Chronic exposure to cadmium and health effects in inhabitants of Kakehashi River Basin, Ishikawa Prefecture, Japan

Teruhiko Kido
(Kanazawa University, Japan)

Main items in this lecture

Ⅰ. Epidemiological study on renal dysfunction in inhabitants living in Kakehashi River Basin, Ishikawa Prefecture

Ⅱ. Cadmium induced renal effects

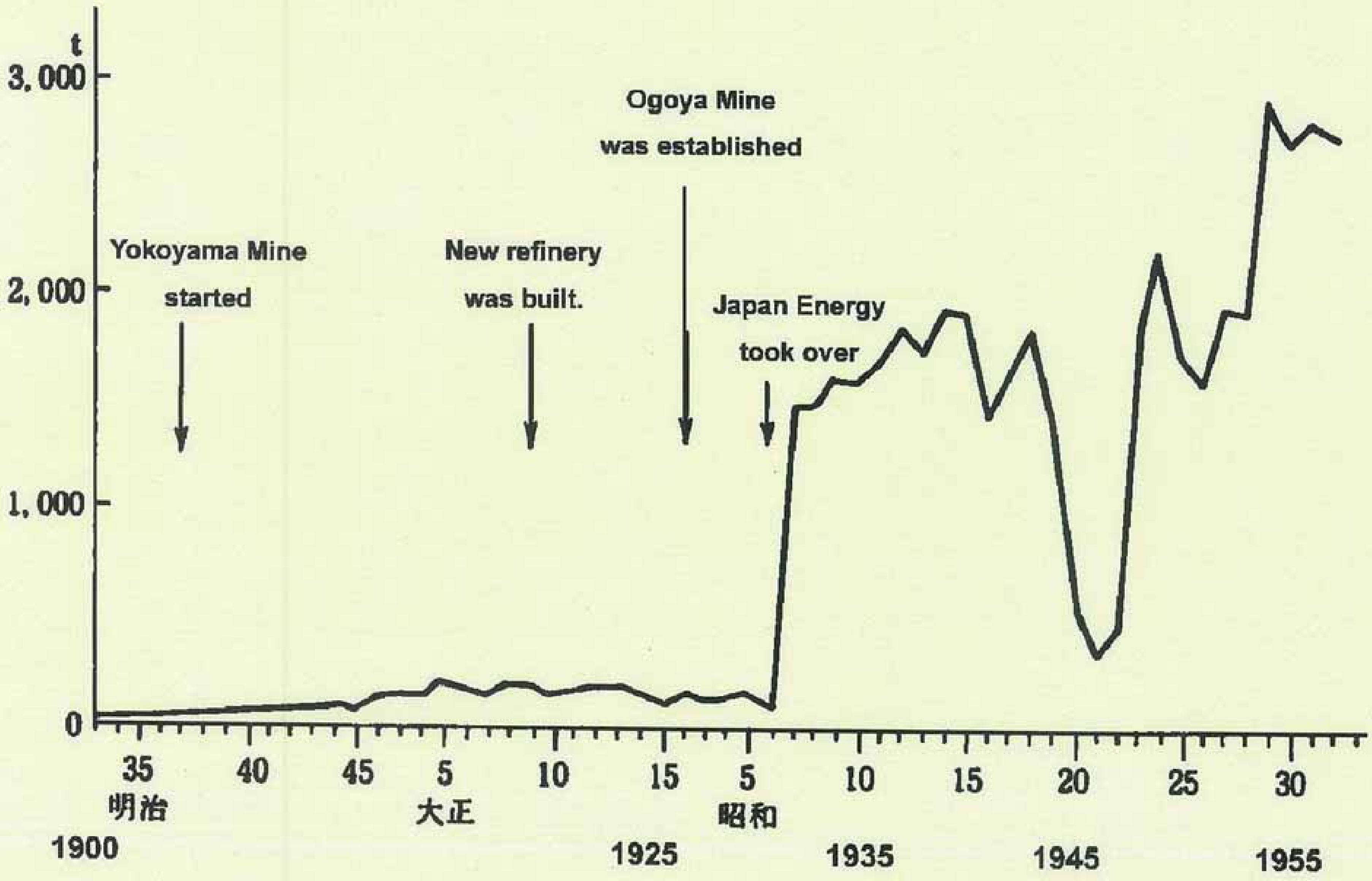
Ⅲ. Cadmium induced bone effects

Ⅳ. Dose-response relationship between cadmium exposure and adverse health effects

Ⅰ. Epidemiological study on renal dysfunction in inhabitants living in Kakehashi River Basin, Ishikawa Prefecture

Cadmium polluted areas in Japan

Annual data on cupper production at Ogoya Mine (by history of Nishio Village)



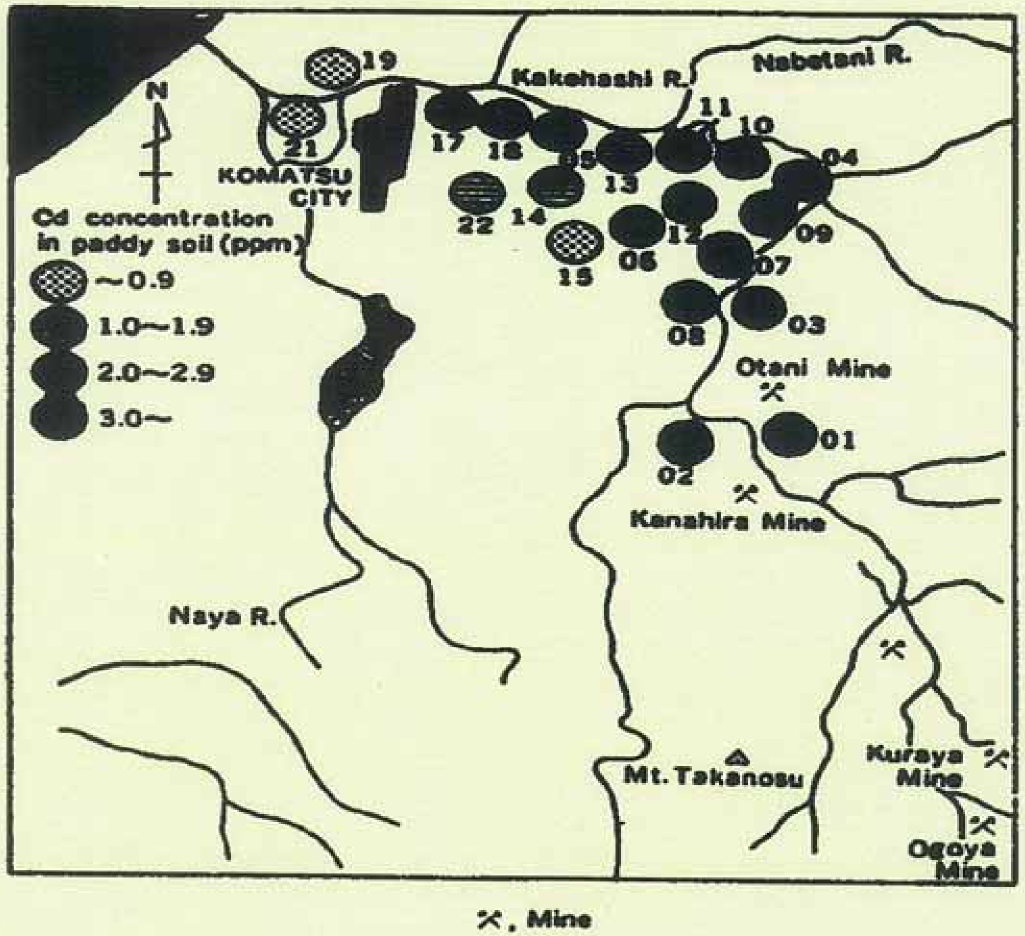


Fig. 6–25. Location of cadmium mines and concentrations of cadmium in paddy soil, Kakehashi River Basin. 1974 survey.
Source: Ishikawa Prefecture 1975C

1 Kanahira	8 Hanasaka	15 Yoshitake
2 Kaneno	9 Nakaumi	17 Sono
3 Gokoji	10 Arakida	18 Kamikomatsu
4 Karumi	11 Sasaki	19 Shimomaki
5 Shirae	12 Yawata	21 Tsurugashima
6 Wakasugi	13 Urushi	22 Oki
7 Shorenji	14 Uchikoshi	

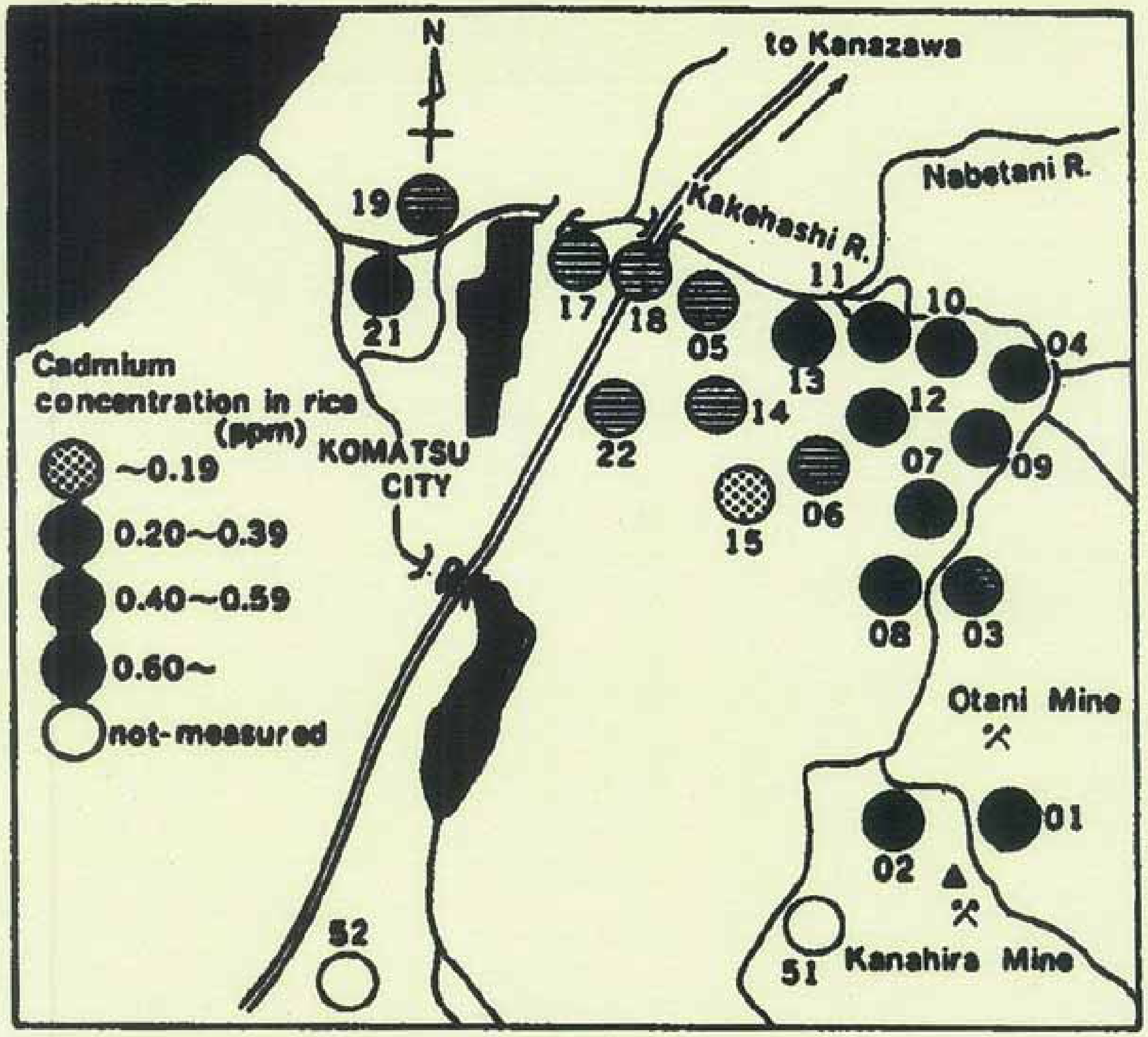
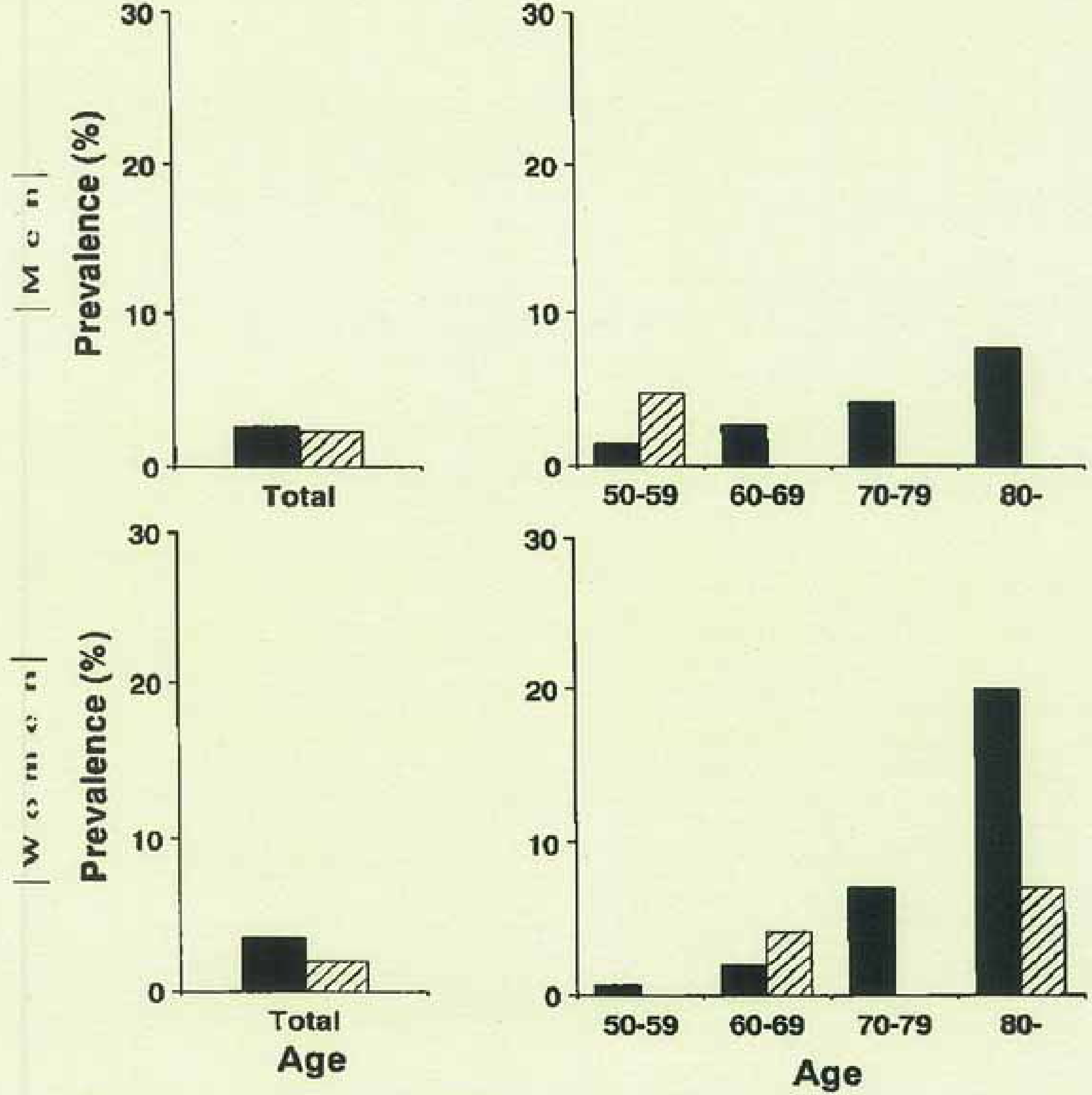


Fig. 6–27. Cadmium concentrations in rice grown in 1974 in the Kakehashi River Basin.
Source: Ishikawa Prefecture 1975C
Note: Numbers correspond to key on Fig. 6–25.
51 Hasadani, 52 Futatsumashi

Table 1 Age and sex distribution of population studied.

Age	Cd-exposed subjects			Nonexposed control subjects		
	Men	Women	Men and women	Men	Women	Men and women
50 – 59	600	713	1313	62	64	126
60 – 69	494	591	1085	38	49	87
70 – 79	265	340	605	26	34	60
80 –	65	110	175	7	14	21
Total	1424	1754	3178	133	161	294

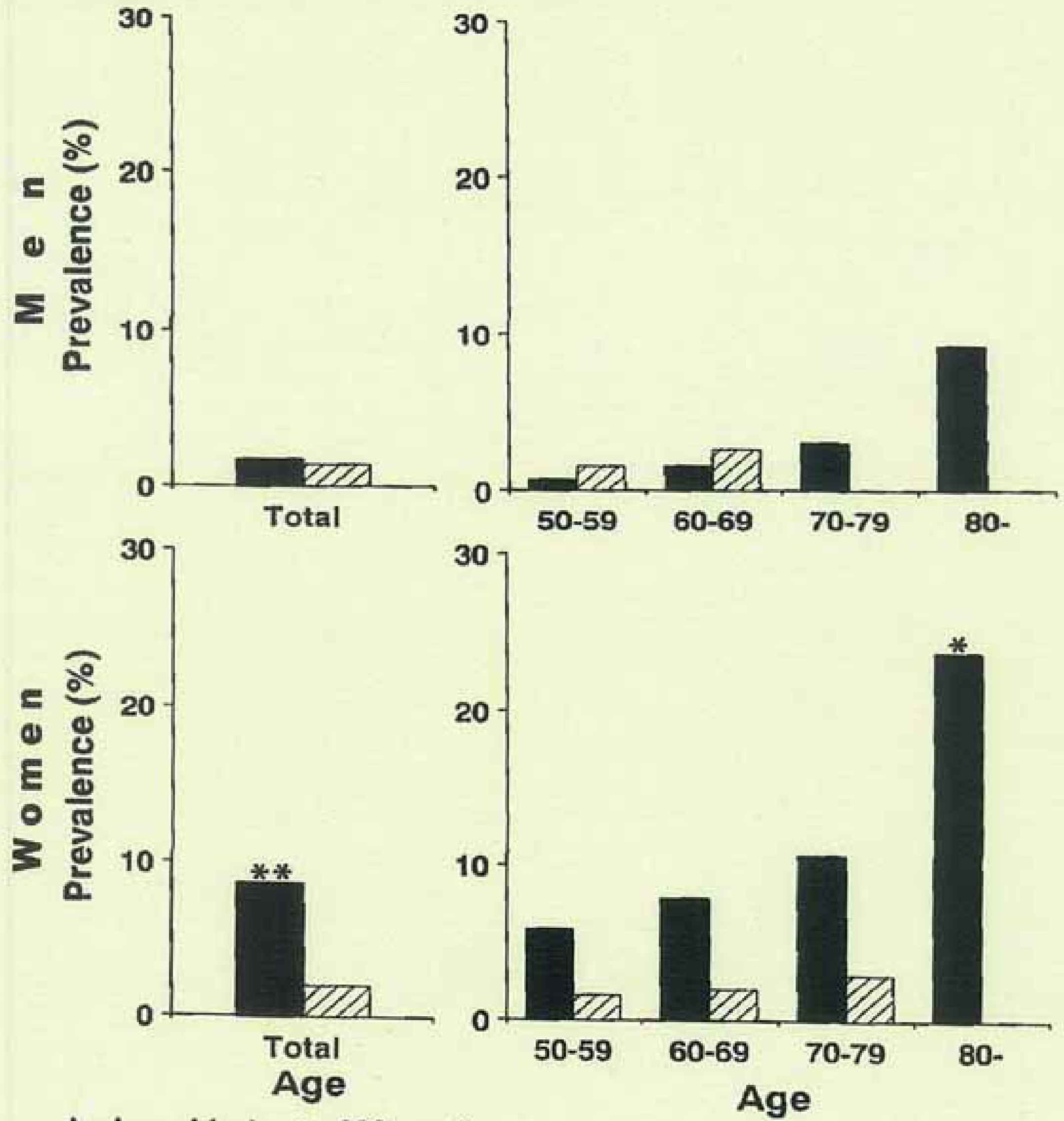
Prevalence of Glucosuria with Proteinuria



Glucosuria ≧ 20 mg/dl, Proteinuria ≧ 5 mg/dl

■ ; Cd-exposed subjects, ▨ ; Nonexposed subjects

Prevalence of Aminoaciduria

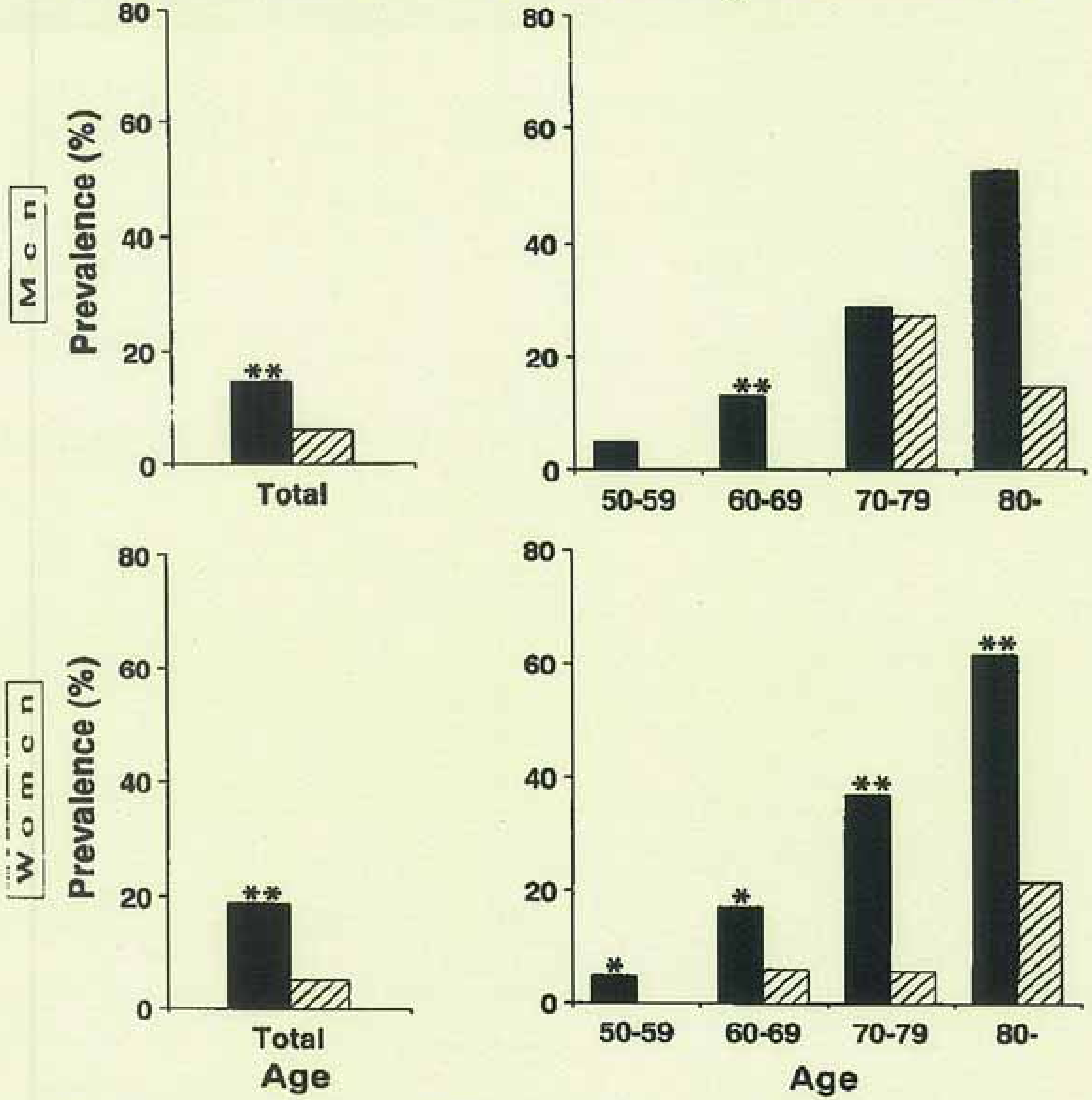


Aminoaciduria ≧ 300 mg/g cr

■ ; Cd-exposed subjects, ▨ ; Nonexposed subjects

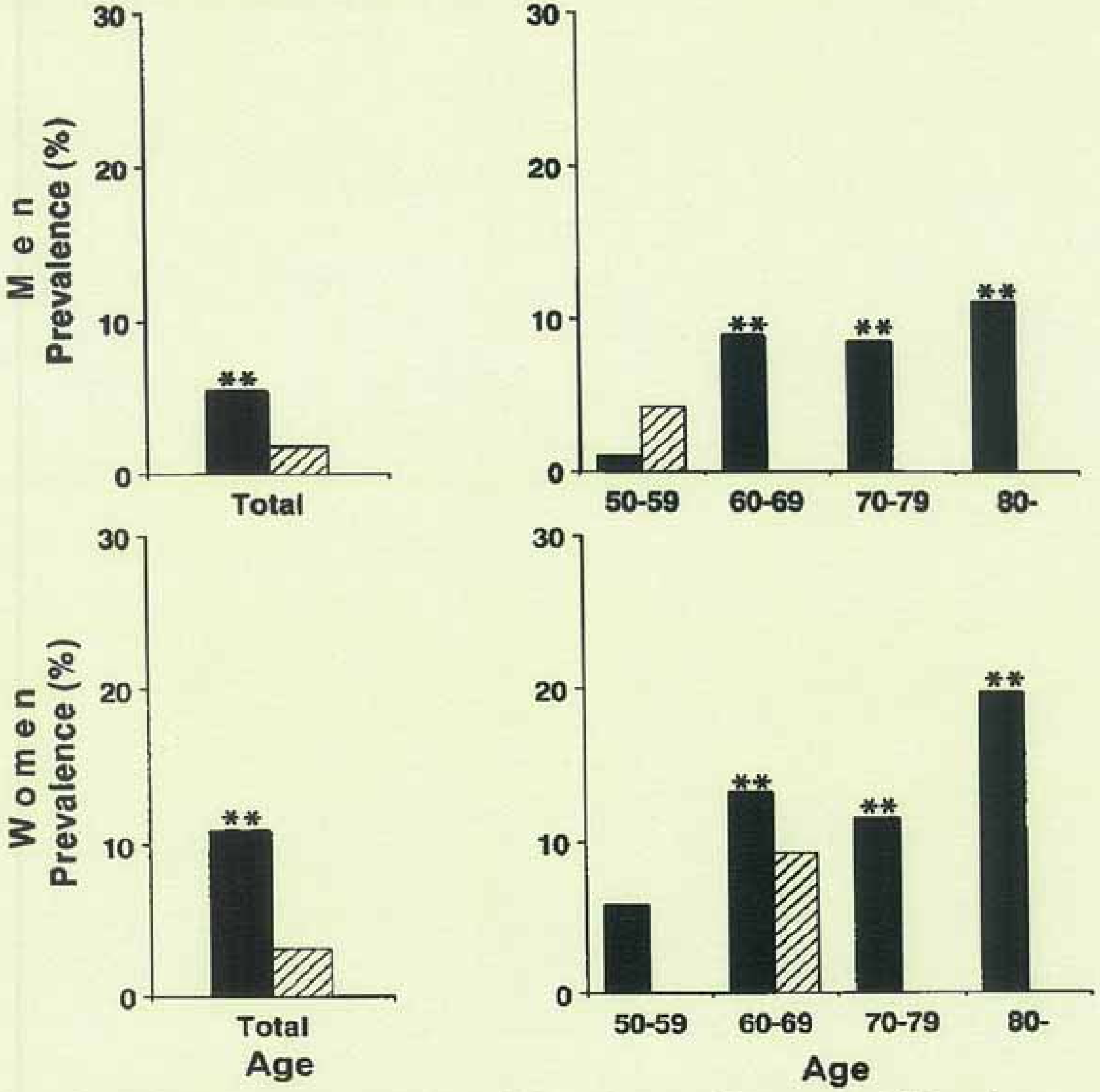
* ; P ≦ 0.05, ** ; P ≦ 0.01

Prevalence of B_2−Microglobulinuria



B_2−Microglobulinuria ≧ 1000 ug/g cr
; Cd−exposed subjects, ; Nonexposed subjects
* ; P ≦ 0.05, ** ; P ≦ 0.01

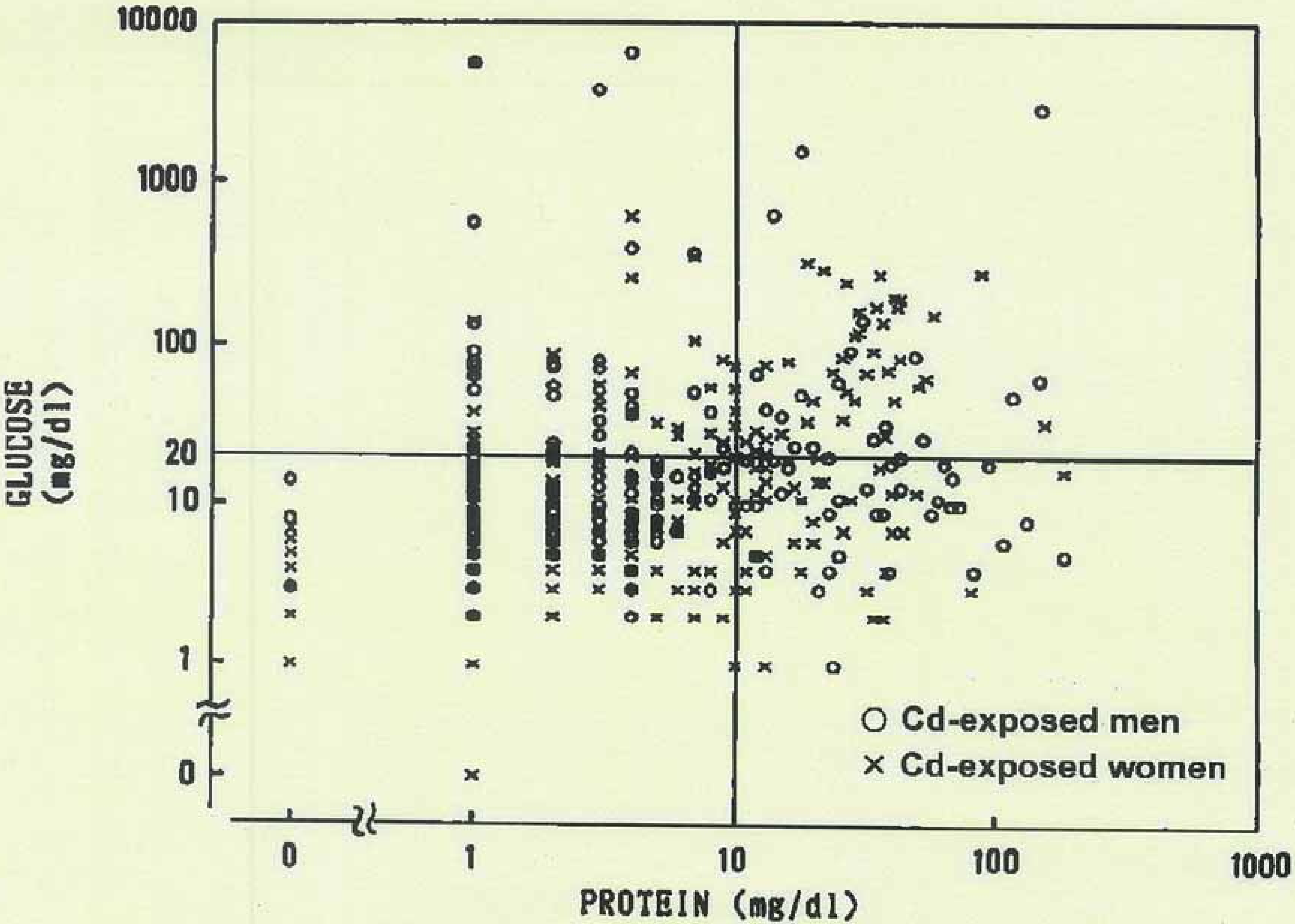
Prevalence of Metallothioneinuria



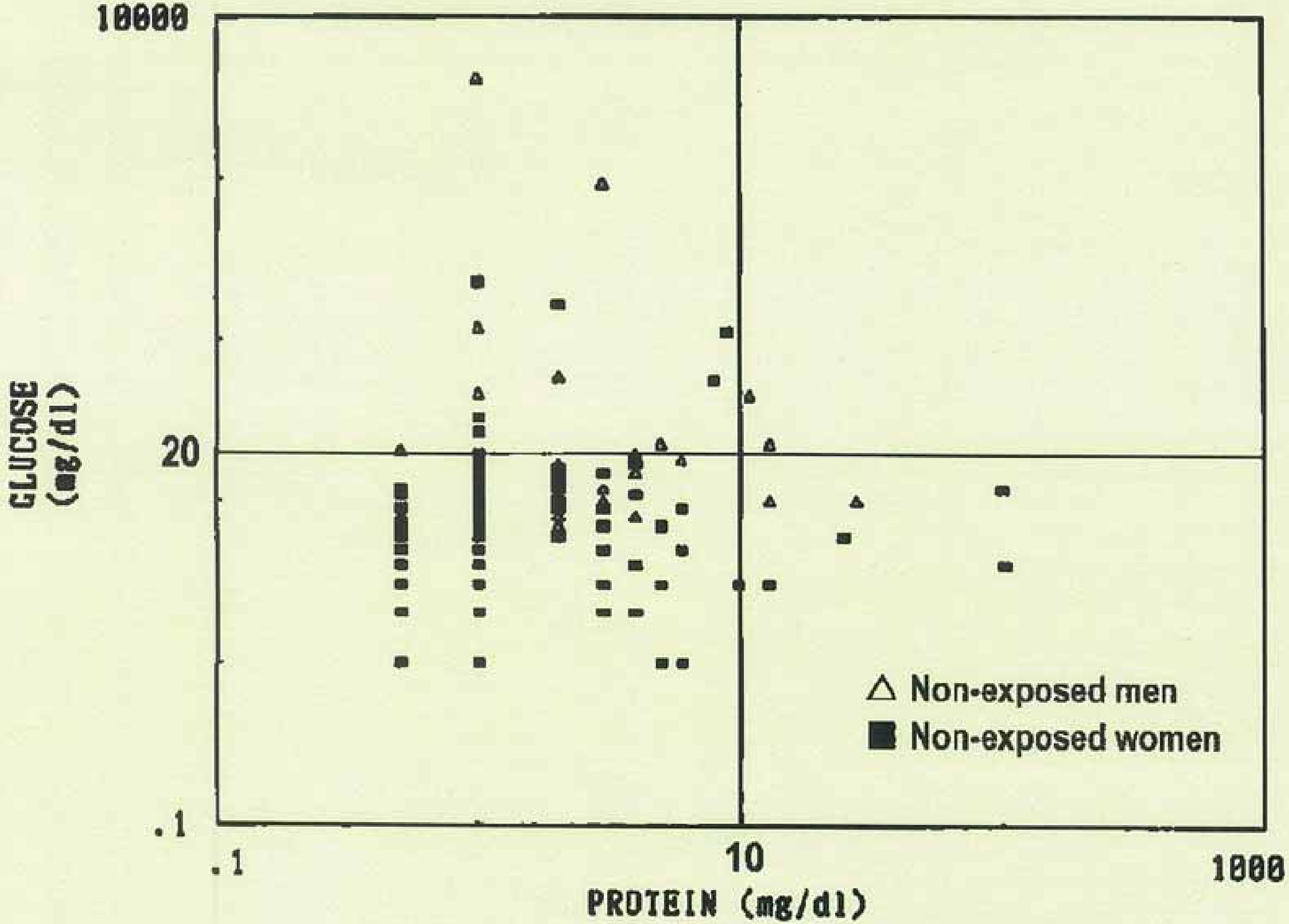
Metallothioneinuria ; Men ≧ 645 ug/g cr , Women ≧ 738 ug/g cr

; Cd-exposed subjects, ; Nonexposed subjects

* ; P ≦ 0.05, ** ; P ≦ 0.01



Urinary findings of glucose and protein in cadmium – exposed inhabitants with β_2 – microglobulin concentration over 1,000 μg / g cr



Urinary findings of glucose and protein in cadmium – exposed inhabitants with β_2 – microglobulin concentration less than 1,000 μg / g cr

Ⅱ. Cadmium induced renal effects

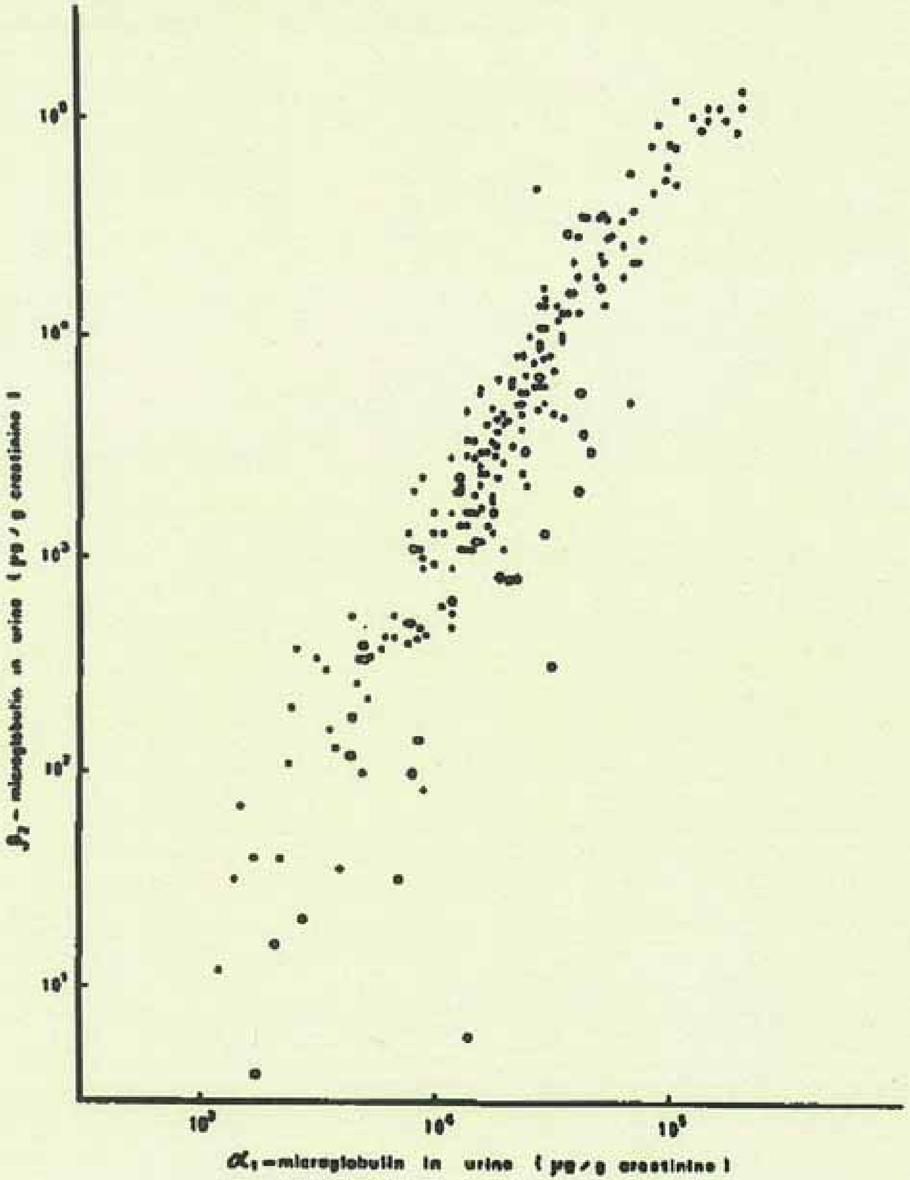


Fig. 5. Relationship between α_1-m and β_2-m concentrations of urine from the Cd-polluted subjects. •, urine pH > 5.8; O, urine pH < 5.6.

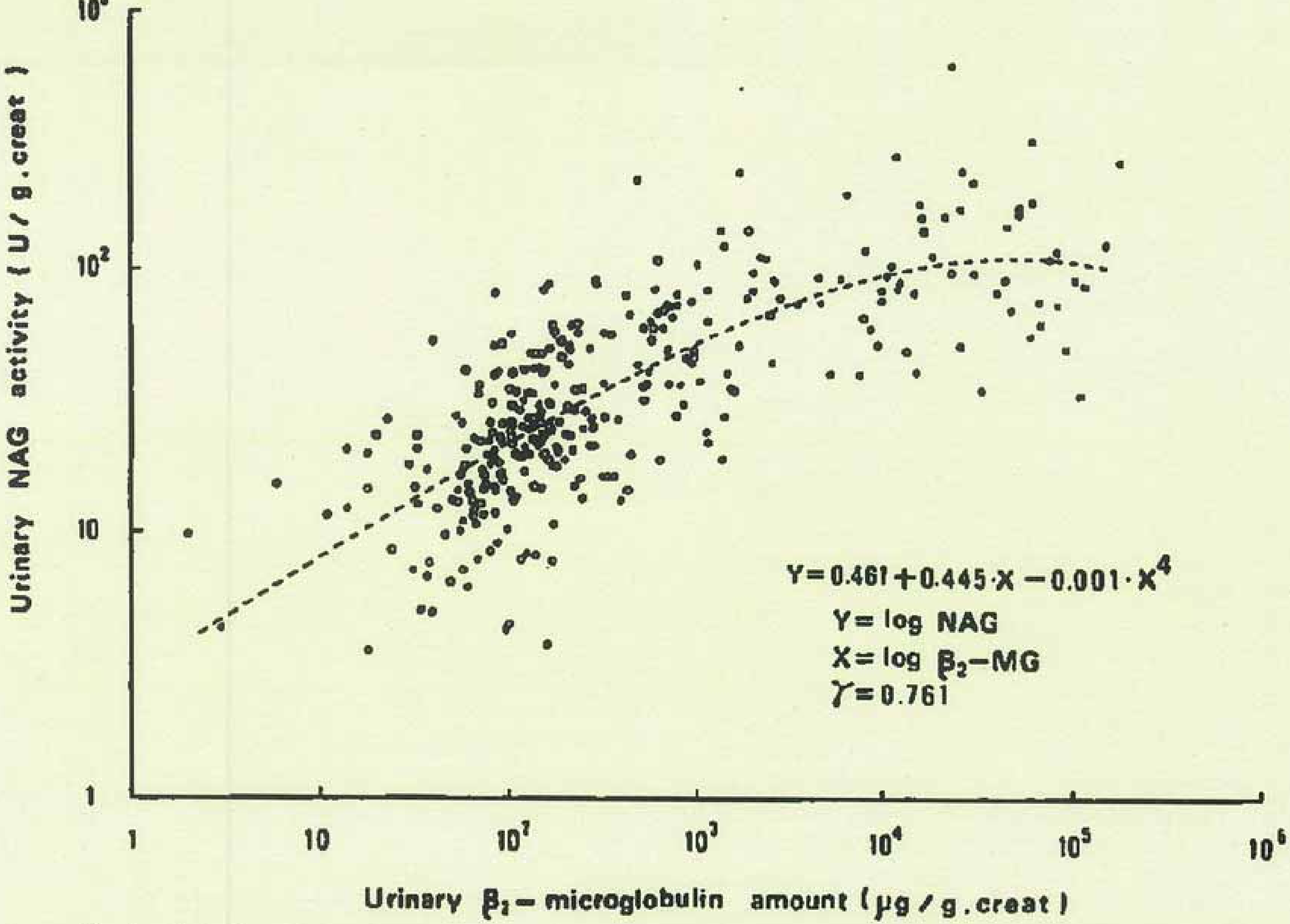


Fig 1. Relationship between urinary β_2-microglobulin concentrations and NAG activities among people from an area free of cadmium (○), inhabtants of a cadmium-polluted area (●) and itai-itai disease patients and suspected patients (×).

5-year follow-up study of Cd-exposed subjects

Table 1. —Sex and Age Distribution of Subjects Examined

Age* (Yr)	Men	Women	Total
50-59	8	19	27
60-69	19	15	34
70-79	5	5	10
80-	0	3	3
Total	32	42	74

*Age in 1981.

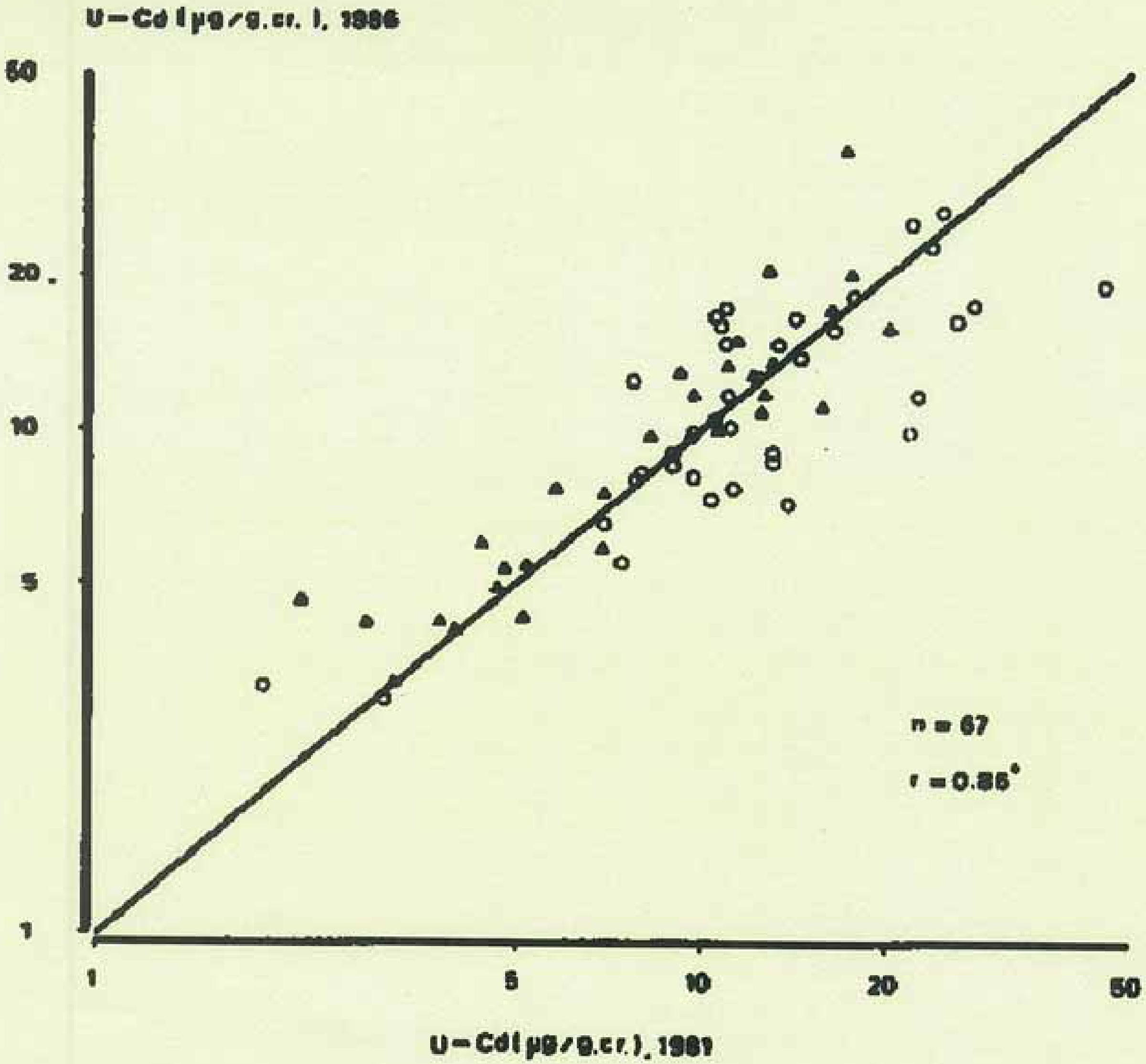


Fig. 5. Urinary excretion of cadmium (µg/g creatinine) in 74 cadmium-exposed inhabitants examined in 1981 and 1986; ▲ = males, ○ = females. The *r* denotes the correlation coefficient. *Significant *r* value at $p < .001$.

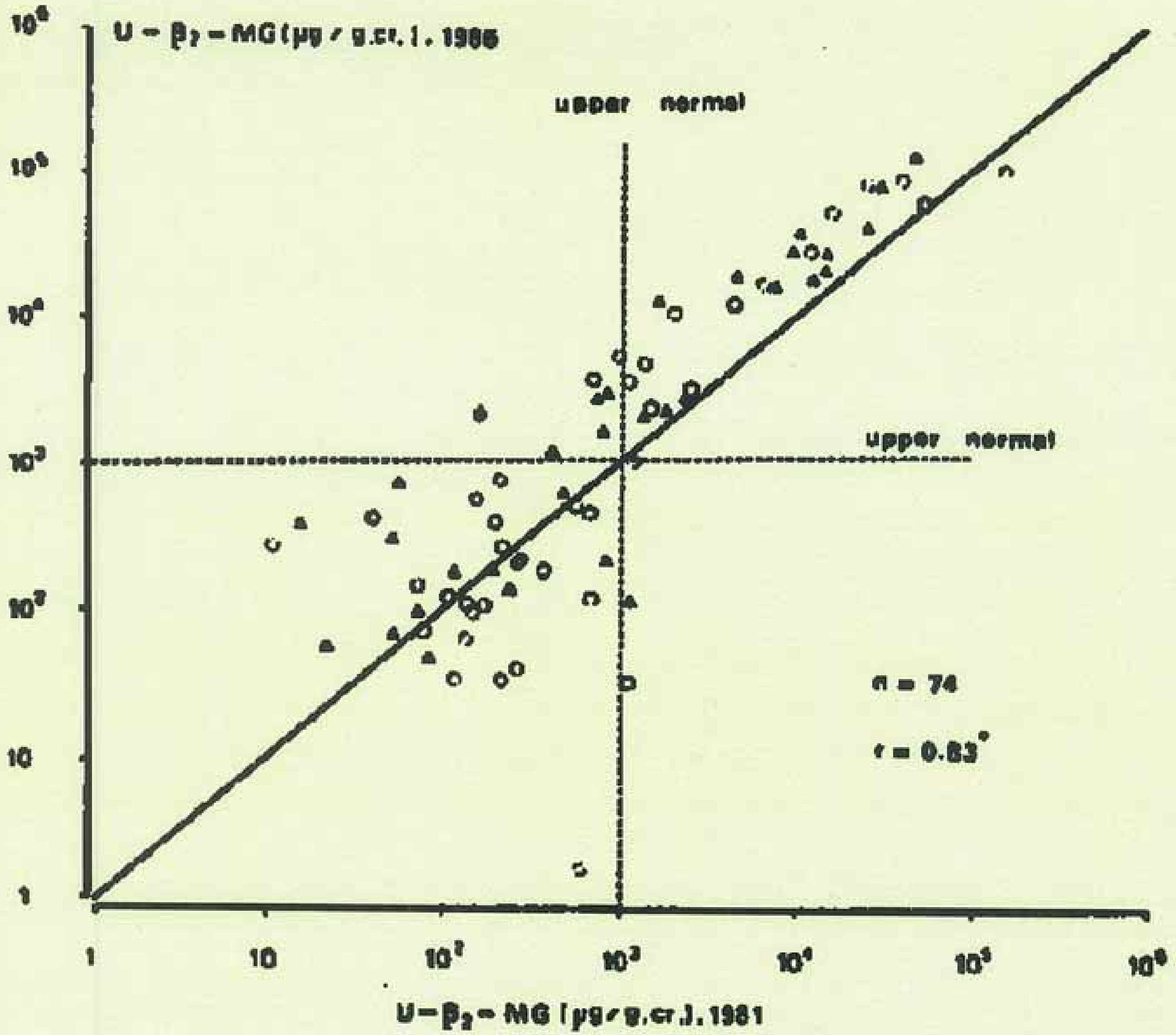


Fig. 1. Urinary excretion of β_2-microglobulin (β_2-MG) (μg/g creatinine) in 74 cadmium-exposed inhabitants examined in 1981 and 1986; ▲ = males, O = females. The *r* denotes the correlation coefficient. *Significant *r* value at $p < .001$.

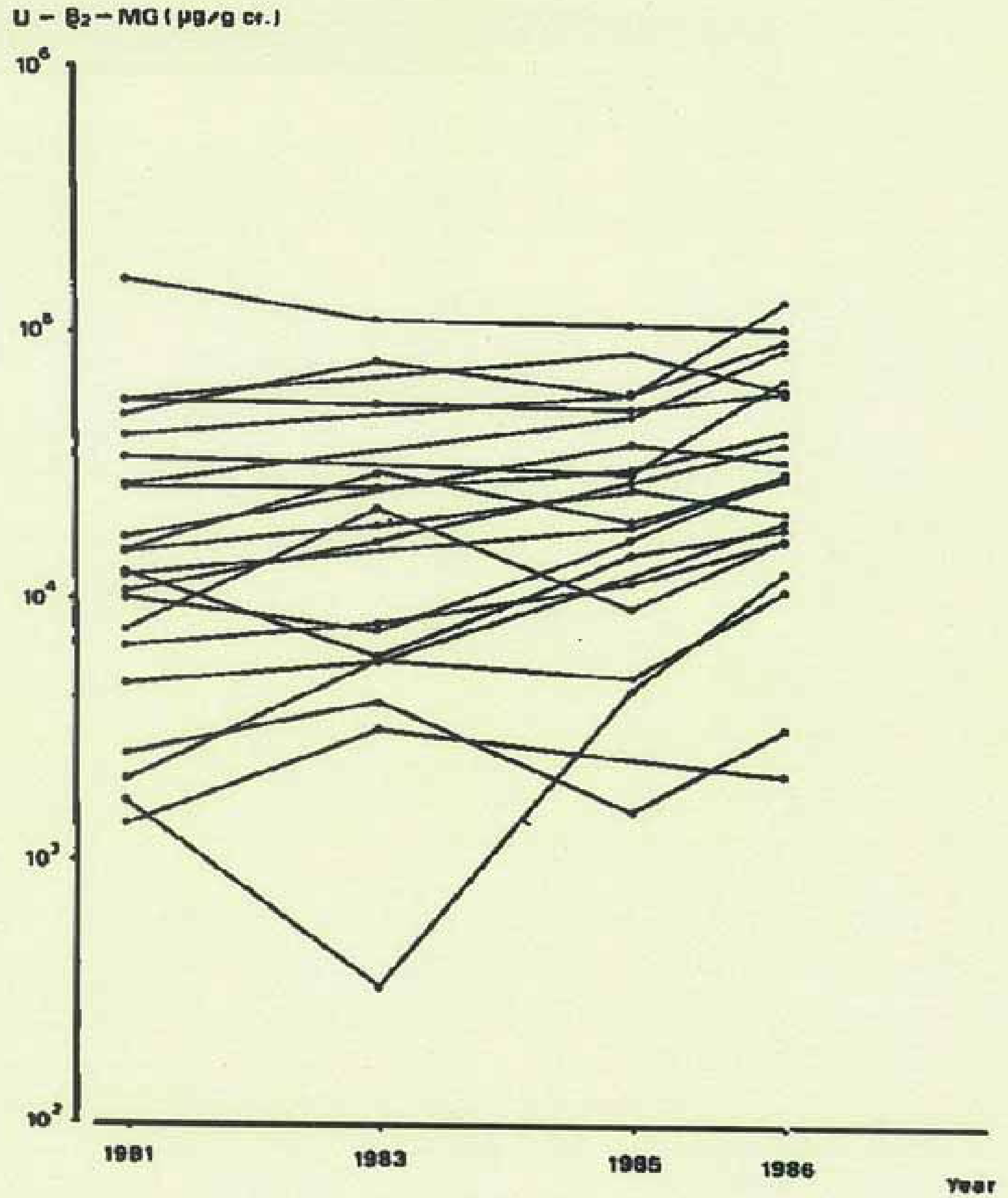


Fig. 2. Urinary excretion of β_2-microglobulin (β_2-MG) (μg/g creatinine) in 22 cadmium-exposed inhabitants examined between 1981 and 1986.

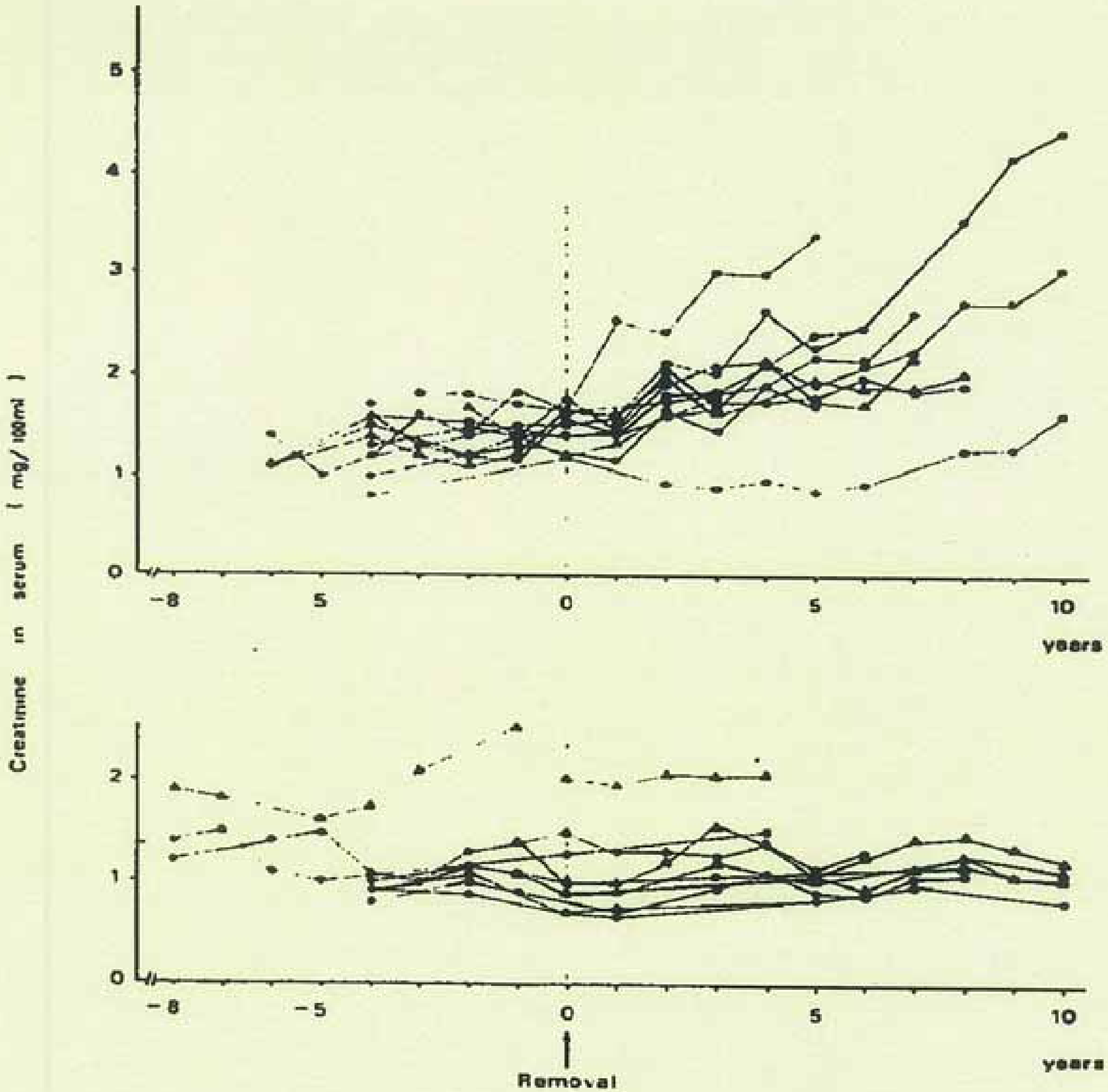


Fig. 1. Annual changes of serum creatinine levels before and after cessation of cadmium exposure. The *top* figure includes all subjects whose serum creatinine levels at their most recent examination were increased by > 20% above baseline values. The *bottom* figure includes subjects whose levels increased < 20% above baseline levels (▲—▲ = males, ●-● = females).

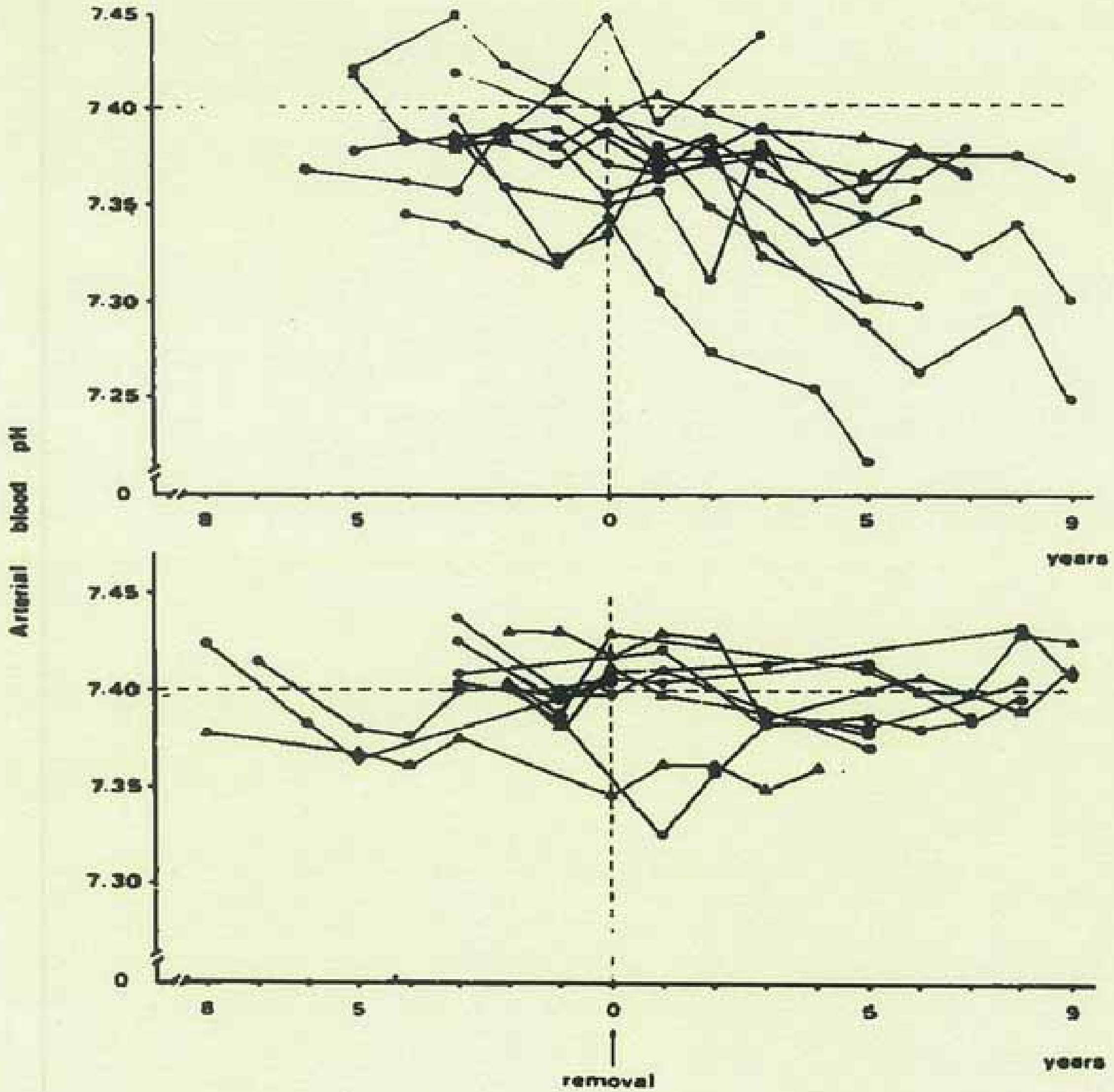
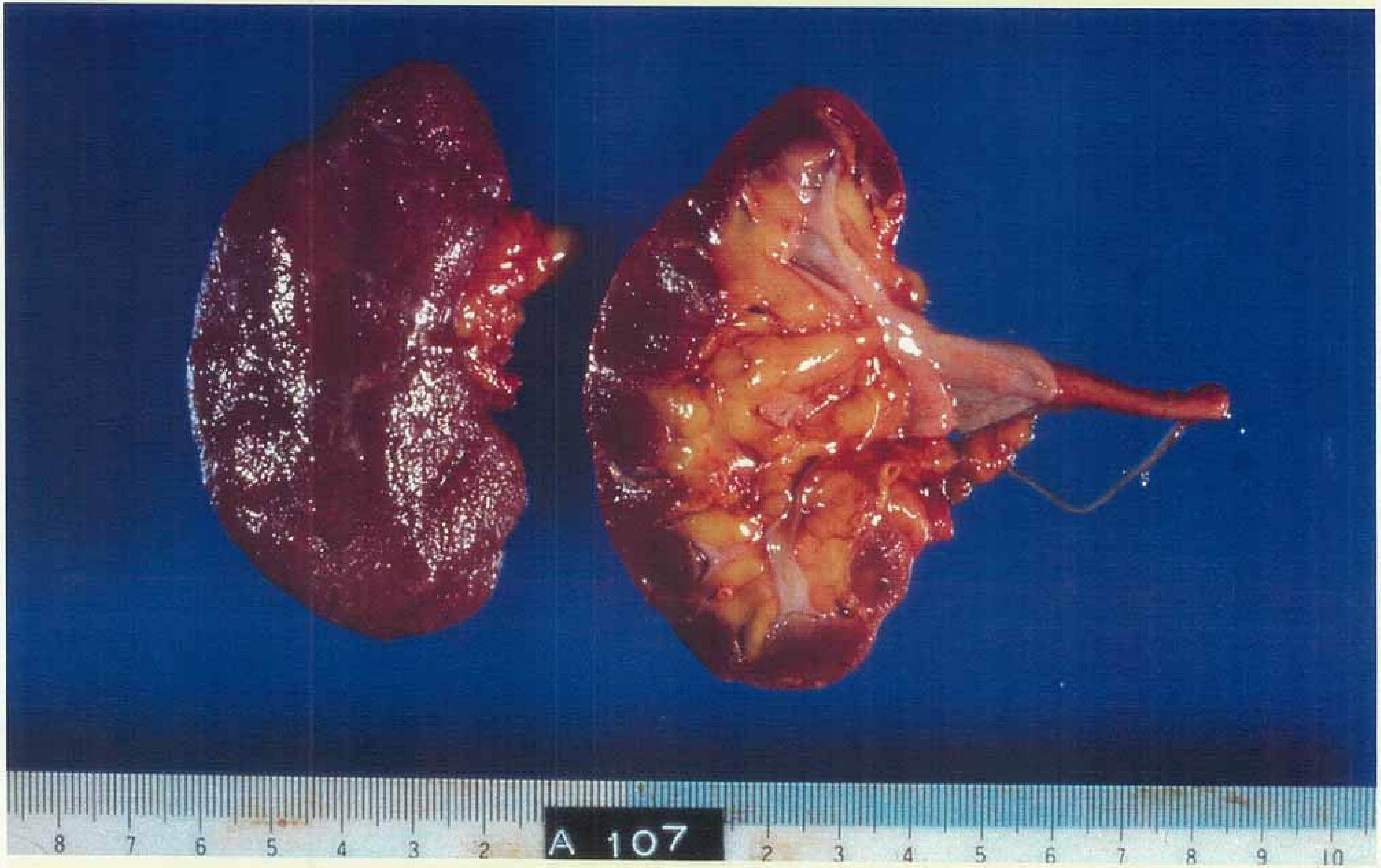


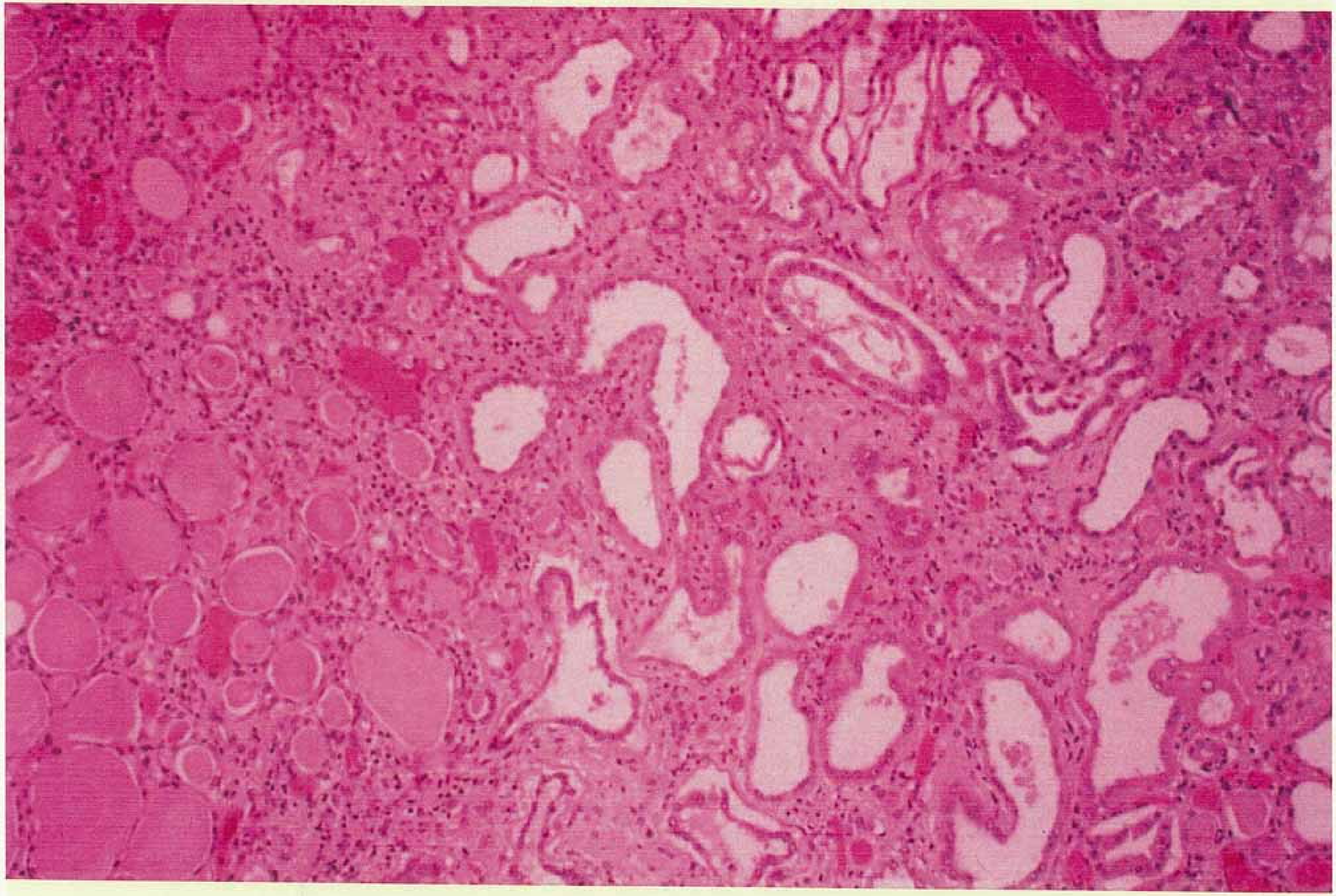
Fig. 2. Annual changes of arterial blood pH values before and after cessation of cadmium exposure. The *top* figure includes all subjects whose serum creatinine levels at their most recent examination were increased by > 20% above baseline values. The *bottom* figure includes subjects whose levels increased < 20% above baseline levels (▲—▲ = males, ●-● = females).

Table 4.—Biological Parameters of the Case Showing Renal Failure

Date of examination	1998
Sex	Female
Age(y)	80
Serum creatinine (mg/dl)	4.38
Blood urea nitrogen (mg/dl)	44.8
Red blood cell ($\times 10^4/mm^3$)	191
Hemoglobin (g/dl)	6.4
Hematocrit (%)	20
Urinalysis	
Glucose (mg/g cr)*	9016
Protein (mg/g cr)	1934
β_2-microglobulin (μg/g cr)	137892
Retinol binding protein (mg/g cr)	167.9
Lysozyme (mg/g cr)	475.7
Cadmium (μg/g cr)	7.9
Creatinine clearance (ml/min)	10.9
Tubular reabsorptive phosphorus (%)	29.9

*g creatinine


8 7 6 5 4 3 2
A 107
2 3 4 5 6 7 8 9 10



18-year follow-up study of Cd-exposed subjects

研究目的

カドミウム（Cd）汚染土壌の改善がなされて18年が経過した石川県梯川流域の1汚染地区住民で、その経過を観察し得た25名の尿中指標の推移を明らかにし、腎機能の可逆性について検討する。

また、Cd非汚染地域住民についても、尿中β_2-microglobulin（β_2-MG）の推移を検討する。

研究方法

対象1：

石川県梯川流域Cd汚染地住民：

最も汚染の強かった1地区住民のうち、

1981年時点50才以上で、その年の健康調査を受診し、その後1986，91，99年の検診にも参加した25名（男11名、1999年の平均年齢75.7才；女14名、72.6才）

対象2:

<u>Cd非汚染地域住民</u>:

1986年と2000年に尿検査を実施した

16名

(男7名、2000年の平均年齢80.7才;

女9名、79.0才)

方法:

各年度、早朝尿を採取し、尿中の糖、アミノ窒素、β_2-MG、Cdを測定した。

但し、尿中Cdについては1981年に2名分が尿量不足のため未測定であったので、その他の年度も23名について解析した。

Fig. 1 Change of Urinary Findings between 1981 and 1999

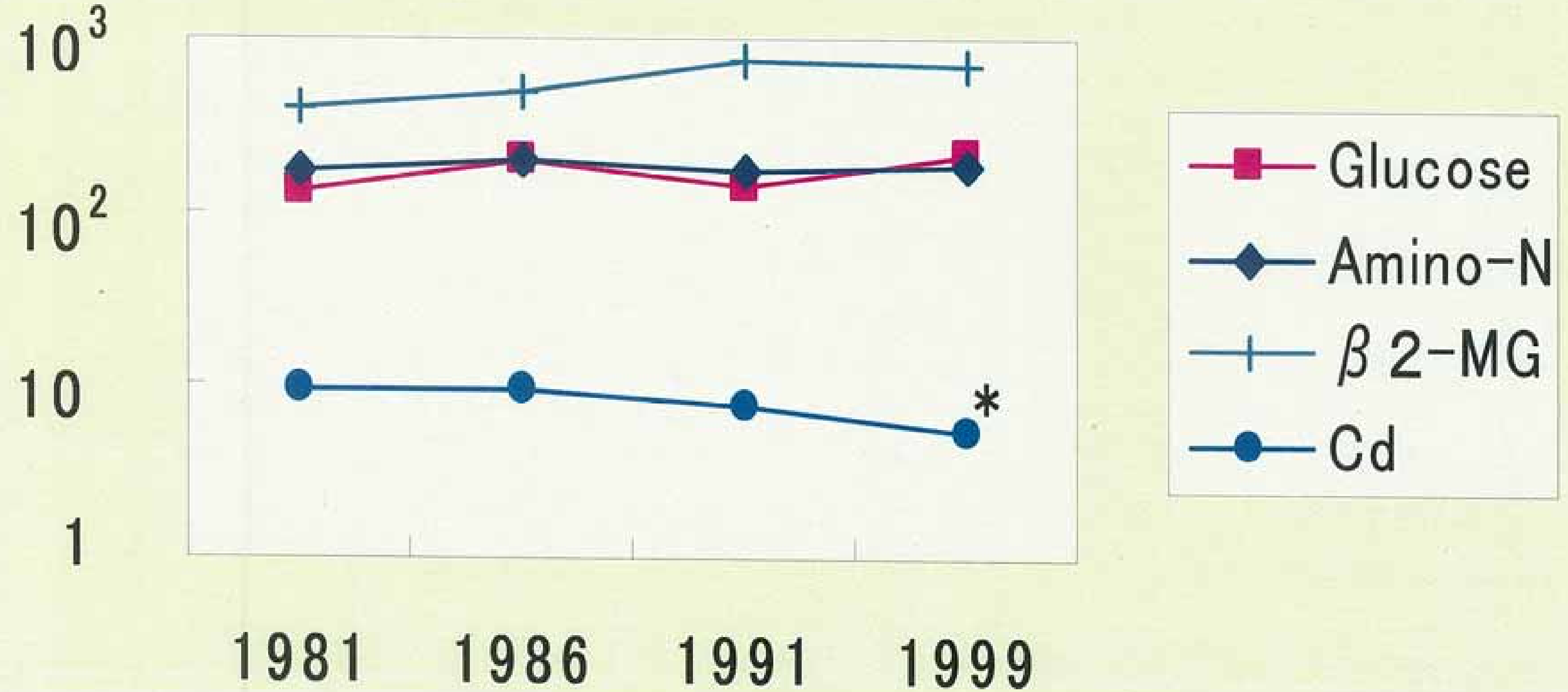


Fig. 2 Relationship between Urinary Glucose in 1981 and 1999

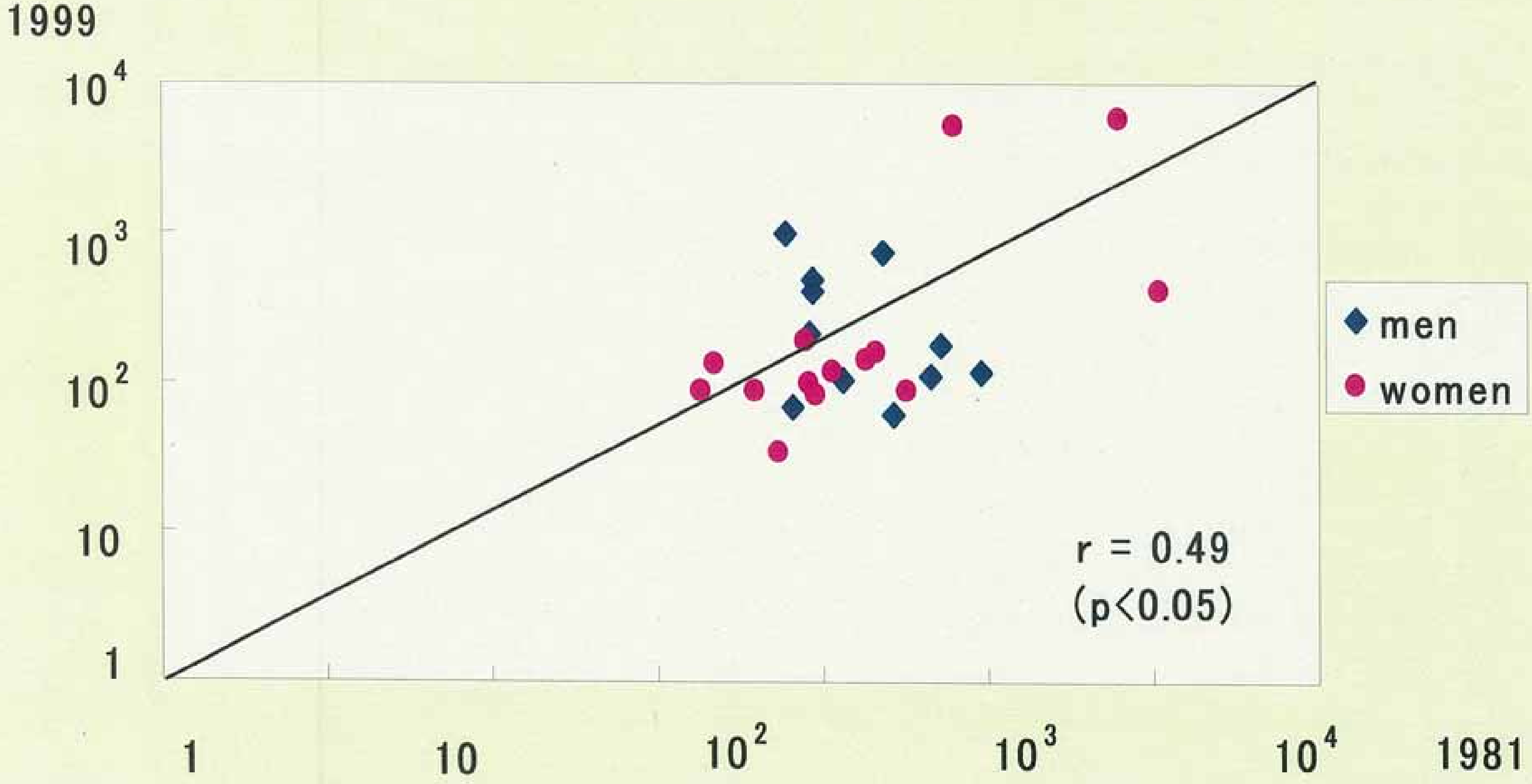


Fig. 3 Relationship between Urinary Amino-N in 1981 and 1999

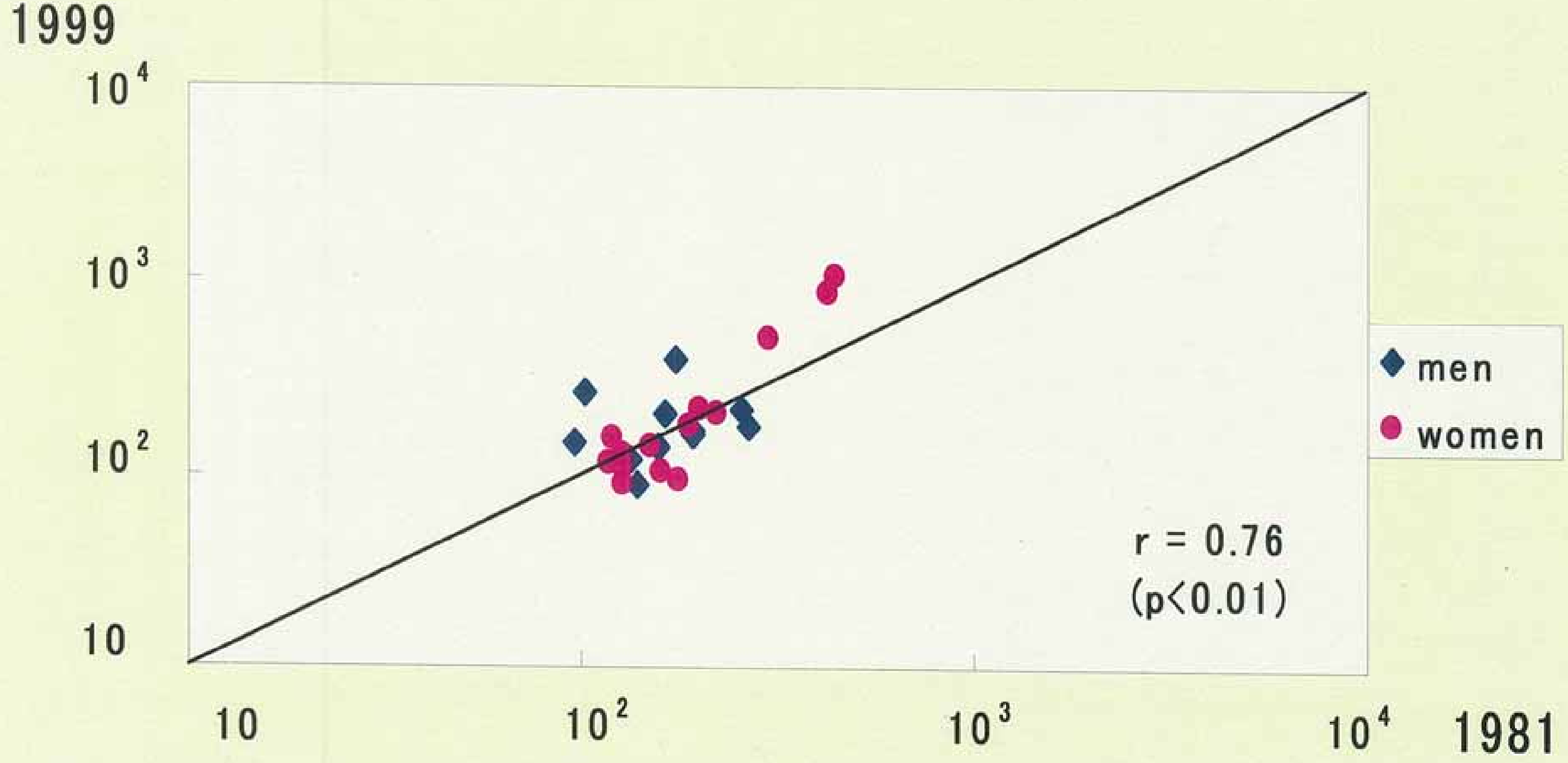


Fig. 4 Relationship between Urinary β_2-MG in 1981 and 1999

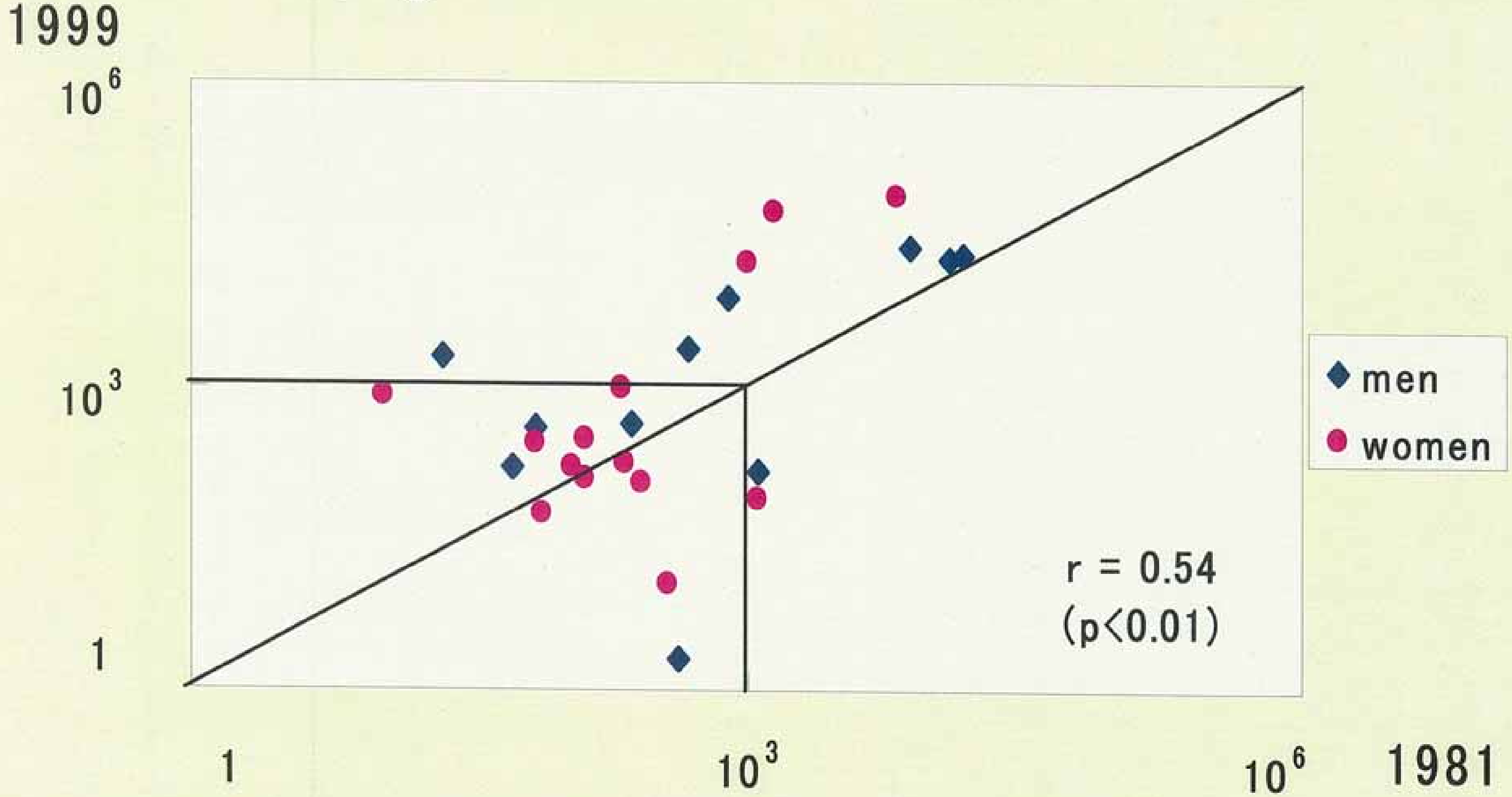
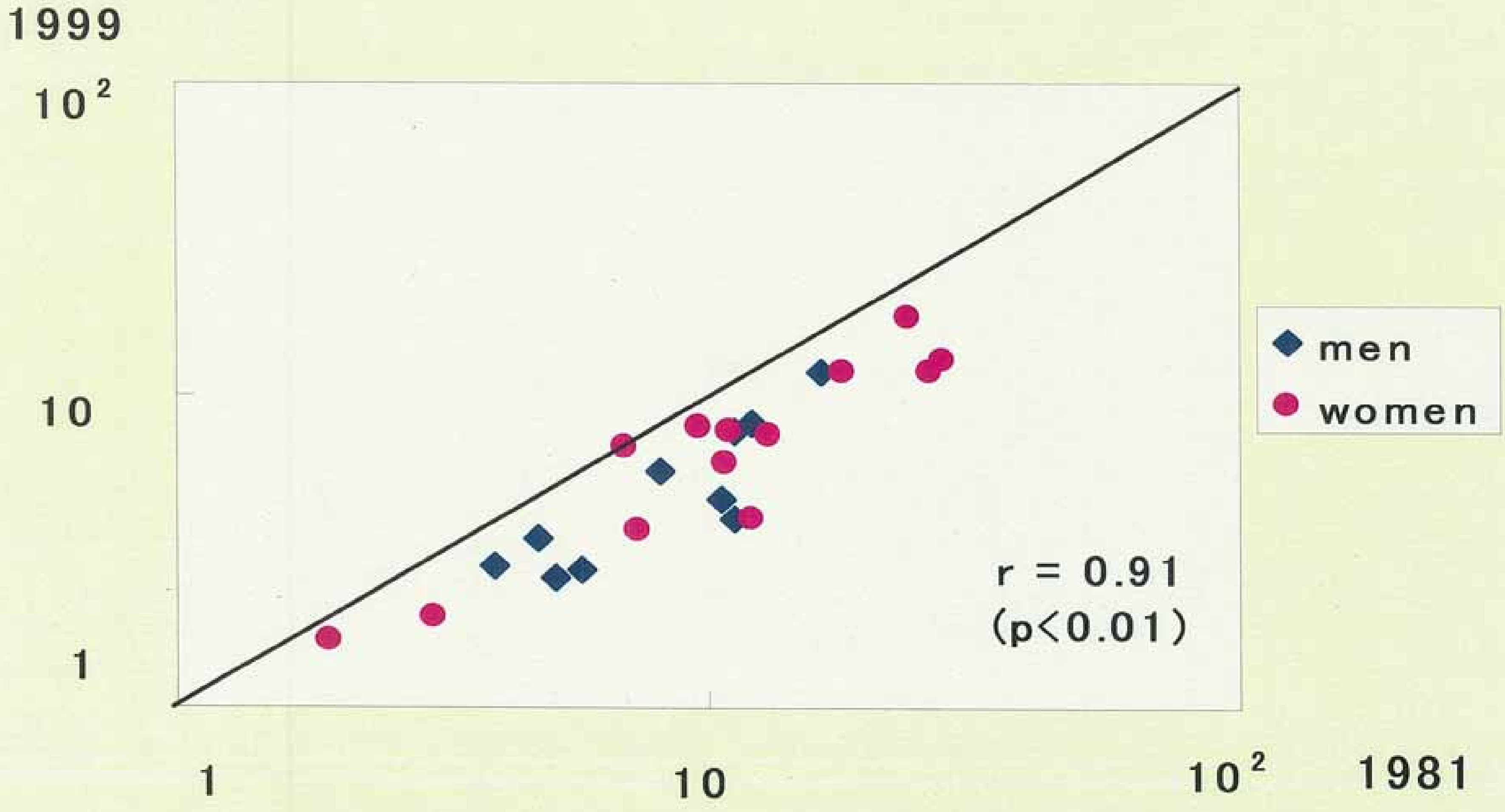


Fig. 5 Relationship between Urinary Cadmium in 1981 and 1999



14-year follow-up study of non-exposed subjects

Fig.6 Urinary β_2-MG in Cd-nonexposed Subjects in 1986 and 2000

Fig. 7 Urinary Cadmium in Cd-nonexposed Subjects in 1986 and 2000

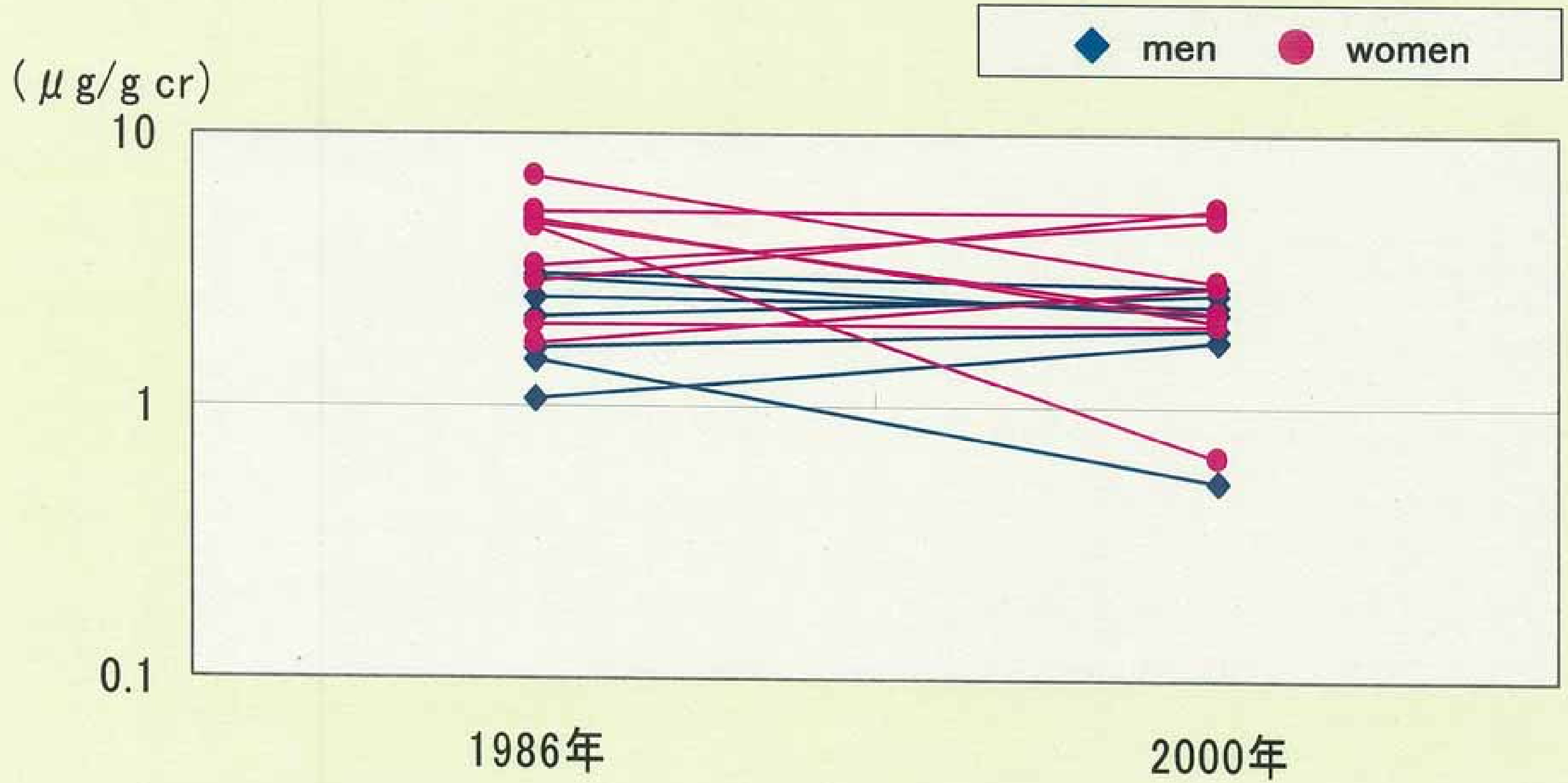


Fig. 8 Relationship between Urinary β_2-MG in 1986 and Cd in 1986

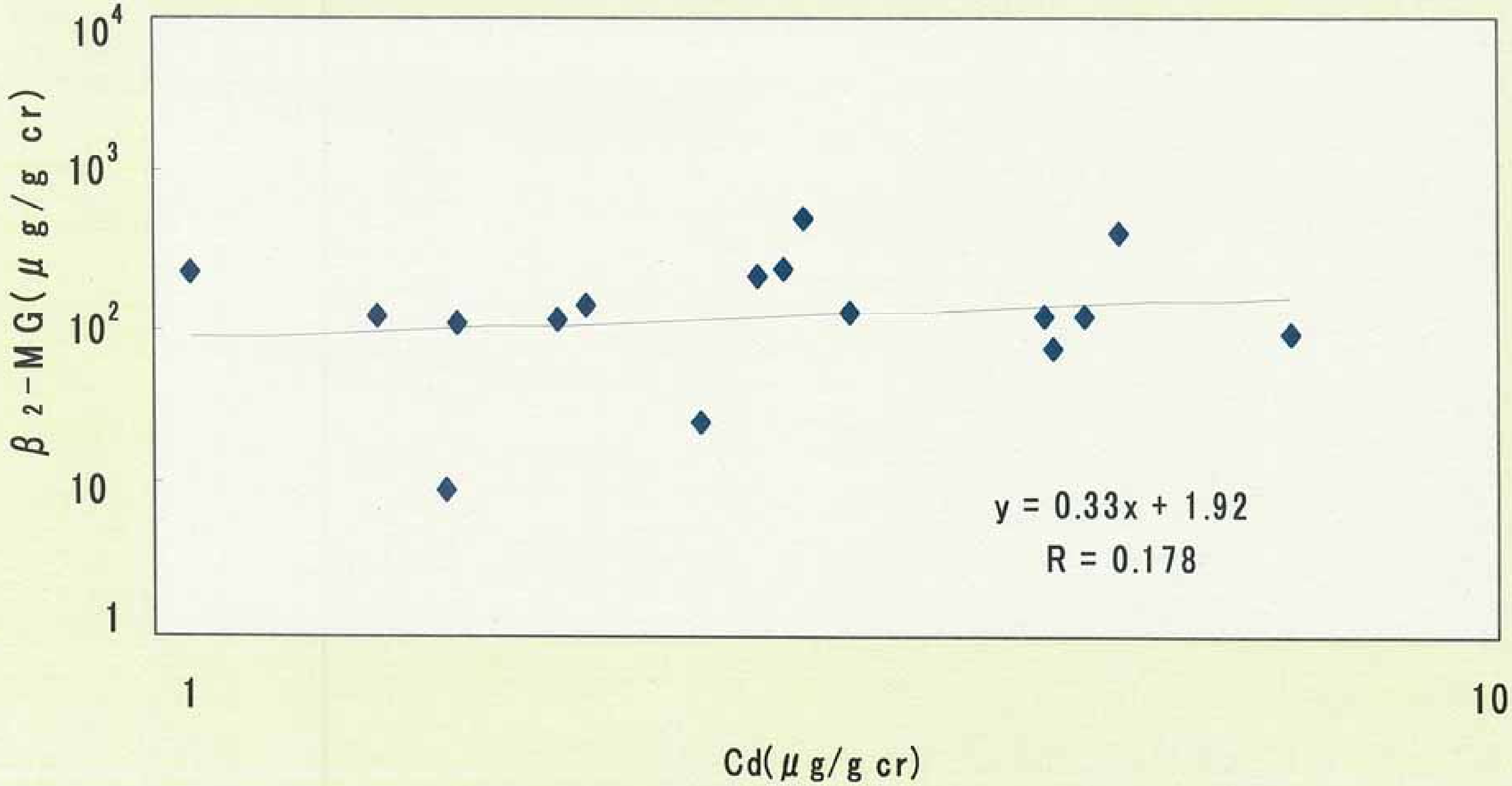
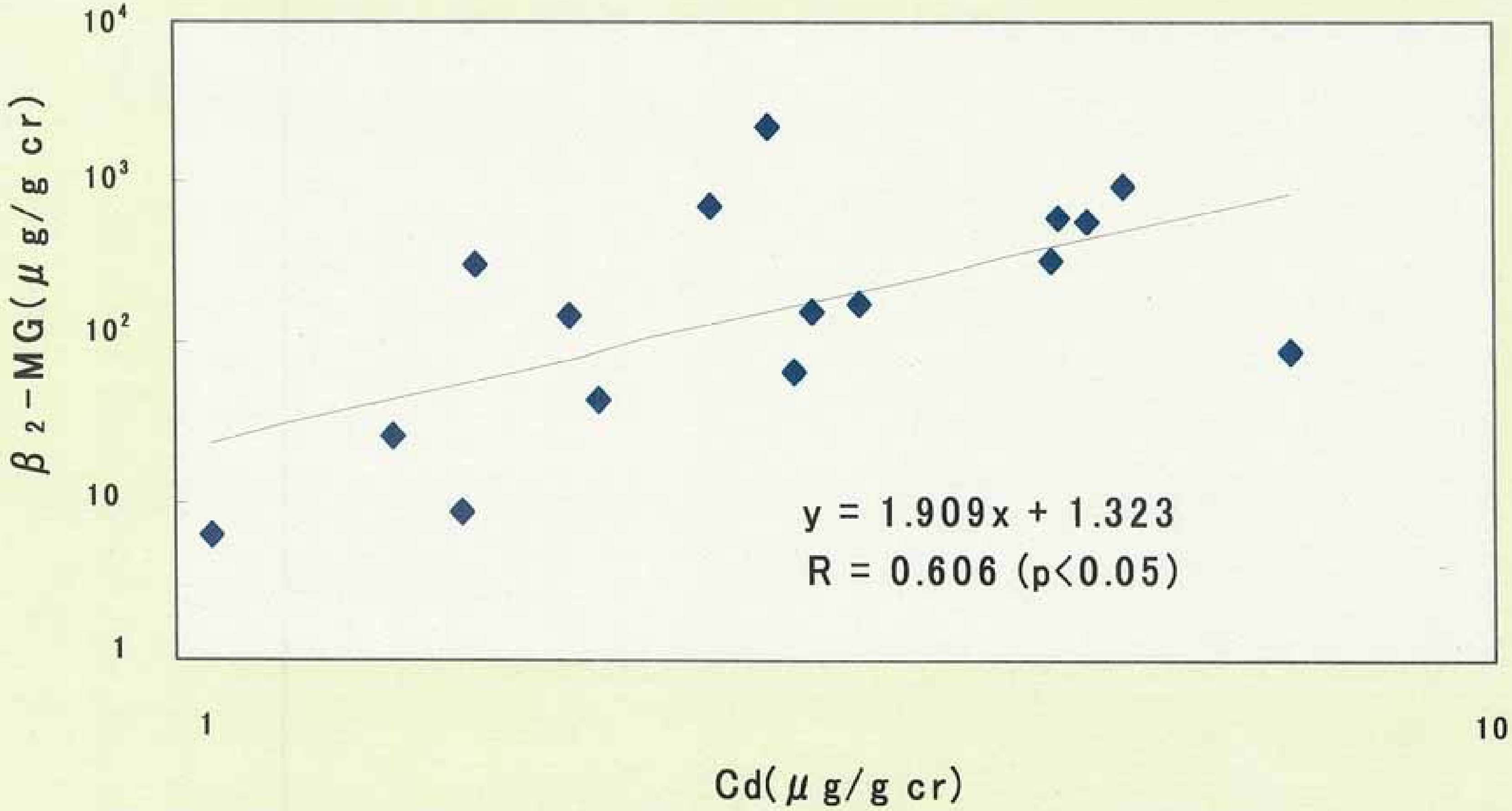
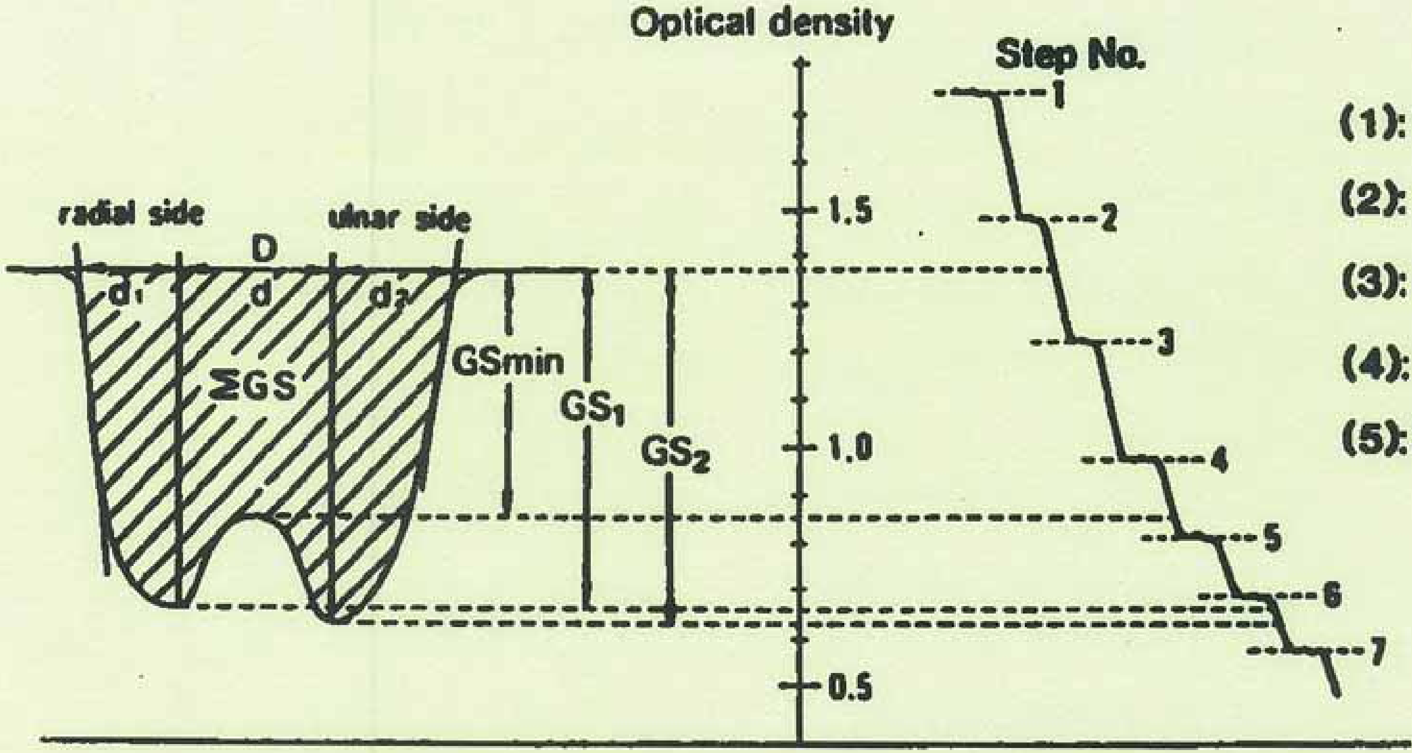


Fig. 9 Relationship between Urinary β_2-MG in 2000 and Cd in 1986



Ⅲ. Cadmium induced bone effects

Densitometer chart



(1): $MCI = \frac{d1 + d2}{D}$

(2): d

(3): GSmin

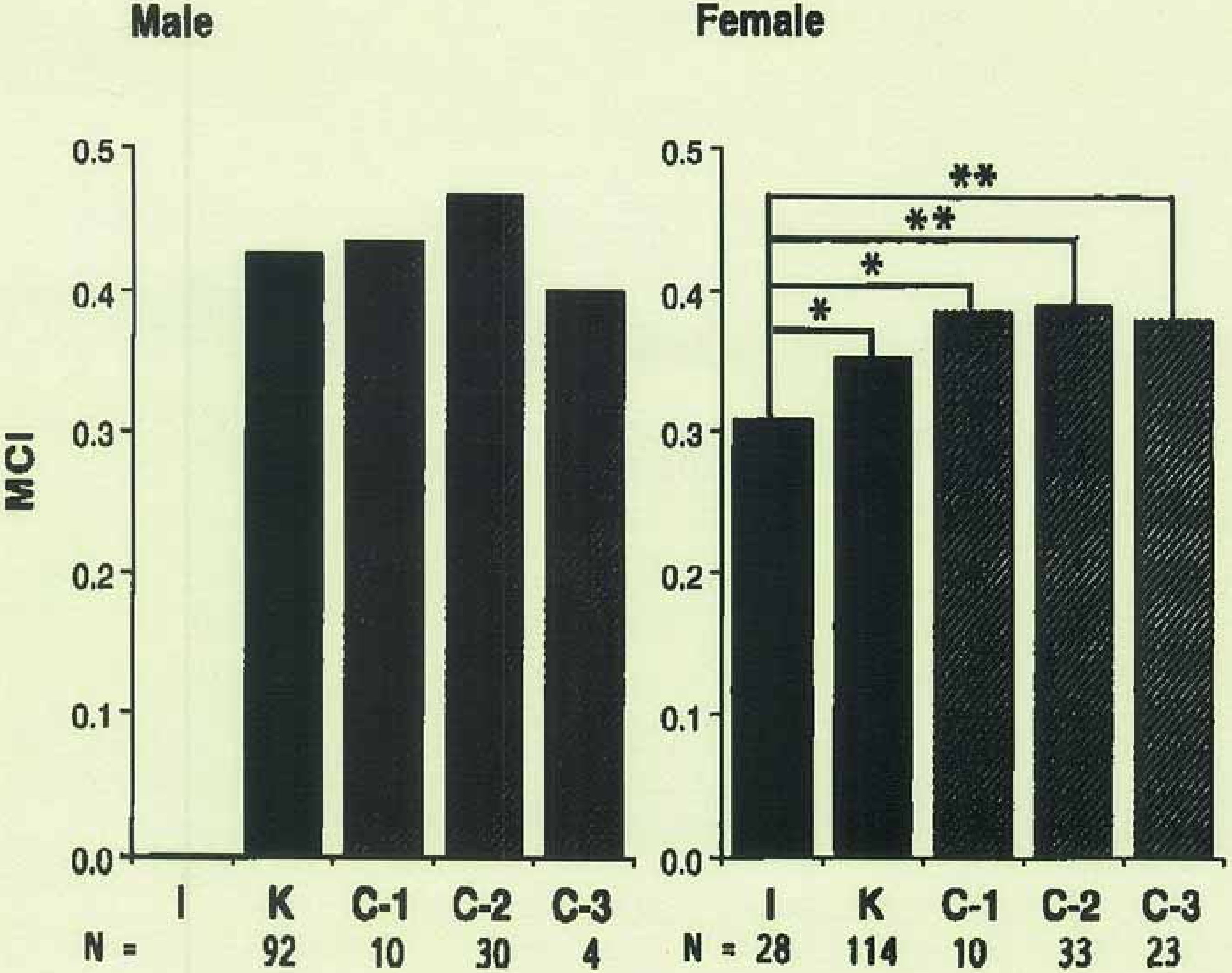
(4): $GSmax = \frac{GS_1 + GS_2}{2}$

(5): ΣGS/D

Number of subjects examined

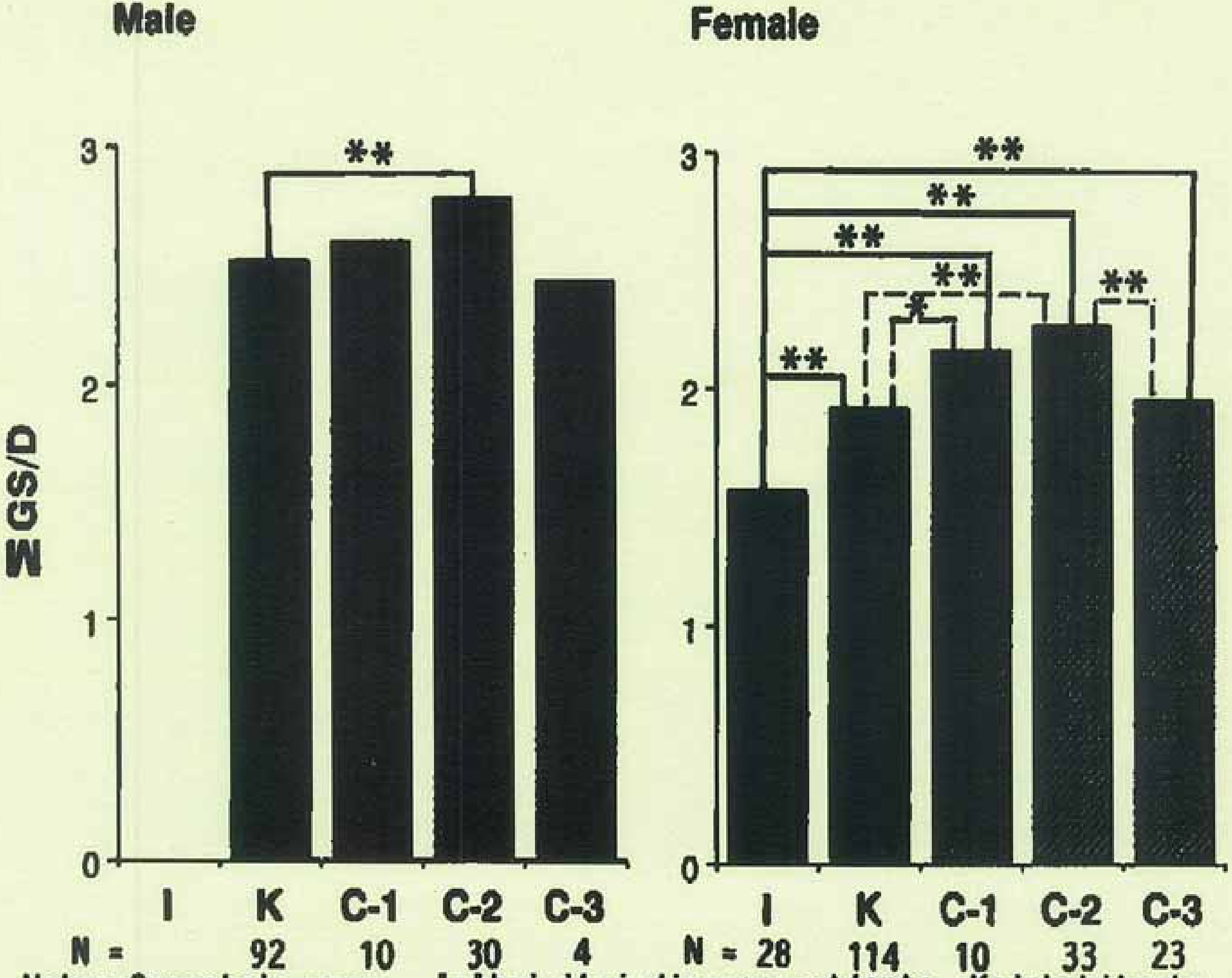
		Male	Female
Cd-exposed	I	-	28
	K	92	114
Nonexposed	C-1	10	10
	C-2	30	33
	C-3	4	23

Microdensitometry indicators in itai-itai disease patients, Cd-exposed and nonexposed subjects



Notes: Geometoric mean. I; Itai-itai disease patients, K; inhabitants in the Cd-polluted Kakehashi River basin, C; nonexposed subjects in three different non-polluted areas. *;P<0.05 **;P<0.01

Microdensitometry indicators in itai-itai disease patients, Cd-exposed and nonexposed subjects



Notes:Geometric mean. I;Itai-itai disease patients, K;inhabitants in the Cd-polluted Kakehashi River basin, C;nonexposed subjects in three different non-polluted areas. *;P< 0.05 **;P<0.01.

Biological parameters selected by the stepwise backward regression analysis and significance of their standard partial regression coefficients to microdensitometrical indices (Male)

Cd-exposed subjects (N=91)

	MCI	d	GSmax	GSmin	ΣGS/D	Sum of given scores
Age	*			**	*	
log(U-Cd/Cr)						
log(U-β_2-mg/Cr)	**	**	*	**	**	**
log(S-Cr)	**	**	**	**	**	**
S-Ca		*				*
S-P						
log(B-Cd)						
R	0.51 **	0.51 **	0.43 **	0.50 **	0.43 **	0.47 **

Nonexposed subjects (N=25)

	MCI	d	GSmax	GSmin	ΣGS/D	Sum of given scores
Age						
log(U-Cd/Cr)			*			
log(U-β_2-mg/Cr)						
log(S-Cr)						
S-Ca		*				
S-P						
log(B-Cd)						
R	0.45	0.60	0.43	0.48		0.41

R:Multiple correlation coefficient.
*:Significant ($P<0.05$). **:Significant ($P<0.01$).

Biological parameters selected by the stepwise backward regression analysis and significance of their standard partial regression coefficients to microdensitometrical indices (Female)

Cd-exposed subjects (N=112)

	MCl	d	GSmax	GSmin	ΣGS/D	Sum of given scores
Age	**	**		**	**	
log(U-Cd/Cr)						
log(U-β_2-mg/Cr)	*	*	**	**	**	**
log(S-Cr)						
S-Ca						
S-P						
log(B-Cd)						
R	0.53 **	0.42 **	0.35 **	0.49 **	0.44 **	0.25 **

Nonexposed subjects (N=55)

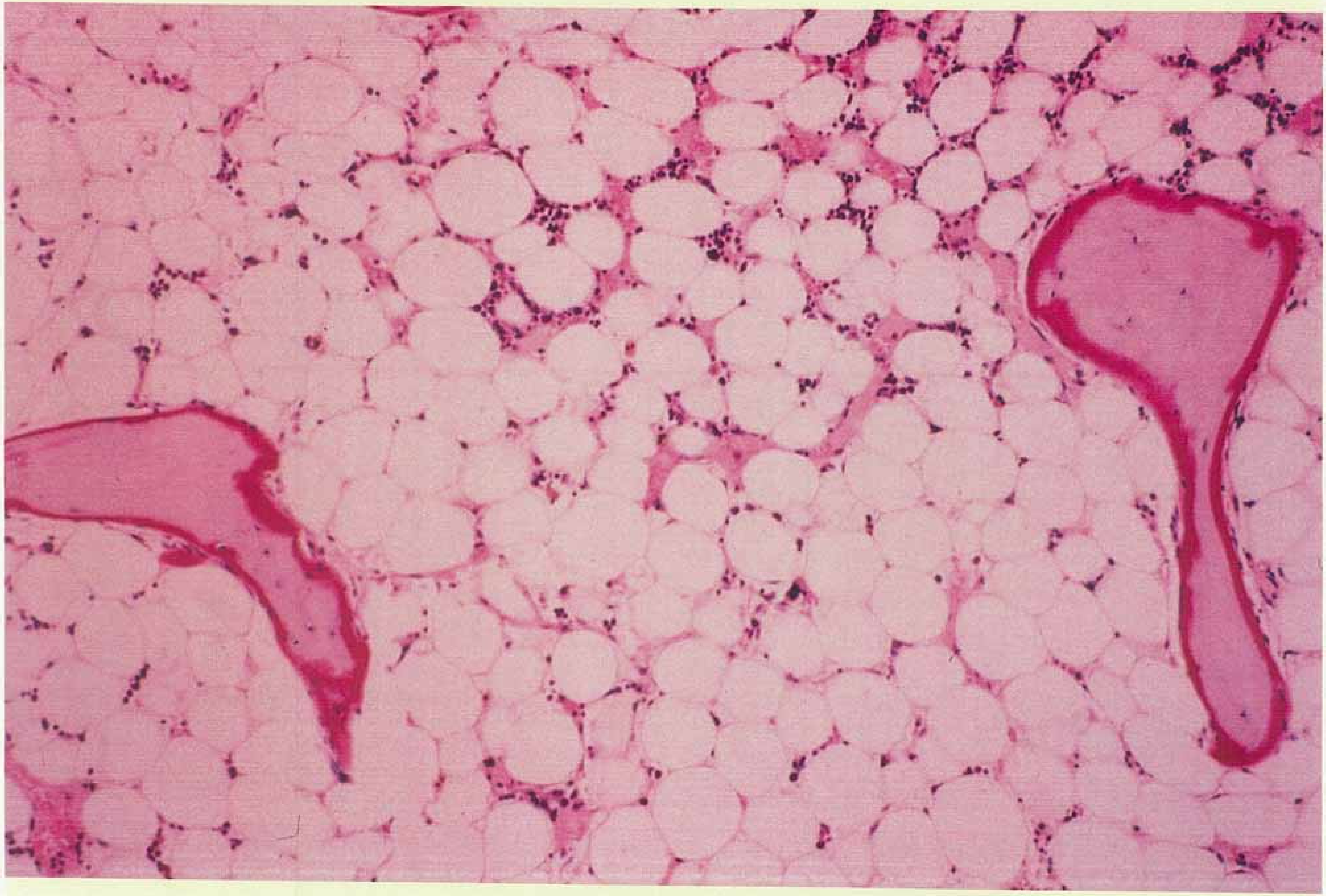
	MCl	d	GSmax	GSmin	ΣGS/D	Sum of given scores
Age	**			**	*	
log(U-Cd/Cr)						
log(U-β_2-mg/Cr)						
log(S-Cr)			*			
S-Ca						
S-P						
log(B-Cd)		*	*			
R	0.41 **	0.37 *	0.37	0.54 **	0.46 **	0.38 *

R:Multiple correlation coefficient.
*:Significant ($P<0.05$). **: Significant ($P<0.01$).

Table 4.—Biological Parameters of the Case Showing Renal Failure

Date of examination	1998
Sex	Female
Age(y)	80
Serum creatinine (mg/dl)	4.38
Blood urea nitrogen (mg/dl)	44.8
Red blood cell ($\times 10^4/mm^3$)	191
Hemoglobin (g/dl)	6.4
Hematocrit (%)	20
Urinalysis	
Glucose (mg/g cr)*	9016
Protein (mg/g cr)	1934
β_2-microglobulin (μg/g cr)	137892
Retinol binding protein (mg/g cr)	167.9
Lysozyme (mg/g cr)	475.7
Cadmium (μg/g cr)	7.9
Creatinine clearance (ml/min)	10.9
Tubular reabsorptive phosphorus (%)	29.9

*g creatinine



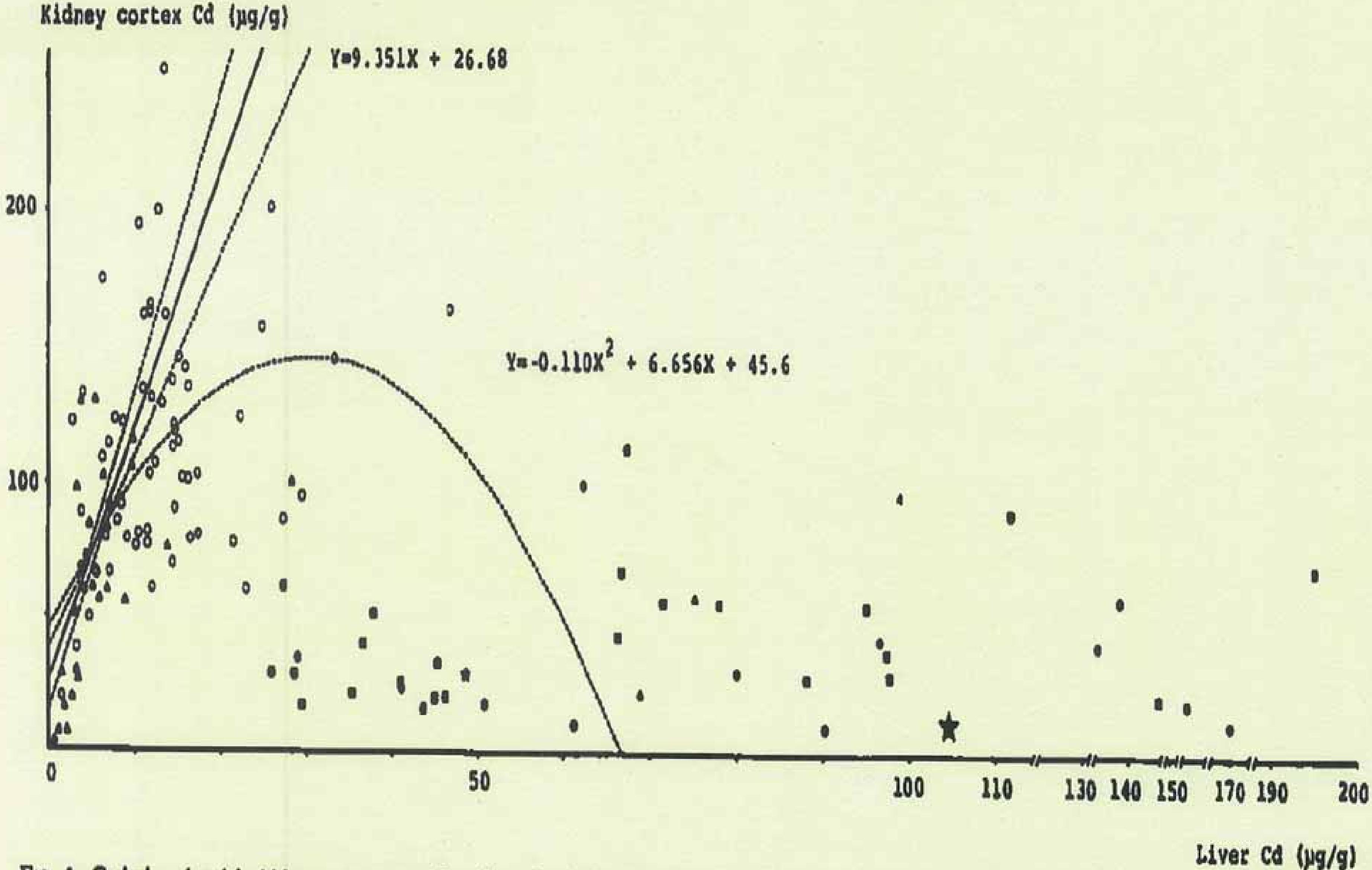


FIG. 1. Cadmium level in kidney cortex as a function of cadmium level in liver for the polluted persons (●, Itai-Itai disease patients; ■, suspected patients; ▲, inhabitants in the Cd-polluted Ichi River basin; ★, inhabitants in the Cd-polluted Jinzu River basin) and the control persons (○, subjects ages over 50; △, subjects ages less than 50).

カドミウム暴露中止後18年経過した住民の尿中 Type 1 collagen cross-linked N-teleopeptides

表志津子、城戸照彦、西条旨子、中川秀昭、
諏訪園靖、小林悦子、能川浩二、
金沢大学、金沢医科大学、千葉大学

研究の背景

- Cadmiumの慢性暴露による健康影響

石川県梯川流域に発生したカドミウム汚染 （1968年）

土壌改善後

➢腎尿細管障害を有する住民への骨障害の存在

- Cadmiumと骨障害の関連

➢骨密度と尿中β2-MGに相関

➢非汚染地域に比して骨代謝機能の亢進

（Bone Gla-protein, ALP）

- 骨障害の測定

➢破骨細胞による骨吸収を反映

（Type 1 collagen cross-linked N-teleopeptides（NTx））

研究目的

土壌改善後18年経過したCadmium汚染地域に暮らす住民の、慢性Cadmium中毒による骨への影響を、尿中NTxを用いて、汚染地域、非汚染地域の比較により検討

NTx(1992 Hanson):

- 算出されたNTx量は骨吸収面積の増加と相関する
- 骨粗鬆症の診断に有用

対 象

- 汚染地域(Cd暴露群)　　石川県梯川流域
  50歳以上の住民106名
  男性　49名　　平均年齢65.2歳
  女性　57名　　平均年齢67.1歳
- 非汚染地域(Cd非暴露群) 石川県内
  50歳以上の住民60名
  男性　22名　　平均年齢76.5歳
  女性　38名　　平均年齢73.7歳

➢二次的骨粗鬆症に関連する疾患・治療なし
➢本人の同意を得て調査を実施
➢ 1999年12月に調査実施

方 法

- 検診時の早朝尿あるいは午前中の尿を採取
- 健康影響は尿中物質を指標
- 採取尿を-20℃で凍結保存後分析

統計学的処理
- 65歳以上, 65歳未満を分析・・・・年齢影響の排除
- 汚染地域と非汚染地域　:　65歳以上を比較
- 汚染地域：・指標ごとの相関

  ・NTxと指標との関連

  NTxを従属変数として重回帰分析
- SPSS12.0を使用

結果

暴露群、非暴露群間の比較　-65歳以上-

男性

	Cd−暴露群			非暴露群			
	N	Mean	S.D.	N	Mean	S.D.	
Age (year) §	27	73.5	7.57	22	76.5	5.67	
β_2−MG (μg/g cr.)	27	239	17.0	22	53.4	3.58	*
Cd (μg/g cr.)	27	4.01	1.65	22	1.84	1.56	**
Mg (mg/g cr.)	27	69.4	2.01	22	42.6	6.17	
Ca (mg/g cr.)	27	111	1.69	22	68.2	1.81	**
P (mg/g cr.)	27	579	1.35	22	438	1.66	*
NTx (nM BCE/nM cr.) §	26	33.2	17.8	20	26.0	18.9	

* $P<0.05$　** $P<0.01$

§ : 算術平均, それ以外は幾何平均

暴露群、非暴露群間の比較 -65歳以上-

女性

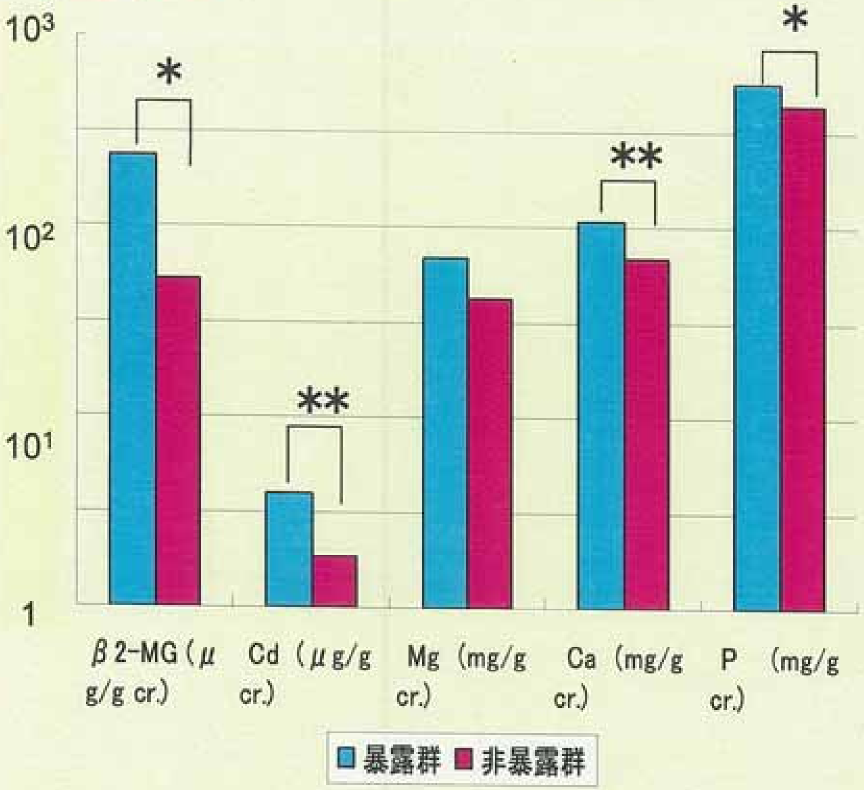
	Cd−暴露群			非暴露群			
	N	Mean	S.D.	N	Mean	S.D.	
Age (years) §	34	73.4	6.19	38	73.7	8.62	
β_2−MG (μg/g cr.)	34	336	11.1	32	229	2.81	
Cd (μg/g cr.)	34	6.03	2.37	35	2.86	1.82	**
Mg (mg/g cr.)	34	94.7	1.76	37	52.6	4.92	*
Ca (mg/g cr.)	34	157	1.66	37	109	1.79	**
P (mg/g cr.)	34	638	1.31	37	552	1.56	
NTx (nM BCE/nM cr.) §	34	73.1	39.9	35	37.3	17.2	**

* $P<0.05$ ** $P<0.01$

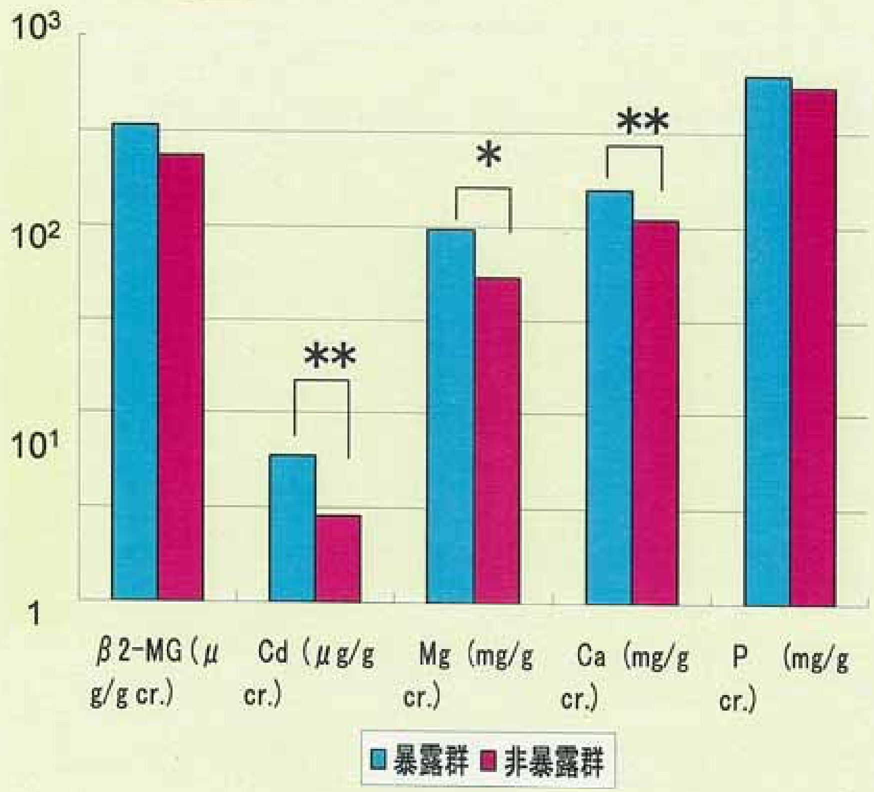
§：算術平均，それ以外は幾何平均

暴露群、非暴露群間の比較　-65歳以上-

男性



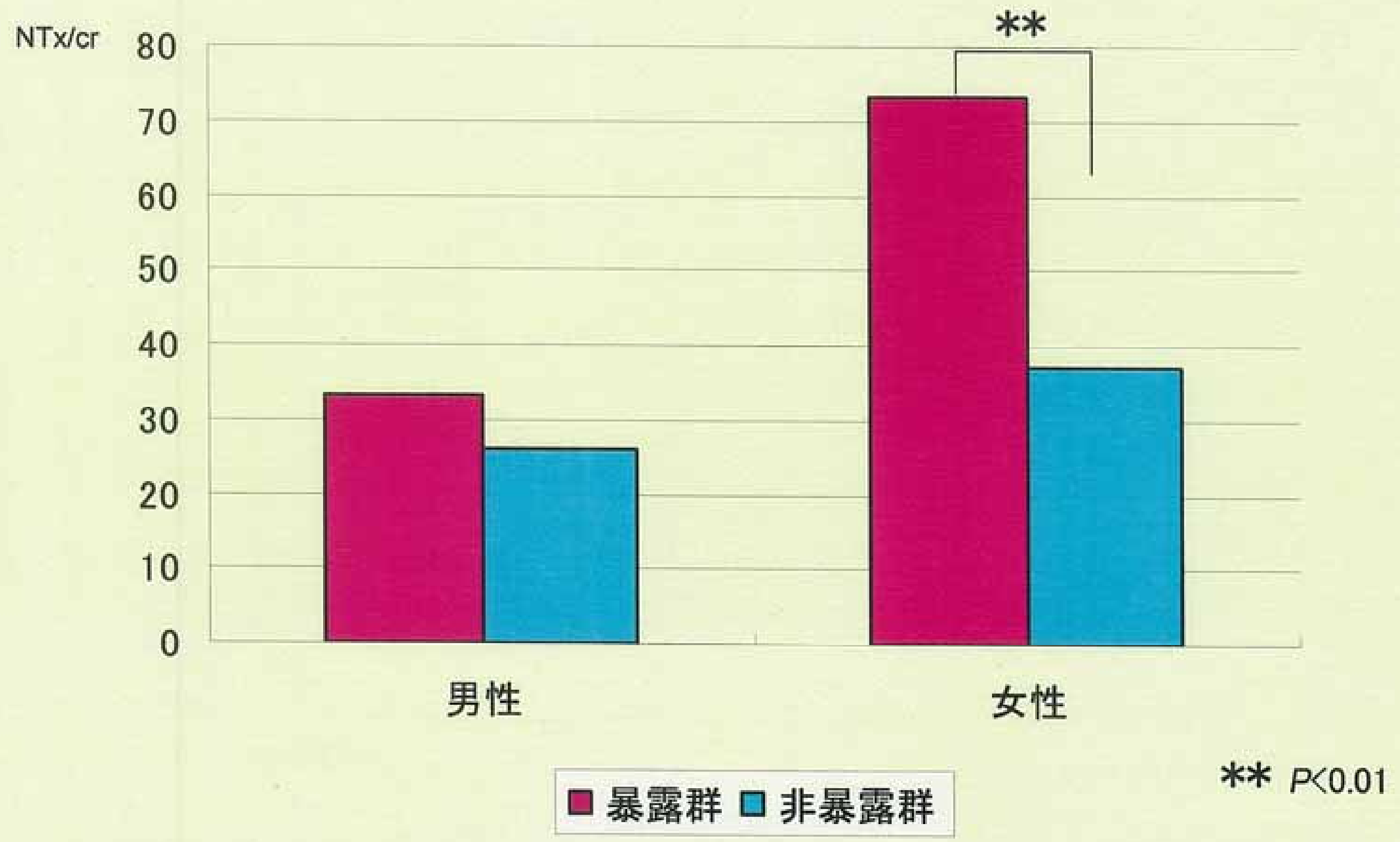
女性



* $P<0.05$　** $P<0.01$　幾何平均

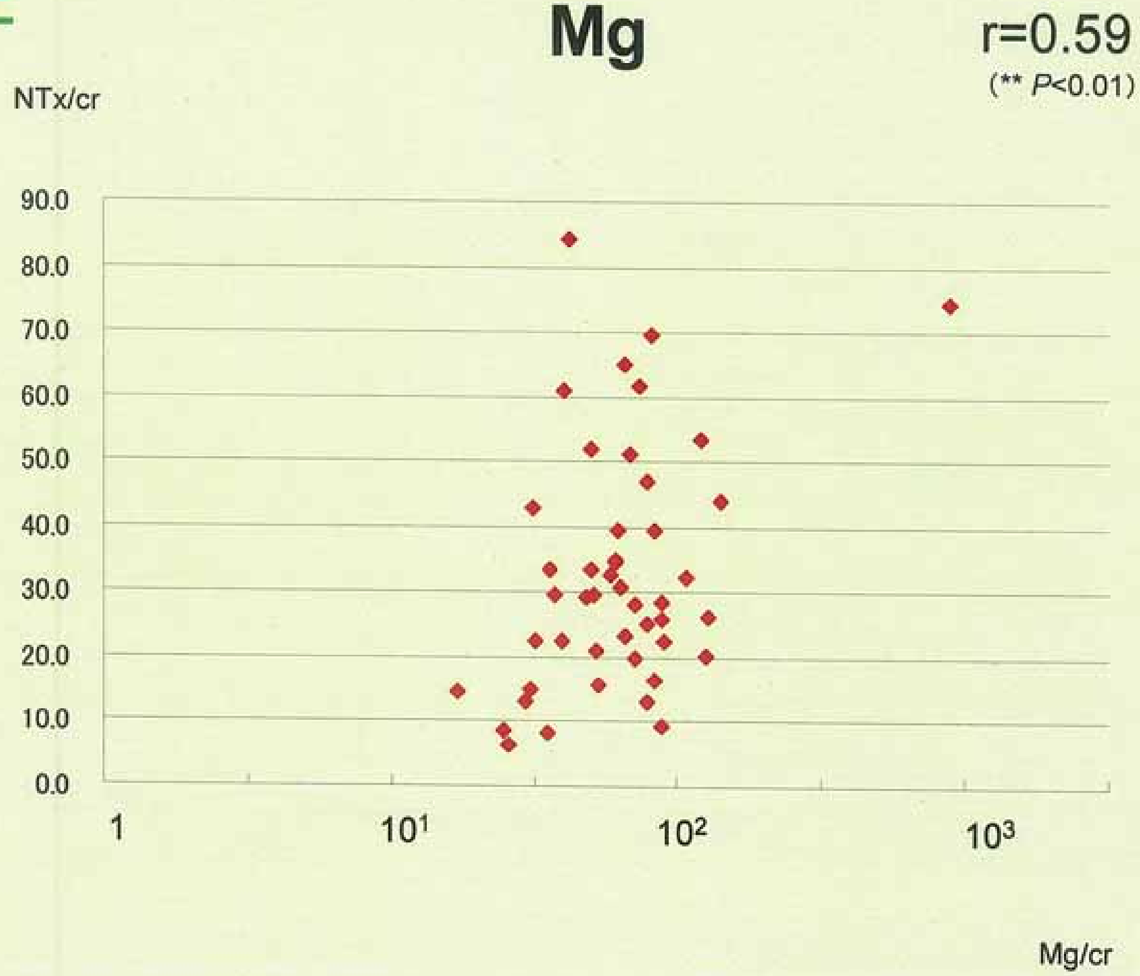
暴露群、非暴露群間の比較　-65歳以上-

NTx男女比較



NTxとの相関 -Cd汚染地域-

男性



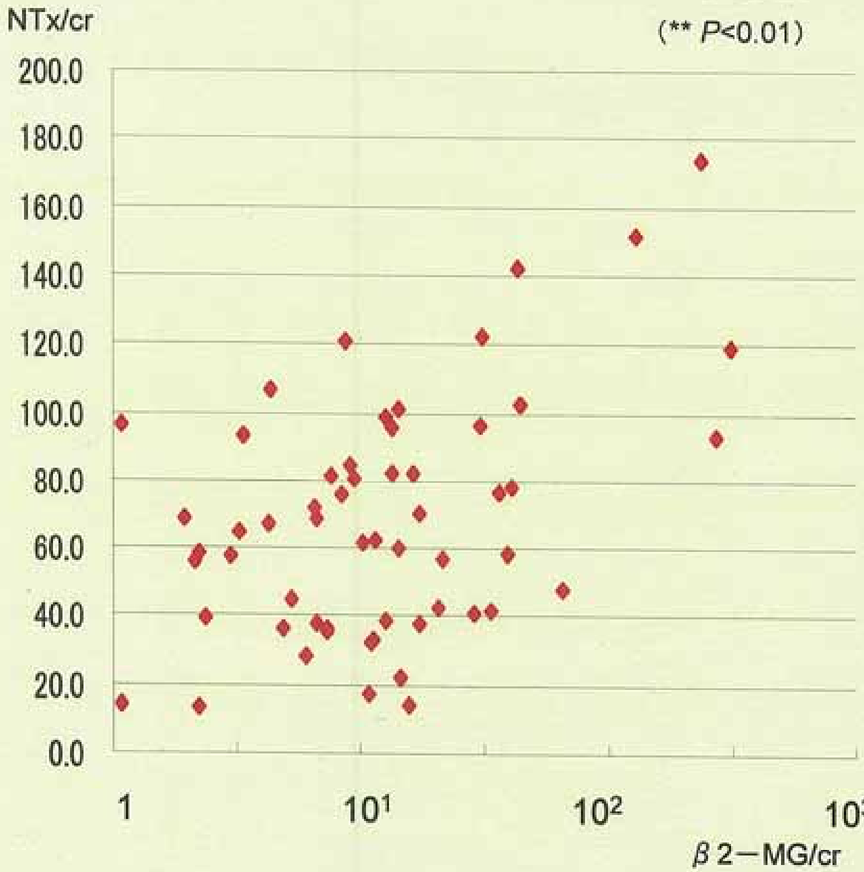
NTxとの相関 -Cd汚染地域-

女性

β2−MG

r=0.52

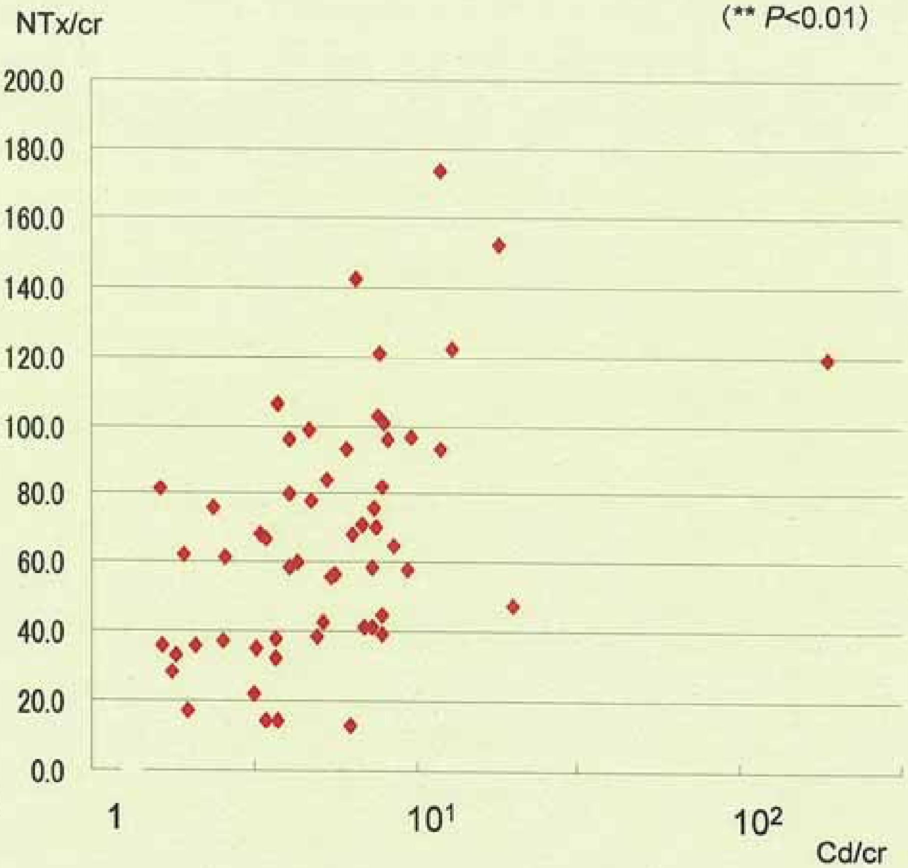
(** $P<0.01$)



Cd

r=0.58

(** $P<0.01$)



尿中NTxと生化学指標の関連 -Cd汚染地域-

	男性				女性		
	N	β			N	β	
Age	47	−0.045		Age	57	−0.047	
log aminoN	47	−0.157		log aminoN	57	0.327	**
log NAG	47	0.043		log NAG	57	0.072	
log Total Protein	47	0.071		log Total Protein	57	0.119	
log β_2-MG	47	−0.034		log β_2-MG	57	0.195	
log Cu	47	0.099		log Cu	57	−0.049	
log Cd	47	0.085		log Cd	57	0.339	**
log Mg	47	0.378	**	log Mg	57	−0.022	
log Ca	47	−0.338		log Ca	57	0.144	
log P	47	−0.131		log P	57	0.106	
R		0.378	**	*R*		0.564	**

β：標準化回帰係数　　*R*：重相関係数

* *P*<0.05　** *P*<0.01

結　論

- NTxを指標とした骨障害は、Cadmium汚染地
  の女性のみ観察
  - 汚染地の女性は加齢に伴う骨の再吸収に加えてCadmiumによる骨障害が進行する可能性が示唆
  - 男性の骨への影響は明らかにならなかった
- Cadmium汚染地では土壌改善後も、長期にわたり健康影響があり、経過観察が必要

Ⅳ. Dose-response relationship between cadmium exposure and adverse health effects

TABLE IV

PREVALENCE RATES OF β-MICROGLOBULINURIA IN RELATION TO URINARY CADMIUM CONCENTRATIONS AMONG INHABITANTS OVER 50 YEARS OF AGE

Men													
Cd (μg/g.cr.)	0.0–0.9	1.0–1.9	2.0–2.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10.0–14.9	15.9–19.9	20.0–
Median Cd (μg/g.cr.)	0.8	1.7	2.5	3.5	4.4	5.4	6.4	7.5	8.5	9.4	11.5	18.5	
N	10	111	240	231	208	153	110	82	61	42	116	39	
Prevalence rates (%)													
β_2-mg ≥ 927 μg/l	0.0	4.5	2.9	3.5	6.3	8.5	14.5	14.6	16.4	23.8	43.1	48.7	
β_2-mg ≥ 1129 μg/g.cr.	0.0	3.6	4.6	4.3	7.2	8.5	15.5	14.6	21.3	26.2	42.2	53.8	
Women													
Cd (μg/g.cr.)	0.0–0.9	1.0–1.9	2.0–2.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10.0–14.9	15.9–19.9	20.0–
Median Cd (μg/g.cr.)	0.9	1.7	2.6	3.5	4.5	5.3	6.5	7.4	8.4	9.5	11.8	17.0	23.4
N	4	27	99	140	177	176	188	159	142	112	347	83	62
Prevalence rates (%)													
β_2-mg ≥ 503 μg/l	0.0	3.7	3.0	5.0	7.3	8.0	9.0	8.2	22.5	21.4	32.0	37.3	56.5
β_2-mg ≥ 1059 μg/g.cr.	0.0	7.4	3.0	5.0	7.3	9.1	8.5	8.8	21.1	18.8	31.4	41.0	59.7

N: Number of persons examined.

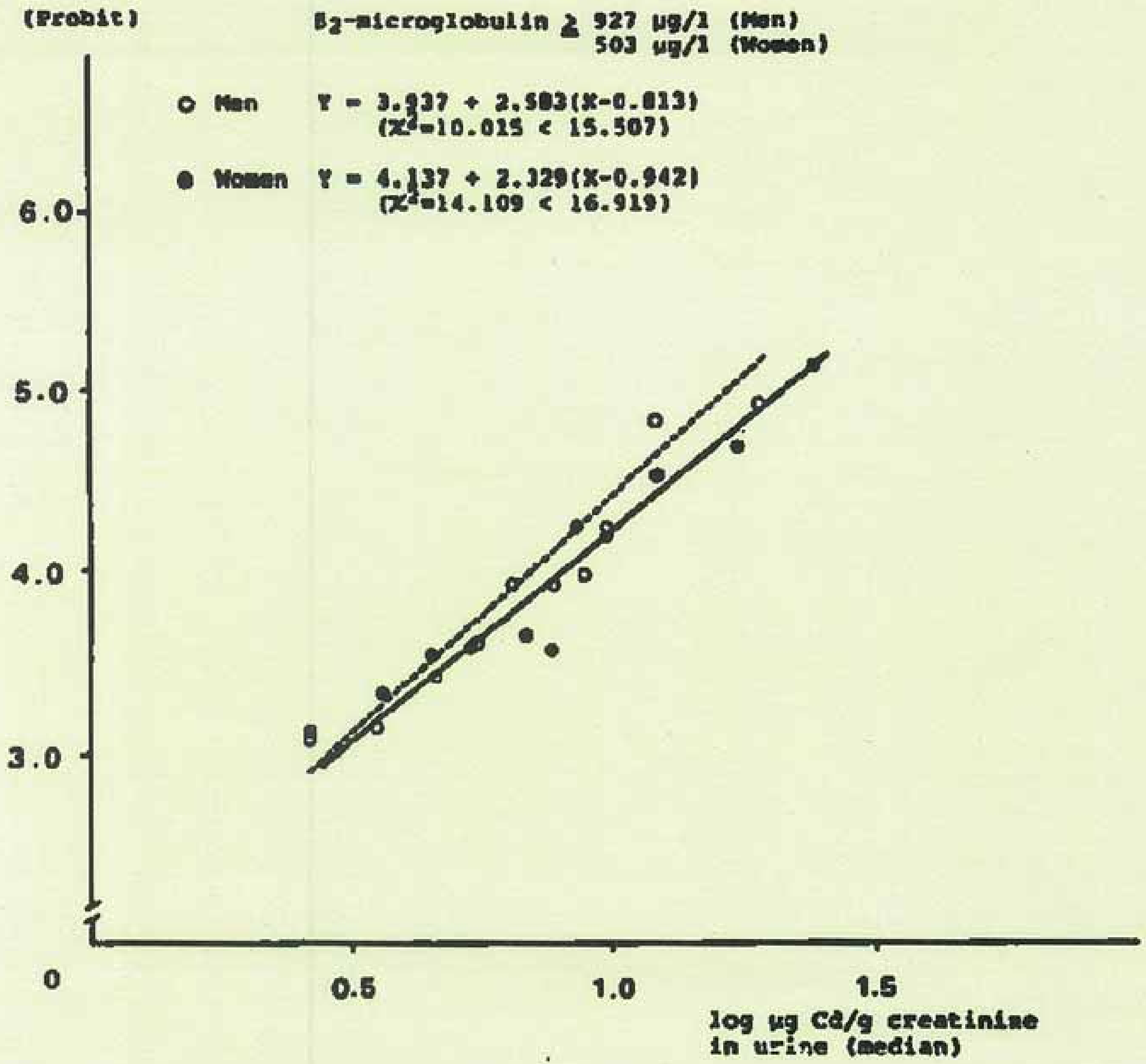


Fig. 1. Probit linear regression line between urinary cadmium concentration and prevalence of β_2-microglobulinuria.

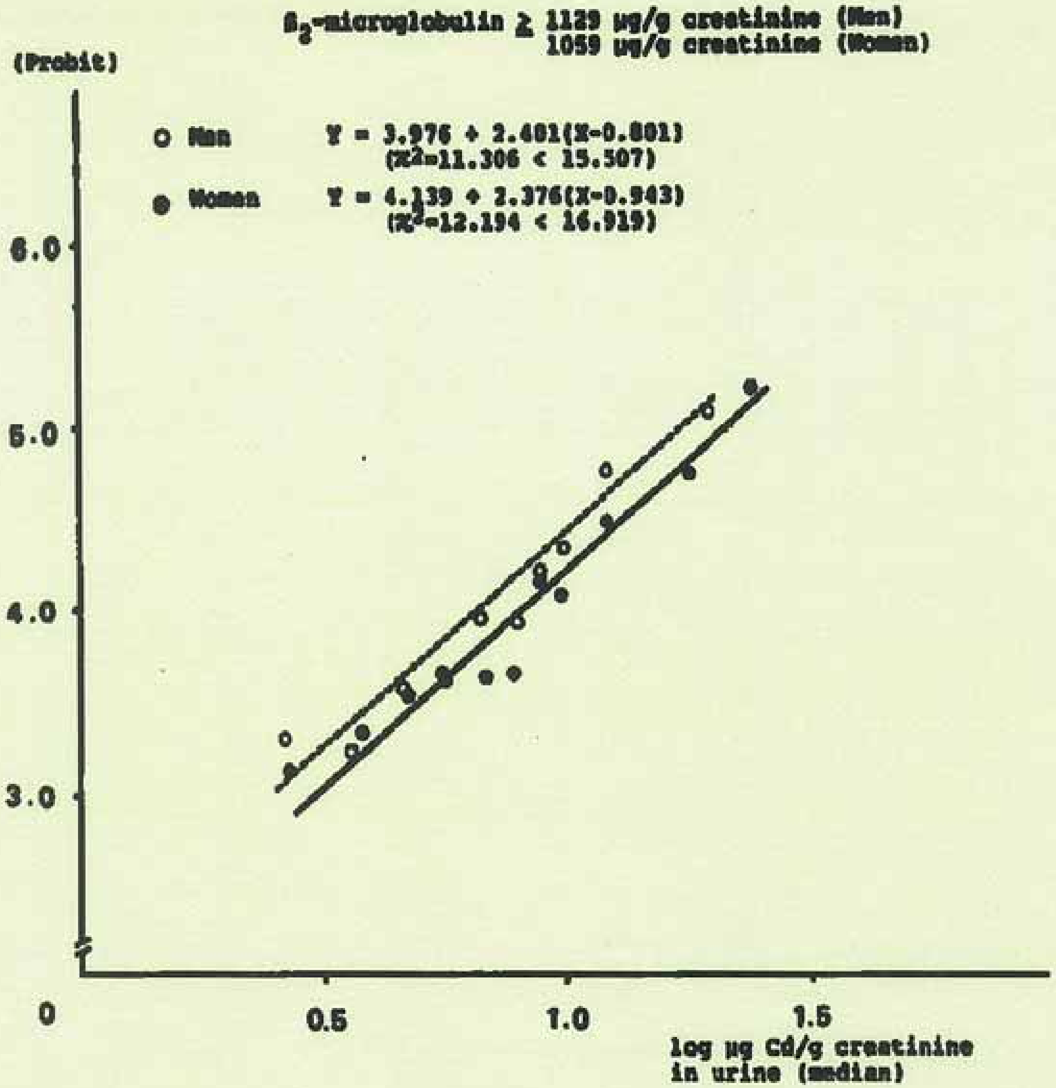
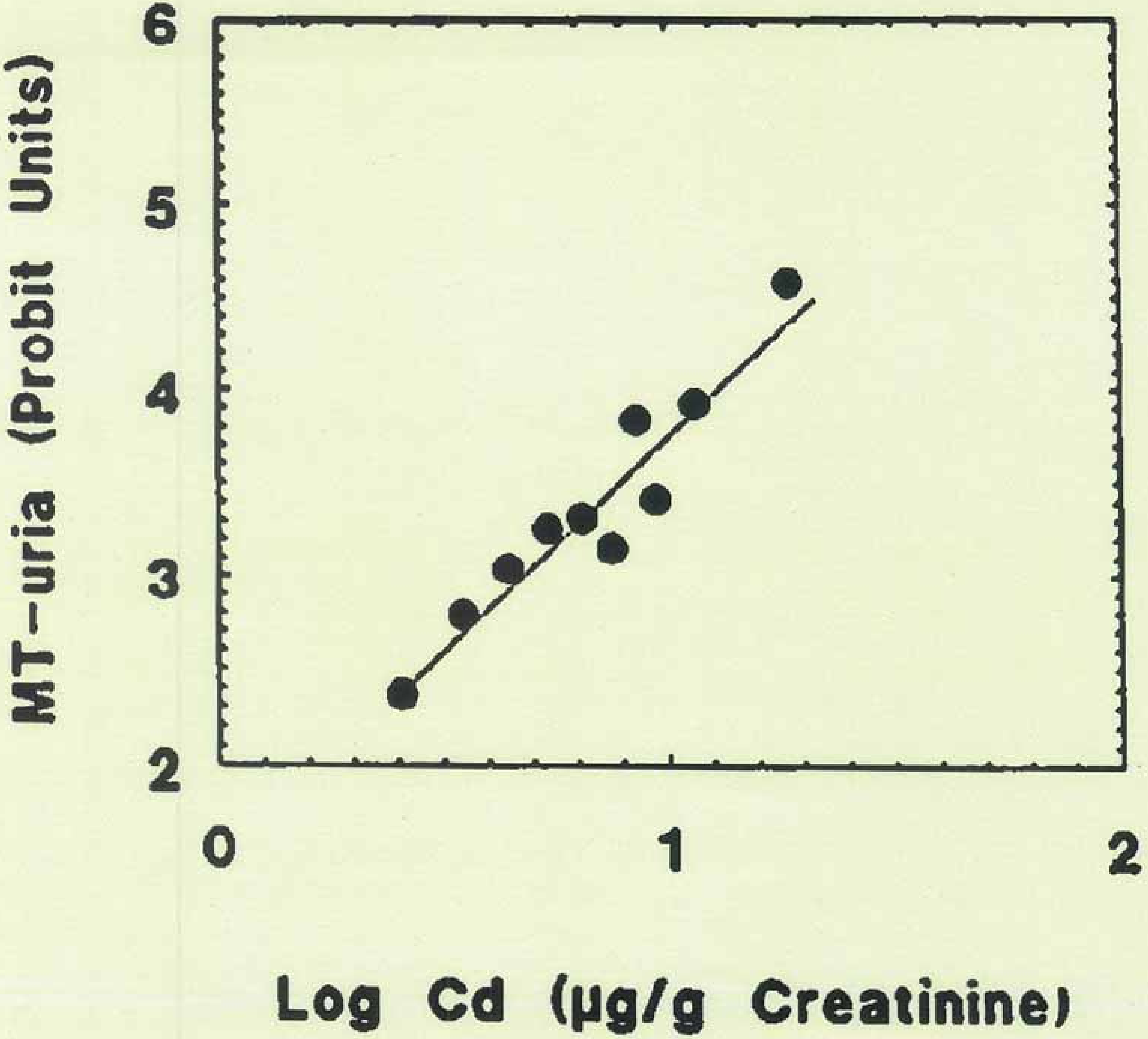
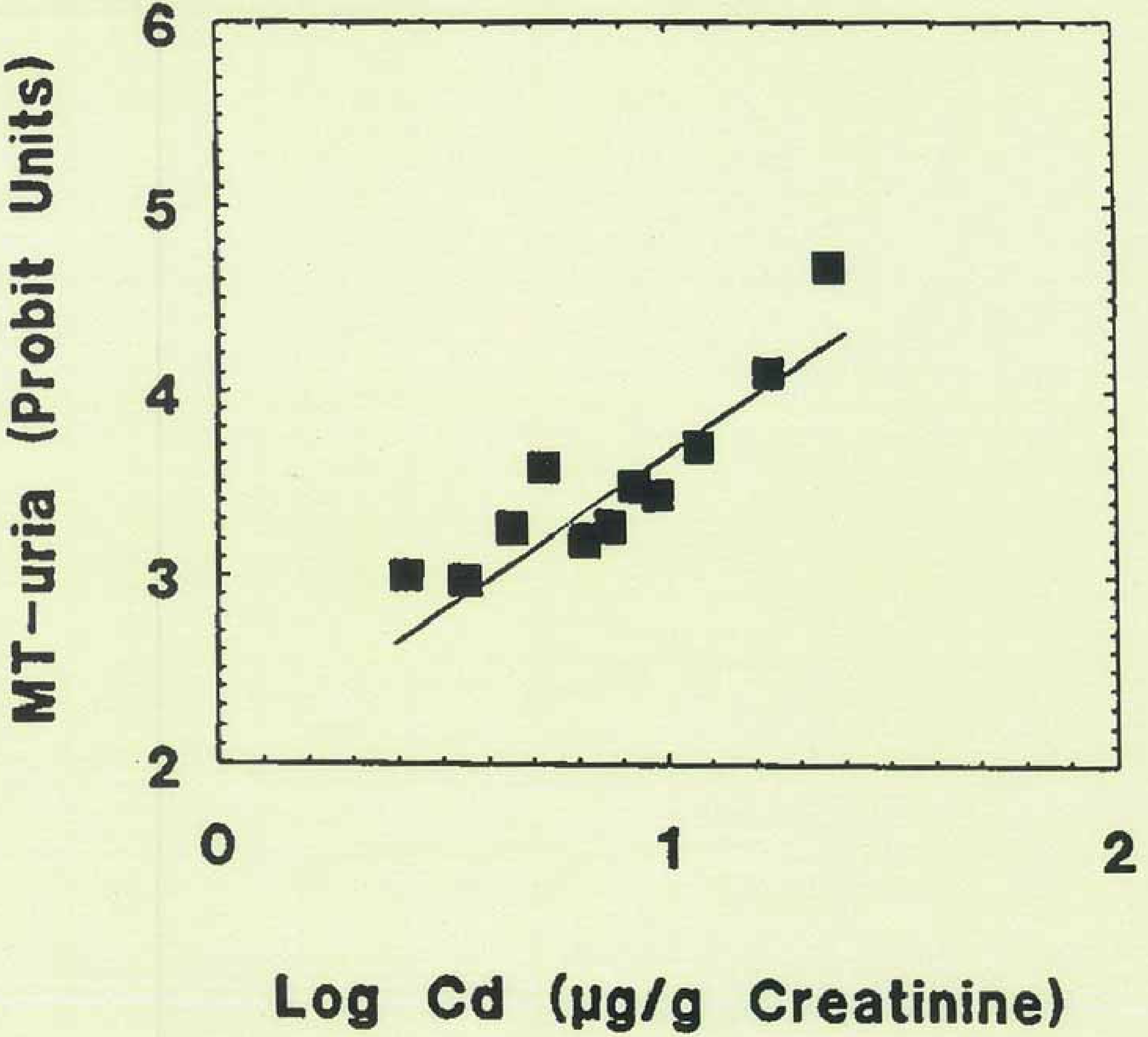


Fig 2. Probit linear regression line between urinary cadmium concentration and prevalence of β_2-microglobulinuria.



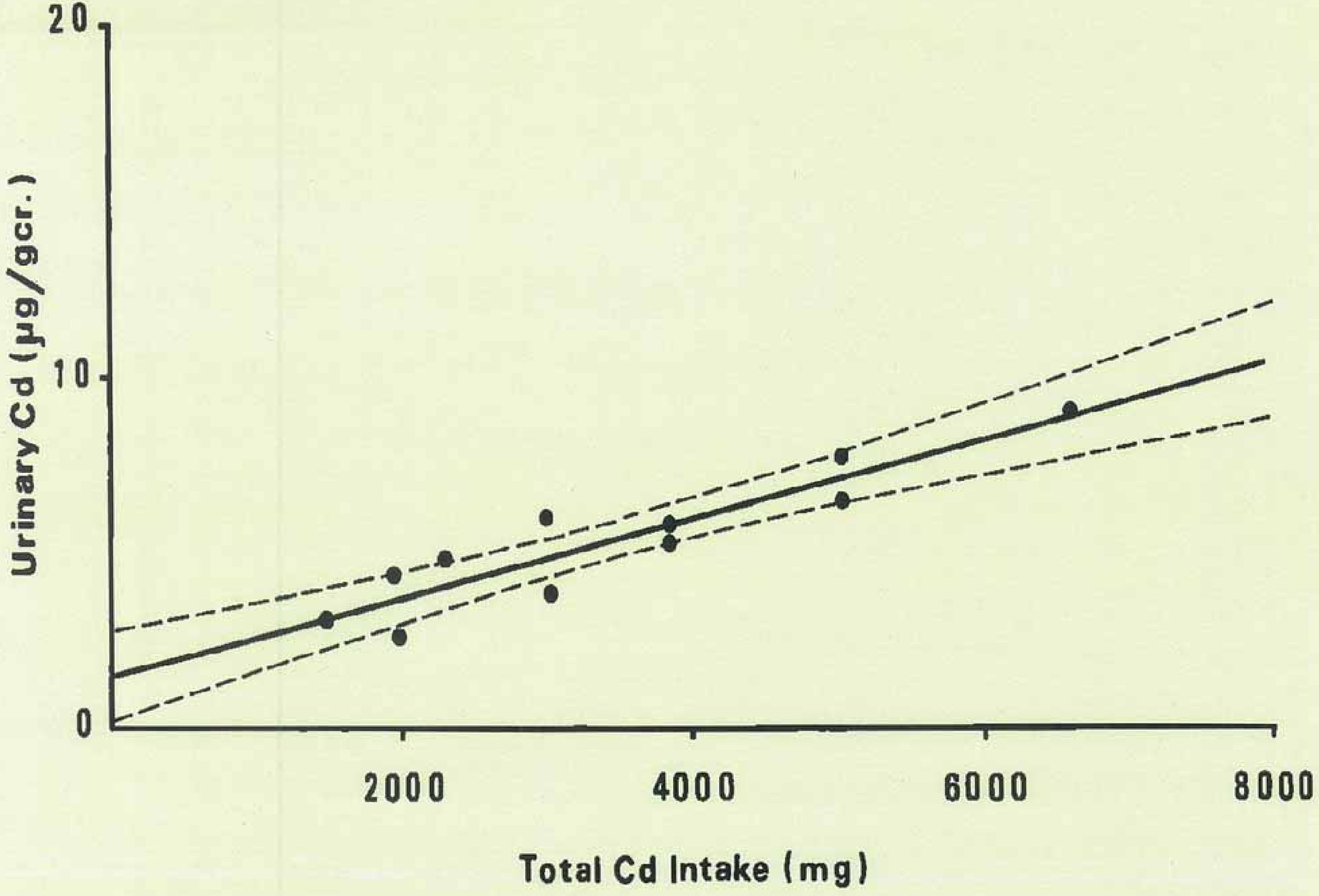
6
5
4
3
2
0
1
2
MT-uria (Probit Units)
Log Cd (µg/g Creatinine)



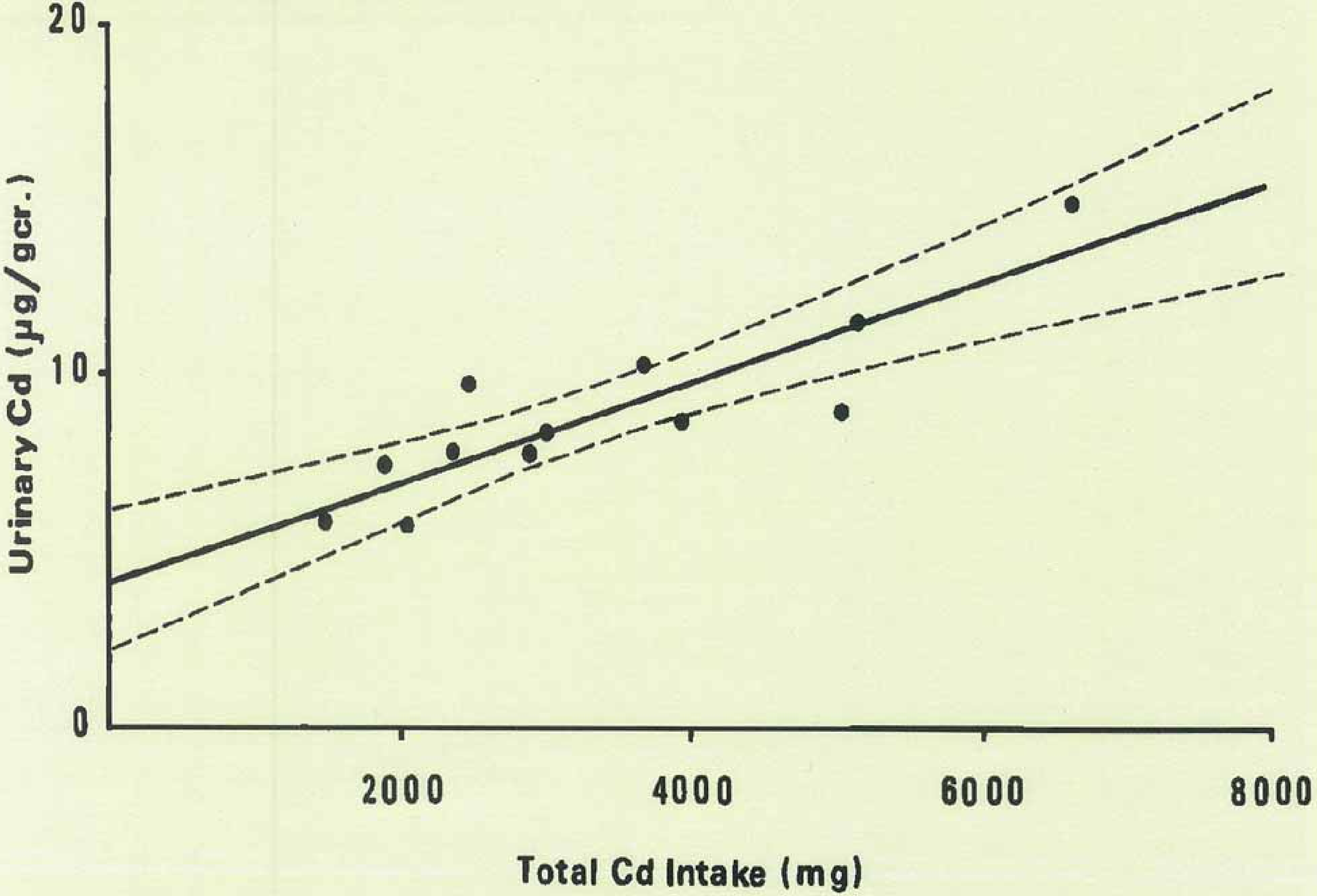
MT-uria (Probit Units)
6
5
4
3
2
0
1
2
Log Cd (µg/g Creatinine)

Total Cd intake calculated by formula as follows.

([village average Cd concentration in rice] × [the average daily intake of rice] + [daily intake of Cd from foods other than rice]) × [duration of residence in the Cd-polluted areas] + [average daily intake of Cd in non-polluted areas of Japan] ×[duration of residence in non-polluted areas].



20
10
0
Urinary Cd (µg/gcr.)
2000
4000
6000
8000
Total Cd Intake (mg)



20
10
0
Urinary Cd (µg/gcr.)
2000
4000
6000
8000
Total Cd Intake (mg)

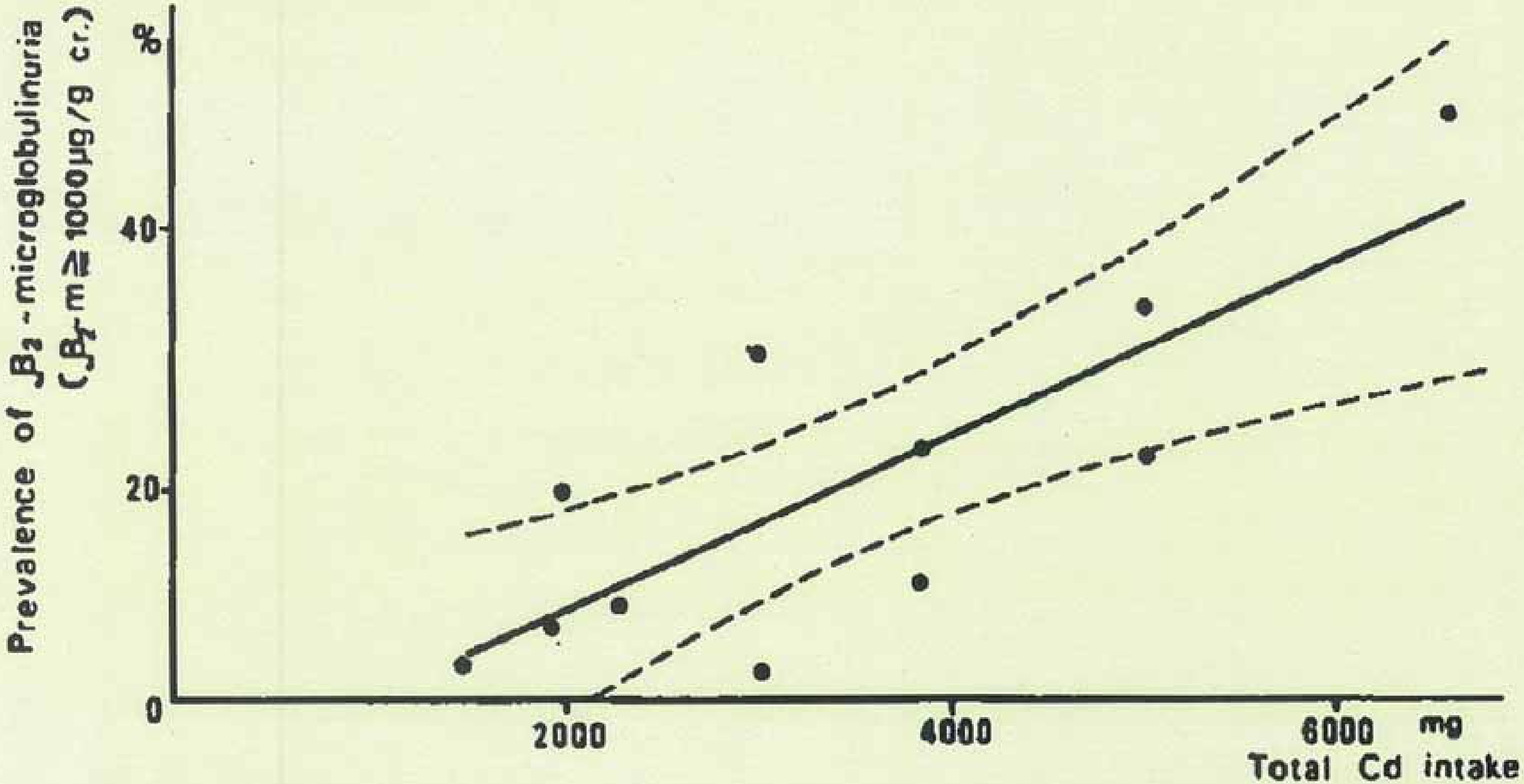


FIG. 2. Correlation between total Cd intake and prevalence of β_2-m-uria (β_2-m $\geq$ 1000 µg/g cr.) for the Cd-exposed male group. The regression line is $Y = 0.0083X - 7.93$ ($r = 0.81$; $P < 0.01$).

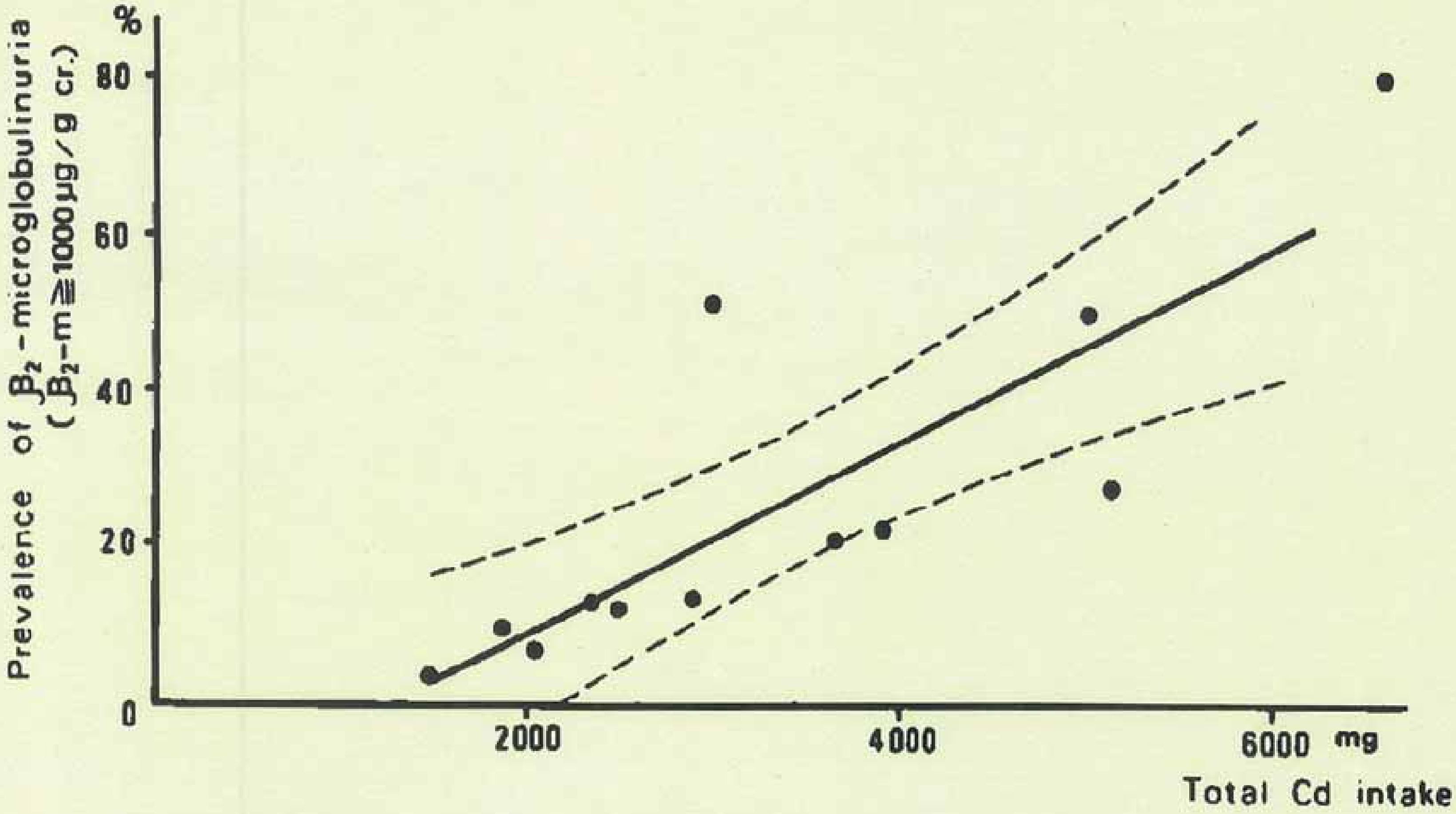
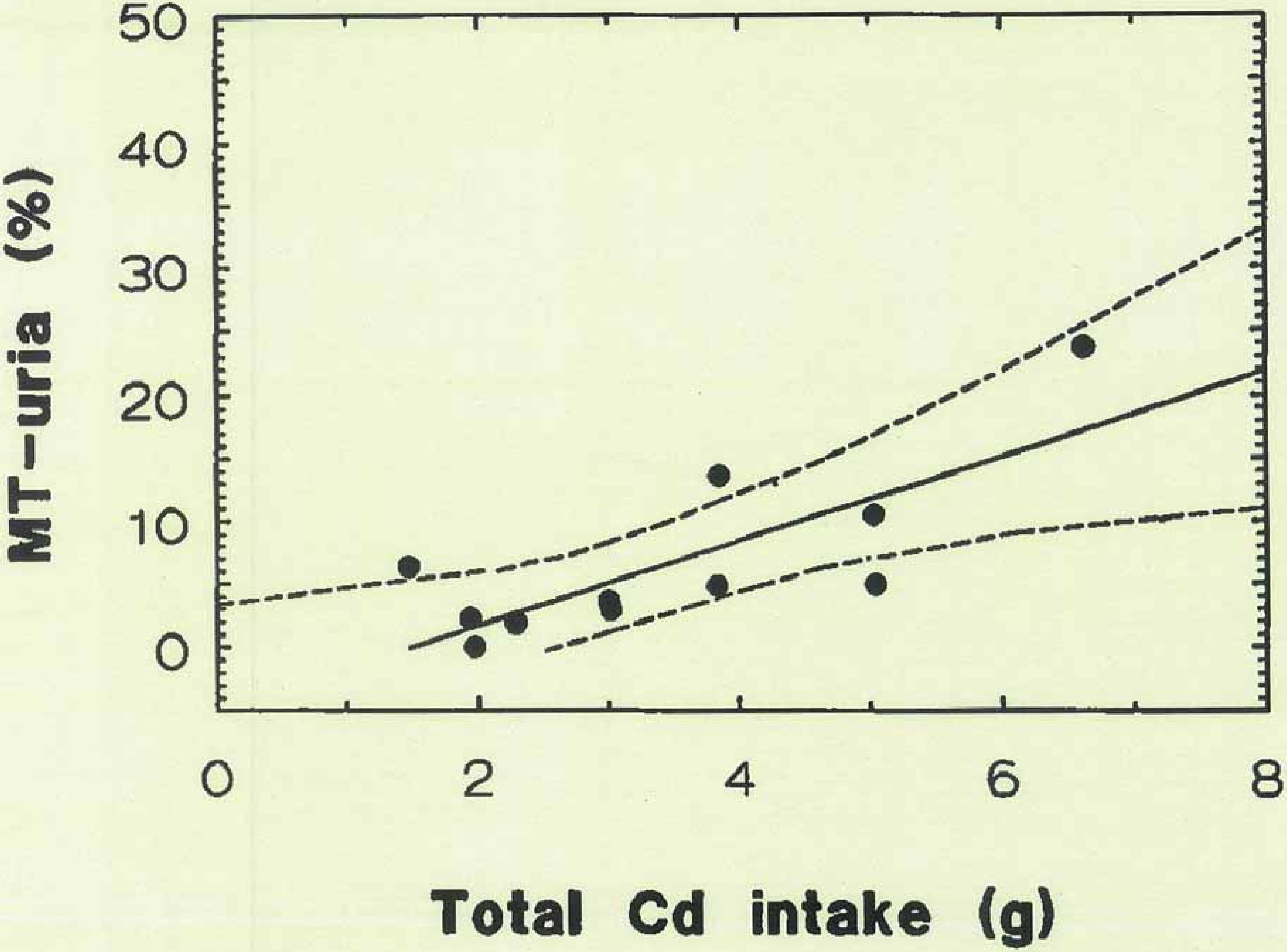
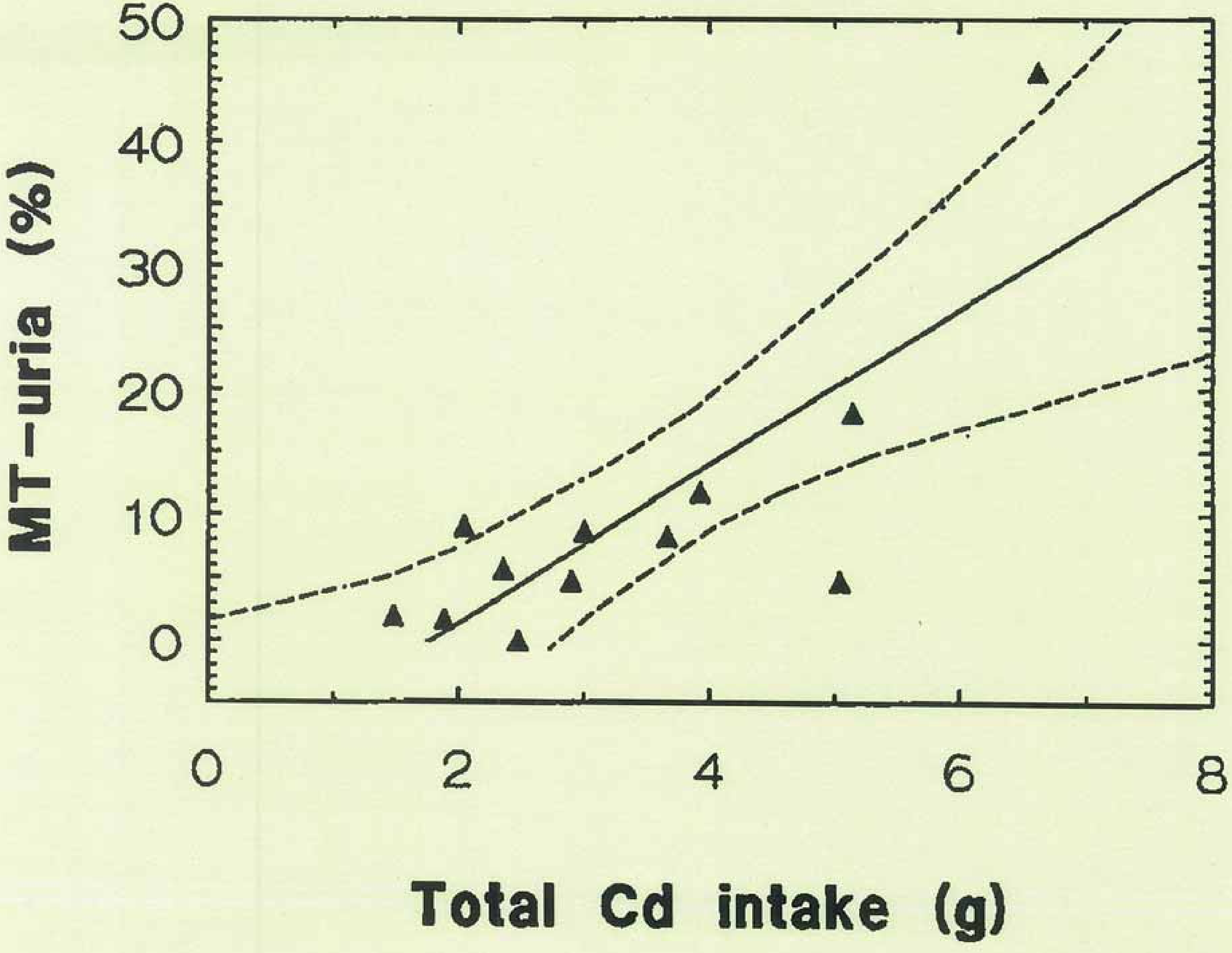


FIG. 4. Correlation between total Cd intake and prevalence of β_2-m-uria (β_2-m $\geq$ 1000 μg/g cr.) for the Cd-exposed female group. The regression line is $Y = 0.012X - 16.16$ ($r = 0.84$; $P < 0.001$).



50
40
30
20
10
0
MT-uria (%)
0
2
4
6
8
Total Cd intake (g)


MT-uria (%)
50
40
30
20
10
0
0
2
4
6
8
Total Cd intake (g)

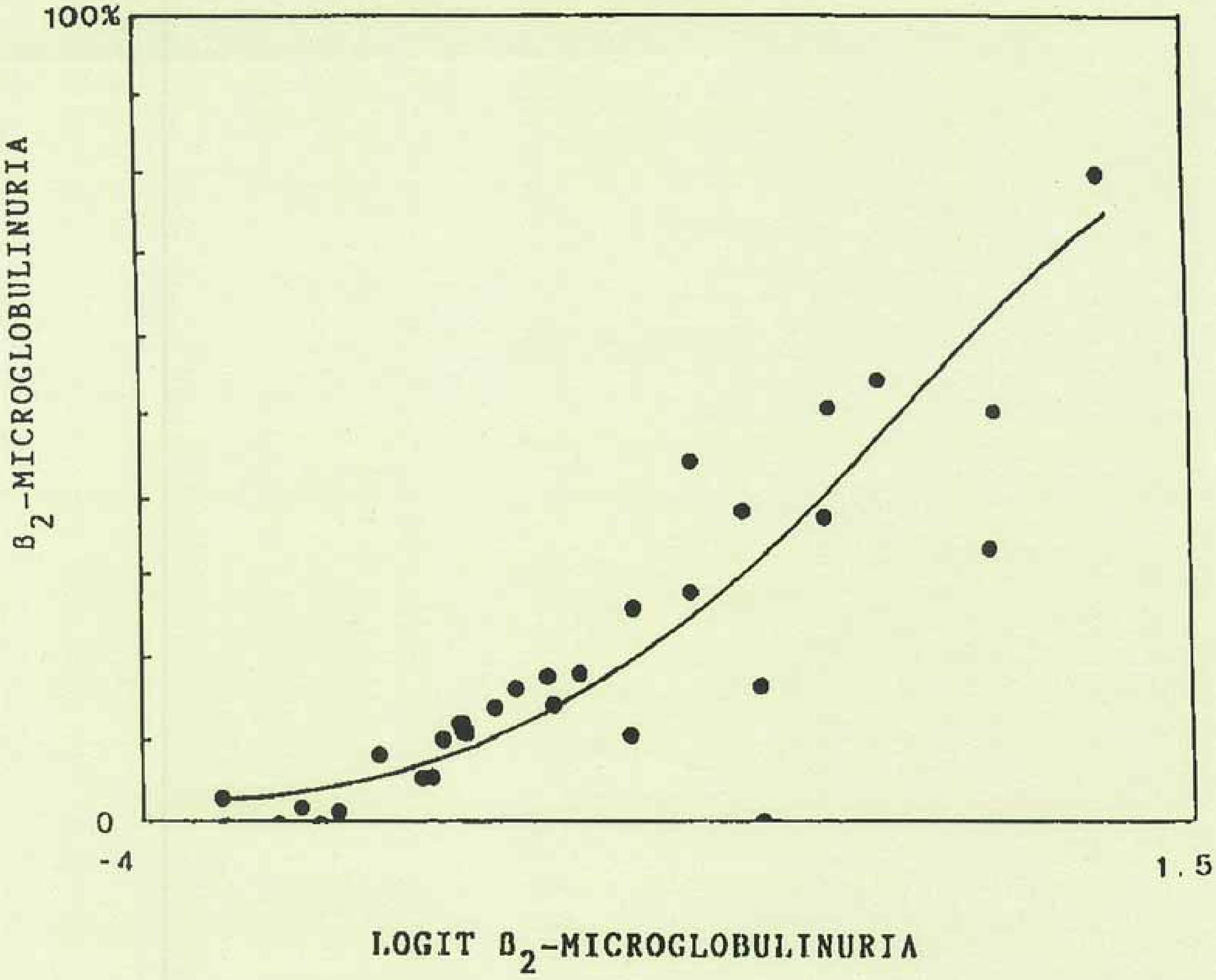


Fig. 1. Prevalence of β_2-MG-uria in the Cd-exposed women and their logistic model in the case of β_2-MG expressed as $\mu g/g \cdot cr$.

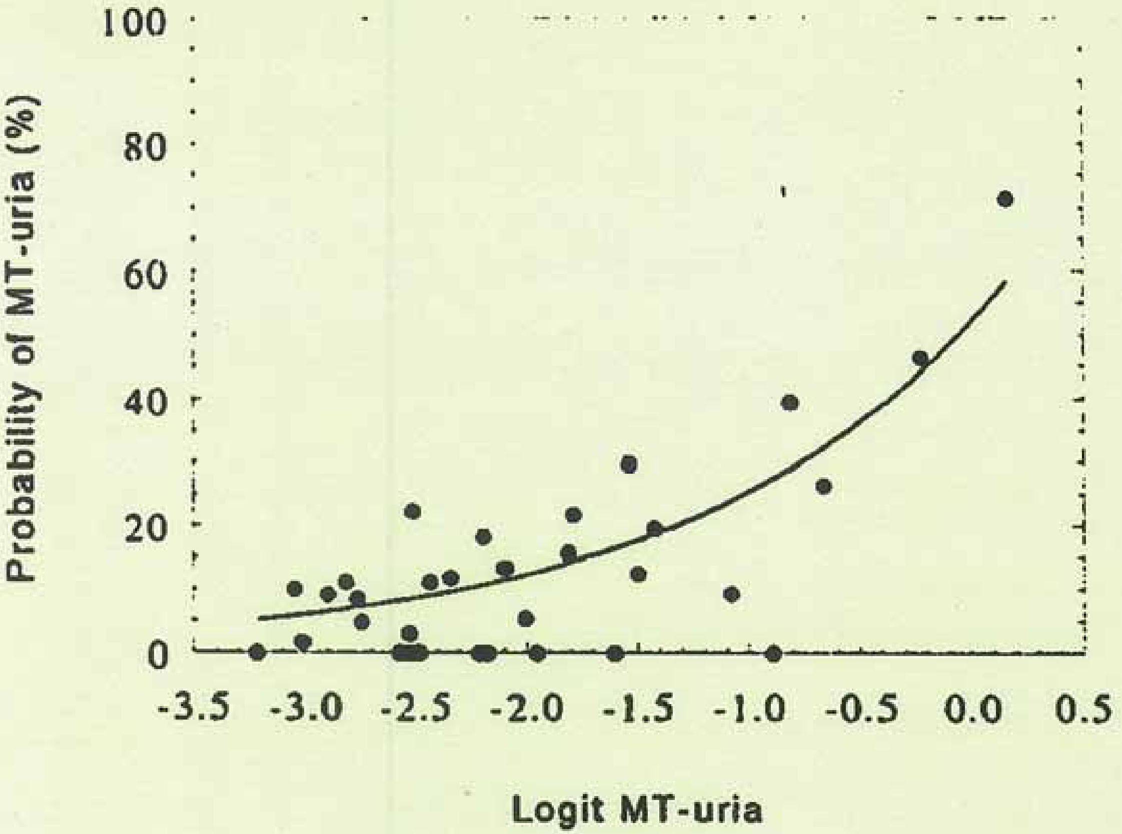


Fig. 1. Logistic regression analysis of the prevalence of MT-uria in the Cd-exposed women. Data are for MT values expressed as μg/g creatinine. The probability of MT-uria (prevalence, %) and ln odds (logit) MT-uria are plotted. Exponential fit, correlation coefficient = 0.75.

Logit MT-uria = –4.6773 + 0.0119 (Age) + 0.000566 (Total Cd intake)

Fig. 7 Prevalence of metallothioneinuria (μg/l) corresponding to each age and total cadmium intake calculated by general linear model

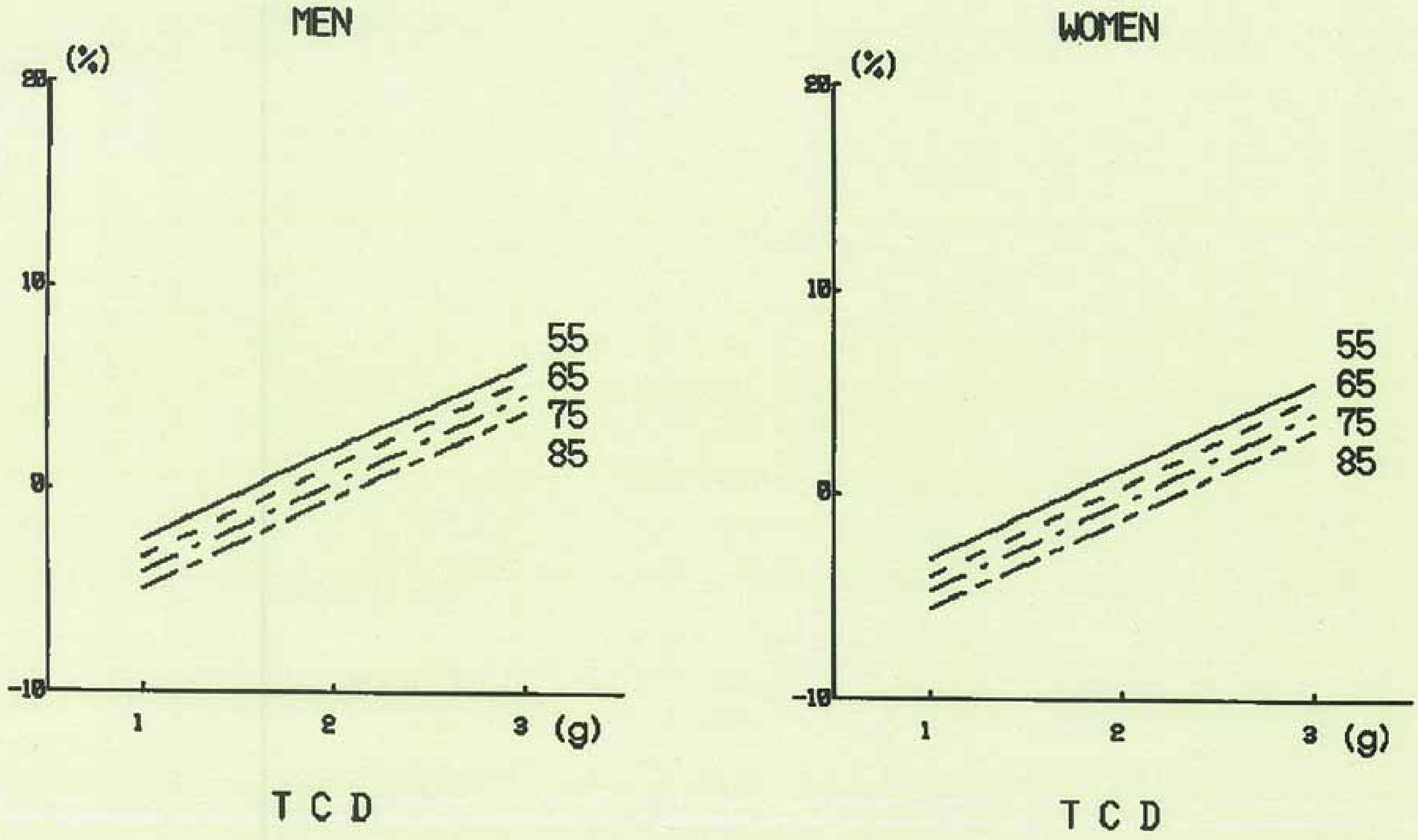
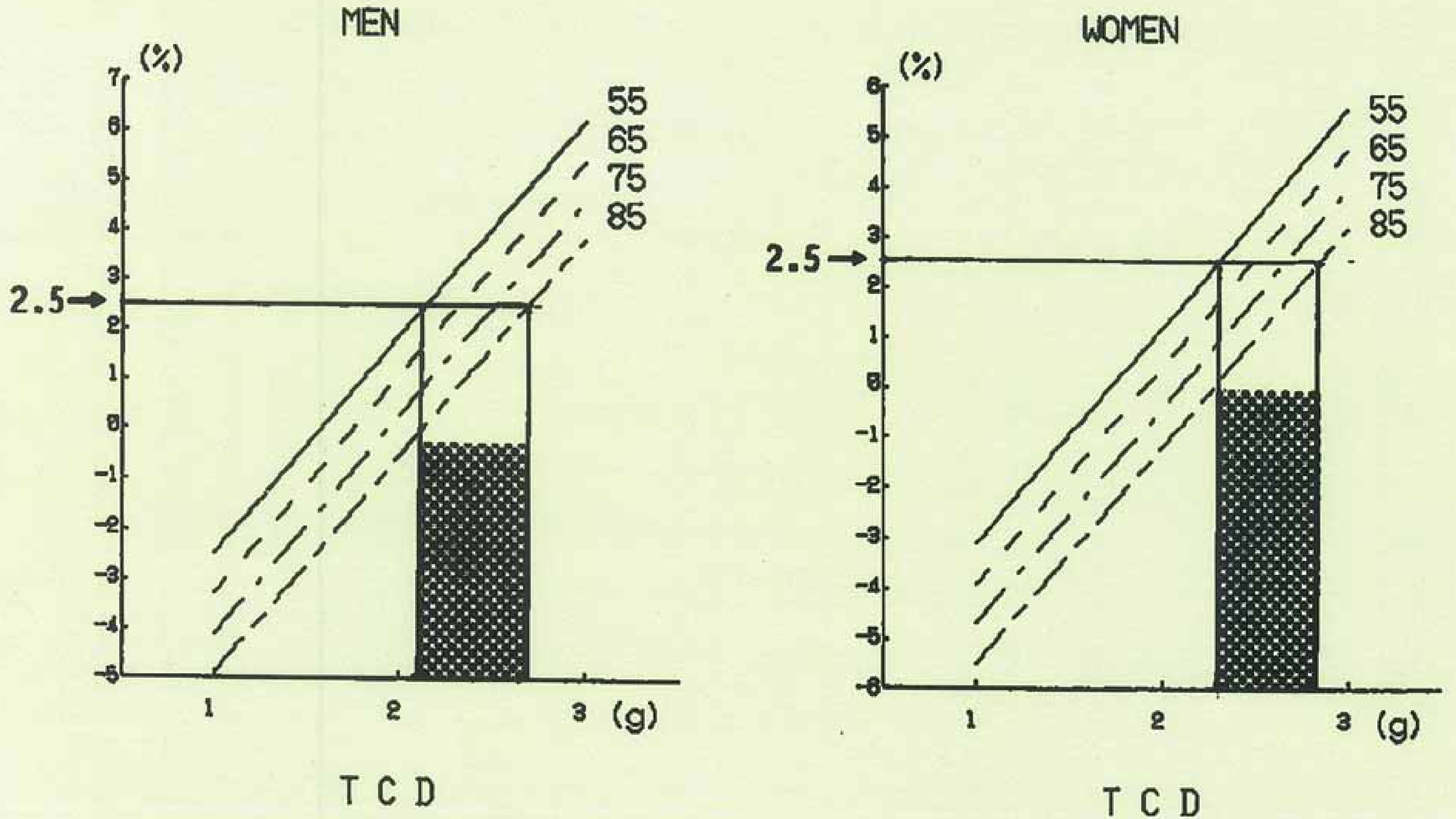


Fig. 10 Ranges of total Cd intakes corresponding to 2.5 % of prevalence of metallothioneinuria in the nonexposed men and women



2g of total Cd intake

[Example]

In case of 80 yr is

= 25 mg / yr (2000 mg / 80 yr)

= 68 μg / day (25,000 μg / 365 days)

< 80 μg (0.4 ppm x 200 g) + α

Cut-off value of rice in Japan

Other foods

Conclusion(1)

- Prevalence of β_2-MG-uria (> 1,000 μg / g cr.) was 14.3 % in men and 18.7% in women in Cd-polluted areas of Kakehashi River basin, while it was 6.0 % and 5.0 % in men and women in unpolluted areas, respectively.

Conclusion(2)

- Once Cd-induced renal tubular dysfunction occured, it was **irreversible** even after cessation of Cd-exposure.
- Bone damage such as osteopenia was also found in Cd-exposed subjects with renal tubular dysfunction.

Conclusion(3)

- Total Cd intake corresponding to maximum allowable Cd concentration in urine was calculated as approximately 2 g for both of men and women using linear regression and multivariate analysis.