–19].

The efficacy of altered urinary porphyrin concentrations and excretion patterns as biomarkers of disease or toxicant exposure is contingent upon the availability of established normal reference values, which can vary by both age and gender. Whereas urinary porphyrin concentrations are well established for adult human subjects [1,2,15], normative values of urinary porphyrins for developmentally healthy children and adolescents are not available.

MATERIALS AND METHODS

The Study Population

The children's cohort was derived from the recently completed Casa Pia clinical trial of the health effects of dental amalgam fillings in children [20]. Subjects (n=507) were boys and girls (54:46%), 70% white, aged 8–12 y at inception, who were residents of the Casa Pia school system in Lisbon, Portugal. All subjects who participated in the clinical trial from which the data reported herein were recruited were residents of the same boarding school throughout all years of the trial. As such, they received the same diet and were comparable in all other social respects. Eligibility requirements precluded children with preexisting neurological or developmental disabilities, dental amalgam tooth fillings or blood lead levels ≥ 10 ($\mu\text{g}/\text{dl}$). Subjects were initially randomized to mercury amalgam (treatment) or composite resin (control) dental treatment groups. Because amalgam treatment is suspected to impact urinary porphyrin profiles [21], only subjects receiving composite resin fillings (controls, n = 254) were included in the present assessment of normative porphyrin levels. Children were evaluated at baseline and at 7 subsequent annual intervals after initial dental treatment with an extensive battery of neurobehavioral, neurological, renal function and urinary porphyrin assessments. Follow-up data were obtained on a similar number of subjects in each treatment group. The study protocol was approved by the institutional review boards at the University of Washington and the University of Lisbon. All parents or guardians gave written consent, and all children provided signed assent. Principal design and analytical issues involved in this trial [22] as well as principal outcome measures [20] have been reported.

Procedures for urine collection and measurement of urinary porphyrins and creatinine

A urine sample (~50 ml) was collected from each child at baseline and at each subsequently scheduled annual visit to the University of Lisbon School of Dental Medicine for dental,

neurological and neurobehavioral evaluations. Immediately following urine collection, a 10 ml aliquot was removed and acidified with 1 mol/l HCl for use in mercury analysis by continuous flow, cold vapor spectrofluorometry [23]. Porphyrins were quantified in the remaining unacidified portion of the urine sample by high performance liquid chromatography, as previously described [24]. Urinary creatinine concentrations were also measured in unacidified urine using a standard colorimetric procedure (Sigma, St. Louis, MO).

Statistical analyses

We used separate linear regression models for each porphyrin to test whether gender and age were associated with average urinary porphyrin concentration ($\mu\text{g/l}$) during the study among the composite group. We also tested for age and gender associations with average creatinine adjusted urinary porphyrin levels ($\mu\text{g/g}$). We tested for age effects separately for each gender. Robust standard errors were used to account for possible within-child correlation and heteroskedasticity (variances increased with increasing mean value).

RESULTS

Table 1 presents demographic characteristics at baseline (BL) and at each year of follow-up for all subjects in the composite (control) group for whom porphyrin assay results were available. Subjects at baseline ranged in age from 8 to 12 y, mean 10 y. Table 2 presents distributions (10th, 50th, 90th percentiles), mean values, and 95% confidence intervals for the mean values of unadjusted concentrations ($\mu\text{g/l}$) of individual and total urinary porphyrins by gender and age for children from ages 8–18 y. As shown, unadjusted porphyrin concentrations remain relatively constant throughout the age range of 8 to 18 y for both genders. Notably, however, boys have significantly ($p < 0.05$) higher unadjusted pentacarboxyl- and coproporphyrin concentrations than girls throughout this age range.

Table 3 presents distributions (10th, 50th, 90th percentiles), mean values, and 95% confidence intervals for mean values of creatinine-adjusted concentrations ($\mu\text{g/g}$) of individual and total urinary porphyrins by gender and age for children from ages 8–18 y. As shown, creatinine-adjusted porphyrin concentrations decline significantly ($p < 0.0001$) throughout this age range in both genders. Boys again were seen to have significantly ($p < 0.05$) higher creatinine-adjusted pentacarboxyl- and coproporphyrin levels compared with girls. Additionally, blacks were found to have significantly lower creatinine-adjusted (but not unadjusted) urinary porphyrin levels than whites at all ages. This finding is attributed to significantly higher creatinine excretion among blacks [25].

Table 4 presents individual porphyrin concentrations as a percentage of total porphyrins for each age and gender. Values represent the percent of total urinary porphyrin concentration for each individual porphyrin. Table 5 presents mean creatinine concentrations (g/l) for each age and gender. Values increased by a comparable amount in both boys and girls over the age range of 8 to 15 y, then become relatively stable throughout the remaining 3 y of follow up to age 18 y. No significant differences in creatinine excretion between boys and girls were found. A comprehensive report of longitudinal creatinine excretion values [25] in this subject population is published.

DISCUSSION

An important data gap exists for normative urinary porphyrin concentrations for children and adolescents. Bloom et al. [26] described total urinary porphyrin and creatinine values as functions of age and sex among children aged from 9 months to 18 y. These observations are of limited diagnostic value, however, since urinary concentrations for individual porphyrins were not provided. More recently, Sunyer et al. [10] employed linear regression analysis to

evaluate potential changes in urinary porphyrin excretion in relation to organochlorine compound exposure among 4 y-old children. However, no normative values for urinary porphyrin levels for children of this age were reported. In other studies, Ahmed [27] described biochemical abnormalities in childhood porphyrias, but no normative urinary porphyrin data were provided. Age-dependent reference values for urinary porphyrins among children aged from 0.5 to 15 y were reported by Minder et al. [28]; however, these assessments were restricted only to uro- and copro- porphyrin levels. Isomers of individual porphyrins, which may be of importance in the evaluation of certain diseases or disorders, were not evaluated in the present study.

Of note from the present findings is the observation that total urinary porphyrin concentrations are higher in pre-adolescent children of both sexes and decline to reported adult ranges [1,2, 15,29] only by the late teen years. Although absolute concentrations of coproporphyrin appear to contribute most substantially to higher porphyrin levels observed in younger children (Table 2 and Table 3), it is notable that the proportion of total porphyrin attributable to coproporphyrin increases somewhat from ages 8 through 18 y, whereas the proportion of total porphyrin attributable to uroporphyrin decreases by as much as 2-fold over this age range (Table 4). These findings accentuate the importance of evaluating porphyrin alterations in children in relation to mean porphyrin values for healthy children of the same age, rather than in relation to adult reference values. Also of note is the observation that boys had significantly higher unadjusted urinary concentrations of pentacarboxyl- and copro- porphyrins than girls throughout much of the 8–18 age range. This difference was retained following creatinine adjustment (Table 3), consistent with finding that urinary creatinine levels did not differ significantly between males and females throughout the course of the study (Table 5). Similar finding were reported by Bloom et al. [26], in which total creatinine-adjusted urinary porphyrin concentrations in boys aged 9–18 y were higher than those seen in similarly aged girls. The mechanisms and possible biological significance of this gender distinction remain to be determined. Notably, sex hormones have been reported to influence porphyrin metabolism [30], possibly accounting for this difference.

Also of considerable importance from the present findings is the importance of creatinine adjustment when evaluating porphyrin changes among children of any age, owing to the significant increase in creatinine excretion that occurs throughout late childhood and adolescence. In the present population, urinary creatinine excretion increased over 2-fold from 0.68 g/l to 1.44 g/l between ages 8 and 18 y. These findings are of particular relevance when evaluating porphyrin changes as a biological indicator of disease or disorder among younger children, whose creatinine-adjusted porphyrin levels are likely to differ significantly from those of teen-aged subjects or adults. For comparisons of children of similar age, creatinine-adjustment offers the additional advantage in facilitating interpretation of porphyrin changes in random (“spot”) or incompletely collected 24-h urine samples from children who are unable to provide complete 24-h urine specimens.

In conclusion, this study provides comprehensive normative values for urinary concentrations and ranges for 5 typically excreted porphyrins in healthy children between the ages of 8 and 18 y. These data may facilitate the clinical assessment of pediatric metabolic disorders and may be of particular relevance in evaluating porphyrin changes as a biological indicator of disease or xenobiotic exposure among children and adolescents.

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University of Washington and the University of Lisbon. All parents or guardians gave written consent, and all children provided written assent.

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Table 1
Demographics at baseline (BL) and each year of follow-up for all subjects.

	BL	1	2	3	4	5	6	7
N	242	215	228	187	205	213	185	167
% male	57	57	57	57	57	56	56	56
% white	70	71	71	70	70	69	69	68
Age (mean)	10.0	11.0	12.0	13.0	14.0	14.9	15.8	16.9

Table 2

Unadjusted porphyrin values ($\mu\text{g/L}$), by gender and age

* Uro	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
8	19	1.5	4.8	9.9	5.9	3.7	8.1	14	2.0	5.1	11.6	6.0	3.9	8.1
9	64	3.1	6.9	14.4	7.7	6.6	8.9	45	3.0	6.5	15.1	8.0	6.4	9.7
10	109	1.9	6.9	14.9	7.5	6.6	8.5	84	1.6	6.1	16.2	7.4	6.2	8.6
11	119	1.3	6.1	16.8	8.0	6.7	9.3	88	2.4	6.3	16.3	7.9	6.7	9.1
12	124	1.5	6.6	15.5	7.9	6.9	8.9	94	2.8	6.1	16.0	8.2	6.9	9.4
13	116	2.5	7.6	18.7	9.5	7.9	11.2	92	1.9	7.1	15.3	8.8	7.2	10.3
14	123	2.4	6.7	17.2	8.0	7.1	9.0	93	1.7	5.7	15.4	7.5	6.2	8.8
15	119	2.4	6.0	18.0	8.2	7.0	9.4	94	1.6	5.0	13.4	6.6	5.5	7.6
16	74	2.3	5.9	17.2	8.3	6.6	10.0	59	2.2	5.7	20.1	9.1	6.7	11.4
17	50	1.6	6.8	15.4	8.1	6.3	10.0	33	2.2	7.0	13.5	7.5	5.8	9.2
18	14	2.2	4.9	10.9	5.8	3.8	7.7	14	1.8	3.0	9.0	5.4	1.9	9.0
Hepta														
8	19	0.1	1.0	2.9	1.2	0.7	1.8	14	0.3	1.1	2.7	1.4	0.8	1.9
9	64	0.4	1.6	3.3	1.8	1.5	2.1	45	0.5	1.3	3.1	1.7	1.3	2.1
10	109	0.3	1.4	3.8	1.8	1.5	2.0	84	0.2	1.6	3.4	1.8	1.4	2.1
11	119	0.4	1.6	3.7	2.0	1.6	2.3	88	0.5	1.5	3.7	1.8	1.5	2.0
12	124	0.5	1.6	3.2	1.9	1.7	2.1	94	0.5	1.6	3.4	2.0	1.6	2.4
13	116	0.6	1.7	3.9	2.1	1.8	2.4	92	0.7	1.7	3.5	2.0	1.7	2.3
14	123	0.7	1.6	3.6	1.8	1.6	2.0	93	0.5	1.3	2.7	1.5	1.3	1.8
15	119	0.6	1.5	3.2	1.8	1.5	2.2	94	0.3	1.1	2.4	1.2	1.0	1.4
16	74	0.6	1.3	4.0	1.9	1.5	2.3	59	0.4	1.0	3.5	1.6	1.3	2.0
17	50	0.4	1.2	3.1	1.6	1.2	1.9	33	0.5	1.0	2.0	1.3	1.0	1.6
18	14	0.4	1.2	1.9	1.3	0.8	1.7	14	0.3	0.8	2.0	1.1	0.4	1.7
Hexa														
8	19	0.1	0.2	1.7	0.4	0.1	0.7	14	0.1	0.1	0.8	0.3	0.1	0.5
9	64	0.1	0.3	1.2	0.5	0.3	0.6	45	0.1	0.3	0.9	0.4	0.2	0.7
10	109	0.1	0.3	1.1	0.5	0.4	0.6	84	0.1	0.3	0.9	0.4	0.3	0.5
11	119	0.1	0.3	1.0	0.5	0.4	0.6	88	0.1	0.3	1.0	0.4	0.3	0.5
12	124	0.1	0.4	1.1	0.5	0.4	0.6	94	0.1	0.4	1.0	0.6	0.3	1.0

*	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
13	115	0.1	0.4	1.3	0.6	0.5	0.7	92	0.1	0.4	0.9	0.5	0.4	0.6
14	123	0.1	0.4	0.8	0.4	0.4	0.5	93	0.1	0.3	0.8	0.4	0.3	0.4
15	119	0.1	0.3	0.7	0.4	0.3	0.4	94	0.1	0.2	0.5	0.3	0.2	0.3
16	74	0.1	0.3	1.1	0.4	0.3	0.6	59	0.1	0.2	0.8	0.3	0.2	0.4
17	50	0.1	0.2	0.7	0.4	0.2	0.5	33	0.1	0.2	0.4	0.3	0.2	0.3
18	14	0.1	0.2	0.5	0.3	0.2	0.4	14	0.1	0.2	0.6	0.3	0.1	0.4
<hr/>														
Penta	8	19	0.1	0.9	3.8	1.4	2.0	14	0.3	1.2	2.6	1.3	0.7	1.9
	9	64	0.1	1.3	3.8	1.8	2.1	45	0.1	0.9	3.5	1.5	1.1	1.9
	10	109	0.2	1.3	3.7	1.9	2.5	85	0.1	0.8	3.0	1.3	1.0	1.5
	11	119	0.2	1.6	4.2	1.9	2.2	88	0.1	1.4	3.9	1.8	1.4	2.1
	12	124	0.2	1.8	3.7	2.0	2.2	94	0.5	1.6	3.9	2.0	1.7	2.3
	13	116	0.5	1.6	4.2	2.0	2.4	92	0.4	1.5	3.4	1.8	1.5	2.0
	14	123	0.5	1.5	3.5	1.8	2.0	93	0.4	1.1	3.6	1.5	1.2	1.8
	15	119	0.4	1.3	3.3	1.6	1.8	94	0.2	0.9	2.2	1.2	1.0	1.4
	16	74	0.4	1.3	4.2	2.0	2.5	59	0.2	1.0	4.0	1.5	1.2	1.9
	17	50	0.3	1.3	3.4	1.6	1.9	33	0.4	1.2	2.1	1.3	1.0	1.6
	18	14	0.4	1.0	2.2	1.2	1.7	14	0.3	1.0	2.0	1.2	0.6	1.8
<hr/>														
Copro	8	19	1.4	25.7	78.2	51.2	55.8	14	6.9	28.7	81.2	37.8	20.2	55.4
	9	64	5.2	40.7	98.3	50.0	59.9	45	2.0	30.5	86.0	38.8	28.9	48.7
	10	108	3.0	38.8	80.5	43.4	50.9	84	1.3	24.3	81.9	33.1	26.2	40.1
	11	119	5.2	40.2	89.5	46.5	53.1	88	2.3	33.7	82.7	38.0	31.5	44.5
	12	124	5.5	46.2	89.6	49.2	55.4	94	10.7	35.3	80.5	42.5	36.6	48.3
	13	116	15.3	46.5	96.2	53.5	59.8	92	10.4	35.6	76.3	41.7	35.7	47.7
	14	123	16.7	37.9	85.0	44.7	49.9	93	11.3	34.8	76.9	41.6	35.6	47.6
	15	119	13.4	37.4	76.2	42.5	48.6	94	8.1	25.9	55.9	34.1	27.3	41.0
	16	74	12.7	31.6	106.6	46.2	57.5	59	7.1	25.1	77.3	37.2	28.5	46.0
	17	50	12.9	37.9	90.6	45.8	56.3	33	14.2	36.2	60.2	38.2	30.6	45.8
	18	14	14.0	29.7	67.3	36.2	47.7	14	15.3	26.0	58.4	27.8	19.0	36.6

*	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
Total	19	4.1	32	87.7	60.1	41.8	68.4	14	9.5	42.7	88.8	46.7	27.6	65.9
8	64	11.5	52	114.8	61.8	50.8	72.8	45	10.4	42.3	102.3	50.5	39.7	61.3
9	108	8.5	50.5	100.4	55.0	46.6	63.4	84	4.9	33.7	98.4	43.9	35.8	52
10	119	9.8	48.9	110.7	58.8	51.1	66.5	88	7.2	41.8	103	49.9	42.3	57.5
11	124	9.4	55.6	114.5	61.4	54.2	68.5	94	20.1	46.5	100.6	55.3	48.2	62.3
12	115	24.1	61.3	124.1	68.2	60.7	75.7	92	16.2	46.9	95.5	54.7	47.2	62.2
13	123	22.9	51.1	99.7	56.8	50.9	62.7	93	16.3	45.4	94.8	52.5	45.5	59.6
14	119	17.9	45.9	99.1	54.4	47.2	61.7	94	12.2	34.8	72.8	43.4	35.7	51.1
15	74	17.9	39.7	124.9	58.8	45.7	72	59	11.4	33.8	103.3	49.8	38.7	60.9
16	50	16.9	47.5	106.4	57.4	45.2	69.7	33	20.5	43.4	75.3	48.6	39.3	57.8
17	14	21	39.9	76.8	44.7	31.9	57.5	14	18.3	30	69.8	35.7	24	47.5
18														

* Age in years

Table 3
Creatinine adjusted porphyrin values ($\mu\text{g/g}$), by gender and age

*	Male							Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI	
Uro/creat	8	19	2.5	6.1	20.2	8.5	5.5	11.5	14	3.2	11.6	19.6	12.5	8	17
	9	64	4.1	8.3	15.1	9	8	10.1	45	4.3	9.2	16.4	10.1	8.2	12
	10	109	1.9	7.7	14.3	8.5	7.5	9.5	82	2	8	17.6	8.8	7.4	10.1
	11	116	2.5	6.9	15.5	8.4	7.1	9.7	86	2	8.2	14.1	8.5	7.3	9.7
	12	123	2.7	6.3	12.6	7.4	6.6	8.3	93	2.8	6.6	12.5	7.2	6.1	8.3
	13	115	2.7	6.8	15.9	8.4	7.2	9.5	92	2.7	6.6	13.1	7.6	6.6	8.5
	14	121	1.7	6.3	11.7	6.5	5.8	7.2	91	2.5	5.5	11.2	6.2	5.5	7
	15	118	1.7	4.2	10.6	6	4.6	7.5	92	1.2	4.1	9.8	5.1	4.3	5.9
	16	74	1.6	4.3	11.7	5.3	4.4	6.1	59	1.7	4.8	12	6	4.7	7.4
	17	50	1.9	4.3	12.3	5.7	4.5	6.8	33	1.7	4.1	12.1	5.2	3.9	6.4
	18	14	2.5	3.1	8.2	4.4	2.6	6.2	14	1.6	3.2	4.9	4.1	1.8	6.5
Hep/creat	8	19	0.1	1.1	3.7	2	0.9	3	14	0.4	2.6	4.9	2.5	1.6	3.5
	9	64	0.5	1.7	3.9	2	1.7	2.3	45	0.5	1.7	4.5	2.2	1.7	2.6
	10	109	0.3	1.8	3.8	2	1.7	2.2	82	0.2	1.8	3.6	2.2	1.5	3
	11	116	0.5	1.8	3.7	2.2	1.8	2.5	86	0.5	2	3.2	2	1.7	2.3
	12	123	0.7	1.8	3.2	1.8	1.6	2	93	0.6	1.5	2.6	1.7	1.5	2
	13	115	0.6	1.5	3.5	1.9	1.7	2.2	92	0.8	1.5	2.8	1.7	1.5	1.9
	14	121	0.5	1.3	2.6	1.5	1.3	1.6	91	0.5	1.1	2.4	1.3	1.1	1.5
	15	118	0.4	1	2.1	1.3	1	1.6	92	0.2	0.9	1.7	1	0.8	1.1
	16	74	0.4	0.9	2	1.3	0.8	1.9	59	0.2	0.8	2.1	1.1	0.9	1.3
	17	50	0.3	0.9	2.5	1.1	0.9	1.4	33	0.3	0.7	1.6	0.9	0.7	1.1
	18	14	0.4	0.8	2.1	0.9	0.6	1.3	14	0.4	0.6	1.2	0.8	0.4	1.2
Hex/creat	8	19	0.1s	0.2	2.2	0.6	0.2	1	14	0.1	0.5	1.3	0.6	0.3	1
	9	64	0.1	0.4	1.1	0.6	0.4	0.7	45	0.1	0.3	1.1	0.5	0.3	0.7
	10	109	0.1	0.4	1.3	0.5	0.4	0.6	82	0.1	0.3	0.9	0.4	0.3	0.5
	11	116	0.1	0.4	1	0.5	0.4	0.6	86	0.1	0.4	0.8	0.5	0.4	0.5
	12	123	0.1	0.4	0.9	0.5	0.4	0.6	93	0.2	0.4	0.8	0.5	0.4	0.7

*	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
13	114	0.1	0.3	1.1	0.5	0.4	0.6	92	0.1	0.4	0.7	0.4	0.4	0.5
14	121	0.1	0.3	0.6	0.4	0.3	0.4	91	0.1	0.3	0.5	0.3	0.3	0.3
15	118	0.1	0.2	0.5	0.3	0.2	0.3	92	0.1	0.2	0.4	0.2	0.2	0.2
16	74	0.1	0.2	0.5	0.3	0.2	0.3	59	0.1	0.2	0.5	0.2	0.2	0.3
17	50	0.1	0.2	0.5	0.3	0.2	0.3	33	0.1	0.1	0.3	0.2	0.1	0.2
18	14	0.1	0.1	0.4	0.2	0.1	0.3	14	0.1	0.1	0.4	0.2	0.1	0.2
<hr/>														
Pen/creat	8	19	0.1	1.2	2	1	3	14	0.4	2.3	5.8	2.8	1.5	4
9	64	0.2	1.7	4.5	2.2	1.7	2.7	45	0.2	1.6	5.5	2.1	1.5	2.7
10	109	0.2	1.7	4.8	2.1	1.6	2.6	83	0.1	1.1	3.5	1.6	1.2	1.9
11	116	0.1	1.7	3.9	2.1	1.7	2.5	86	0.1	1.8	4	2	1.6	2.4
12	123	0.4	1.7	3	1.9	1.6	2.2	93	0.4	1.6	3.3	1.8	1.5	2.1
13	115	0.5	1.4	3.6	1.9	1.6	2.2	92	0.6	1.3	2.6	1.5	1.3	1.7
14	121	0.5	1.2	2.5	1.4	1.3	1.6	91	0.5	1	2.3	1.2	1.1	1.4
15	118	0.3	0.9	1.9	1.2	0.8	1.5	92	0.2	0.8	1.7	1	0.8	1.2
16	74	0.3	0.9	2.4	1.2	1	1.4	59	0.2	0.7	1.9	1	0.8	1.2
17	50	0.3	0.7	2.1	1.1	0.8	1.5	33	0.4	0.7	1.6	0.9	0.7	1.1
18	14	0.4	0.7	2	1	0.5	1.4	14	0.5	0.7	1.1	0.8	0.6	1
<hr/>														
Copro/creat	8	19	1.6	32.3	62.1	34	80.2	14	13.4	52.3	171	76.1	39.3	113
9	64	4.5	51.3	118	62.5	50.2	74.9	45	3.3	40.8	139	53.7	38.8	68.7
10	108	3.6	45.2	121	52.6	44	61.3	82	1.4	32	94.2	45.0	34.7	55.3
11	116	4.5	44	109	54.7	46	63.5	86	1.9	32	106	48.6	37.7	59.5
12	123	8.1	42.4	98.5	57.7	41.3	74.1	93	8.4	38	72.4	40.5	34.8	46.2
13	115	12.2	43.9	95.5	53.2	44.6	61.7	92	10	36.5	75.6	38.9	33.8	44
14	121	12.6	30.8	70.9	38.2	33.3	43.1	91	10.8	31.2	81.9	38.7	33.2	44.3
15	118	8.3	23.1	57.4	31.6	24.7	38.6	92	5.8	20.2	61	30.2	23.3	37.1
16	74	8.2	19.9	62.5	29.3	23.5	35.2	59	5	17.3	56.8	26.4	20.4	32.4
17	50	9.4	21.9	70.8	37.4	26.5	48.4	33	11.3	19.9	44.6	26.9	19.7	34.1
18	14	11.6	23.6	66	28.6	17.6	39.7	14	9.2	22.8	43.4	24.3	16.8	31.8

*	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
8	19	5.5	40.4	205.8	75.2	43.8	98.7	14	17	73.6	188.1	94.5	56.1	132.9
9	64	13.7	65.4	138.8	76.3	62.8	89.7	45	11	54.6	148.5	68.6	52.1	85.1
10	108	9.1	58.6	141.1	65.7	56.3	75.2	82	5	47.6	115.8	58.0	46.3	69.8
11	116	11.6	58.9	123.7	67.9	57.9	77.9	86	6.6	45.3	117.6	61.6	49.6	73.5
12	123	12.6	52.7	118.7	69.3	52.6	86	93	15.3	48.6	95.6	51.7	45.1	58.4
13	114	17.5	56	118.3	66.3	56.9	75.8	92	17.5	46	84.9	50.1	44.3	55.9
14	121	16.3	41.5	80.9	47.9	42.4	53.4	91	17.3	41.1	96.2	47.8	41.7	53.9
15	118	12.5	31.1	69.2	40.4	31.4	49.3	92	9.8	25.6	72.9	37.4	29.6	45.2
16	74	13	25.9	76.6	37.4	30.7	44.1	59	8.5	25	73.2	34.8	27.4	42.1
17	50	12.8	29	85.9	45.6	33.5	57.7	33	14.5	27.4	58	34.0	25.8	42.3
18	14	15.4	29.6	78.8	35.2	22.6	47.8	14	12.2	27.7	50.1	30.2	21.7	38.8

* Age in years

Table 4
Porphyrin values as a percentage (%) of total porphyrins, by gender and age

* Uro	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
8	19	5.4	15.0	65.8	24.2	15.0	33.4	14	4.6	16.2	32.2	18.2	11.3	25.0
9	64	5.6	12.9	48.1	19.5	15.0	23.9	45	7.0	18.0	56.4	24.5	18.5	30.4
10	108	5.9	13.3	57.9	21.8	18.1	25.6	84	7.5	20.0	60.5	27.6	23.2	32.1
11	119	5.6	11.9	44.9	18.0	15.1	20.9	88	6.5	16.9	61.3	23.7	19.4	27.9
12	124	5.7	12.7	32.2	17.2	14.4	19.9	94	6.8	14.0	36.3	17.7	15.1	20.4
13	115	5.6	13.3	25.8	15.6	13.8	17.4	92	7.1	16.1	31.6	17.7	15.7	19.7
14	123	5.6	14.6	25.7	16.1	14.2	17.9	93	5.3	13.3	28.0	15.7	13.7	17.7
15	119	7.3	14.7	29.3	16.5	15.0	18.0	94	7.0	16.5	30.3	17.5	15.5	19.5
16	74	7.1	14.1	28.6	17.0	14.7	19.4	59	8.5	18.6	31.6	19.8	16.9	22.7
17	50	4.9	14.1	26.4	16.3	13.3	19.3	33	7.5	13.8	28.3	15.7	13.0	18.4
18	14	6.4	14.8	19.9	13.7	10.5	16.9	14	8.3	11.7	17.5	13.6	9.4	17.7
Hepta														
8	19	1.1	3.6	8.3	5.2	2.1	8.4	14	1.1	3.0	5.1	3.3	2.2	4.3
9	64	1.3	2.7	6.2	3.4	2.8	4.0	45	1.7	3.3	8.0	4.0	3.3	4.8
10	108	1.5	3.1	9.1	4.2	3.6	4.8	84	1.9	3.9	10.9	5.1	4.3	5.8
11	119	1.5	2.9	8.4	4.0	3.4	4.6	88	1.9	3.7	7.4	4.4	3.9	4.9
12	124	1.7	3.1	6.6	3.9	3.4	4.4	94	2.1	3.3	5.2	3.7	3.4	4.1
13	115	1.7	3.0	5.5	3.4	3.1	3.7	92	2.1	3.5	6.3	3.9	3.5	4.3
14	123	1.7	3.2	5.7	3.5	3.2	3.8	93	1.4	2.9	5.1	3.3	2.8	3.7
15	119	1.8	3.3	5.9	3.7	3.1	4.4	94	1.6	3.0	5.1	3.1	2.8	3.4
16	74	1.7	3.1	6.0	4.0	3.1	4.9	59	1.5	3.6	5.8	3.7	3.2	4.1
17	50	1.3	2.5	5.9	3.1	2.5	3.7	33	1.7	2.7	3.7	2.7	2.4	3.0
18	14	1.4	2.7	5.2	3.0	2.1	3.8	14	1.6	2.4	4.5	2.7	1.9	3.5
Hexa														
8	19	0.1	0.6	2.4	0.8	0.5	1.2	14	0.2	0.6	1.1	0.6	0.4	0.9
9	64	0.2	0.6	1.3	0.9	0.5	1.4	45	0.2	0.6	1.2	1.2	0.1	2.4
10	108	0.2	0.6	1.7	1.2	0.6	1.8	84	0.3	0.8	2.0	1.1	0.8	1.4
11	119	0.3	0.6	1.3	0.8	0.6	1.0	88	0.3	0.8	1.5	1.0	0.7	1.3
12	124	0.4	0.7	1.5	0.9	0.7	1.0	94	0.5	0.8	1.7	1.1	0.8	1.3

*	Male						Female							
	N	P10	P50	P90	Mean	95%	CI	N	P10	P50	P90	Mean	95%	CI
13	115	0.4	0.7	1.4	0.8	0.7	0.9	92	0.4	0.7	1.6	0.9	0.8	1.0
14	123	0.3	0.7	1.3	0.8	0.7	0.9	93	0.3	0.7	1.2	0.7	0.7	0.8
15	119	0.3	0.7	1.2	0.7	0.7	0.8	94	0.3	0.6	1.1	0.7	0.6	0.7
16	74	0.4	0.6	1.3	0.8	0.6	1.0	59	0.3	0.6	1.2	0.7	0.6	0.9
17	50	0.3	0.6	1.2	0.8	0.5	1.0	33	0.4	0.5	0.7	0.5	0.5	0.6
18	14	0.3	0.6	0.8	0.6	0.5	0.7	14	0.1	0.6	1.0	0.6	0.4	0.8
<hr/>														
Penta	8	19	1.0	2.8	3.6	2.1	5.2	14	1.5	2.7	4.3	3.2	1.9	4.5
9	64	1.0	2.7	4.2	2.7	2.4	3.1	45	1.2	2.7	4.2	2.7	2.3	3.1
10	108	1.2	2.8	4.4	3.1	2.6	3.7	84	1.1	2.4	4.0	2.6	2.3	2.9
11	119	1.2	2.9	4.5	2.9	2.6	3.2	88	1.0	3.0	6.0	3.4	3.0	3.8
12	124	1.7	2.9	5.4	3.3	2.9	3.7	94	1.5	3.4	5.7	3.5	3.2	3.8
13	115	1.3	2.8	4.3	3.0	2.7	3.3	92	2.0	3.1	4.7	3.2	3.0	3.5
14	123	1.9	3.0	4.3	3.2	2.9	3.4	93	1.6	2.7	4.2	2.8	2.6	3.0
15	119	1.7	2.9	4.2	3.0	2.8	3.2	94	1.4	2.8	4.3	3.1	2.4	3.8
16	74	1.9	3.0	4.9	3.4	3.0	3.9	59	1.3	3.0	5.0	3.1	2.7	3.5
17	50	1.0	2.6	4.7	2.7	2.3	3.1	33	1.9	2.5	4.4	2.8	2.4	3.1
18	14	1.4	2.4	3.7	3.5	1.3	5.7	14	1.4	2.8	5.4	3.2	2.3	4.0
<hr/>														
Copro	8	19	24.4	80.1	66.1	55.0	77.2	14	58.5	76.8	90.9	74.8	67.7	81.8
9	64	40.6	80.6	89.1	73.4	68.5	78.4	45	25.4	74.2	87.8	67.5	60.8	74.3
10	108	28.8	78.8	89.1	69.7	65.5	73.8	84	23.9	71.3	87.1	63.6	58.7	68.4
11	119	46.2	80.2	89.2	74.3	71.0	77.6	88	27.6	74.4	87.3	67.5	62.9	72.1
12	124	54.9	79.4	88.8	74.8	71.7	77.8	94	53.9	78.9	86.7	74.0	71.1	76.9
13	115	64.3	79.4	89.8	77.2	75.1	79.3	92	58.7	76.2	87.0	74.3	71.8	76.8
14	123	63.7	79.2	89.3	76.4	74.2	78.6	93	63.4	80.3	90.5	77.5	75.1	80.0
15	119	61.3	78.0	87.4	76.1	74.2	77.9	94	59.3	76.9	88.1	75.5	73.1	77.9
16	74	59.3	78.8	87.4	74.7	71.6	77.9	59	50.1	74.4	86.9	72.7	69.3	76.1
17	50	58.0	79.5	89.9	77.2	73.6	80.7	33	67.0	78.6	87.5	78.3	75.4	81.1
18	14	66.7	78.1	90.7	79.3	74.4	84.1	14	75.3	82.1	87.4	80.0	74.9	85.0

* Age in years

Table 5
Mean urinary creatinine concentrations (g/L) by age and gender.

Age (years)	8	9	10	11	12	13	14	15	16	17	18
N	33	109	194	207	218	208	216	213	133	83	28
Male	0.74	0.9	0.96	1.03	1.09	1.23	1.32	1.58	1.66	1.48	1.43
Female	0.61	0.86	0.93	1.01	1.23	1.21	1.3	1.42	1.57	1.64	1.44