ORIGINAL ARTICLE

Causes of death and renal tubular dysfunction in residents exposed to cadmium in the environment

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Objectives: To clarify the causes of death of residents with renal tubular dysfunction induced by cadmium (Cd) in the environment.

Methods: A 15 year follow up study was performed with the inhabitants living in the Cd polluted Kakehashi River basin in Japan. Standardised mortality ratios (SMRs) for causes of death, classified by ICD-9, were computed using the person-years method to investigate the excess mortality of subjects with urinary β 2-MG (microglobulin) ≥ 1000 $\mu\text{g/gCr}$. Mortality risk analysis was performed using Cox's proportional model to compare mortality between subjects with urinary β 2-MG ≥ 1000 and < 1000 $\mu\text{g/gCr}$, and to investigate the relationship between the degree of urinary β 2-MG and mortality.

Results: Excess mortality due to heart failure and cerebral infarction in both sexes, and nephritis and nephrosis in men, was observed among subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$. Significant increases in mortality risk for cerebral infarction in men and for malignant neoplasms in women with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$ were observed during the first five year observation period. For nephritis and nephrosis, the mortality risks for men and women with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$ significantly increased over the 15 year observation period. The mortality risks for heart failure and cerebral infarction increased in proportion to the increased urinary β 2-MG in both sexes. Increased mortality risks for nephritis and nephrosis were identified in the subjects with urinary β 2-MG ≥ 10000 $\mu\text{g/gCr}$ in both sexes.

Conclusion: Renal tubular dysfunction induced by Cd affected the causes of death, and mortality for heart failure, cerebral infarction, and nephritis and nephrosis was increased among inhabitants living in a Cd polluted area in Japan. In women, cancer mortality may have been increased while Cd pollution was ongoing.

Previously, we followed up inhabitants exposed to environmental cadmium (Cd) in the Kakehashi River basin, and reported higher mortality in the subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$ or urinary retinol binding protein (RBP) ≥ 4 mg/l, in order to highlight the poor life prognosis of subjects with renal tubular dysfunction induced by Cd exposure.^{1–5} In the Cd polluted Jinzu River basin in Toyama, Matsuda *et al* reported a high mortality risk of subjects with protein and glucose-uria, and increasing mortality risk in proportion to the amount of urinary protein.⁶ Iwata *et al*^{7,8} found that the standardised mortality ratio (SMR) for all causes in subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$ was higher in a Cd polluted area in Nagasaki, Japan, and that urinary β 2-MG and urinary amino acid levels were significantly associated with mortality in a follow up study in a Cd polluted area in Akita, Japan.⁹ However, only few reports have examined the relationship between renal tubular dysfunction and mortality due to special causes of death in inhabitants exposed to Cd in Japan.^{1–4}

In other countries, the causes of death among inhabitants exposed to Cd have been of major concern, and the relationship between exposure to Cd and cancer mortality, especially lung and prostate cancer, has been discussed in studies of industrial workers.^{10–13} Mortality from renal diseases is also an interesting issue, with respect to the prognosis of renal tubular dysfunction induced by Cd, and increased mortality has been reported in Swedish Cd battery workers,¹¹ and in Cd polluted areas in Belgium.^{14–15} Moreover, Inskip *et al* conducted a 40 year follow up study of Shipham residents in the UK, and reported an excess of deaths from all

genitourinary diseases in men.¹⁶ However, these studies did not investigate the relationship between mortality and markers of adverse health effects, such as urinary low molecular weight protein.

We investigated the causes of death in a nine year follow up study of the inhabitants of the Kakehashi River basin, and reported increased mortality from heart failure, cerebral infarction, and renal diseases in inhabitants with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$.⁴ However, the number of deaths observed among urinary β 2-MG positive subjects was too small to investigate the increase in mortality due to special causes of death in proportion to the degree of renal tubular dysfunction. In addition, the mortality due to Cd exposure may have changed over a longer period, due to the restoration of polluted paddy fields in the Kakehashi River basin undertaken between 1977 and 1988.

Therefore, a 15 year follow up study of the subjects examined in the 1981–82 health impact survey was conducted in the present study. We investigated the relationships between amount of urinary β 2-MG excretion and mortality due to special causes of death, as well as the trend in mortality over 15 years to clarify the changes in mortality after the restoration of rice fields had been completed.

METHODS

A 15 year follow up study, from the day of their initial examination of urinary β 2-MG until 30 November 1996, was

Abbreviations: Cd, cadmium; ICD-9, International Classification of Diseases, Ninth Revision; RBP, retinol binding protein; SMR, standardised mortality ratio

Table 1 Positive rates of urinary $\beta 2$ -microglobulin and person-years in three observation periods

	Men			Women		
	$\beta 2$ -MG(-)	$\beta 2$ -MG(+)	Total	$\beta 2$ -MG(-)	$\beta 2$ -MG(+)	Total
Subjects (n)	1219	205	1424	1425	329	1754
($\beta 2$ -MG positive rate %)		14.4			18.8	
U-Cd (mean (SD))* $\mu\text{g/gCr}$	4.2 (1.8)	7.8 (1.9)		6.5 (1.8)	10.8 (1.8)	
Person-years observed						
1981-86	5320.9	828.2	6149.1	6287.1	1378.5	7665.6
1987-91	5242.9	604.2	5847.1	6449.5	1103.8	7553.3
1992-96	4310.4	408.8	4719.2	5527.6	706.0	6233.6
Total	14974.2	1841.2	16815.4	18264.2	3188.3	21452.5
Mean observed year/person	12.3	9	11.8	12.8	9.7	12.2

$\beta 2$ -MG(-), urinary $\beta 2$ -microglobulin $<1000 \mu\text{g/gCr}$; $\beta 2$ -MG(+), urinary $\beta 2$ -microglobulin $\geq 1000 \mu\text{g/gCr}$; U-Cd, urinary cadmium, which was measured in 1403 men and 1716 women.

*Geometrical mean (geometrical standard deviation).

performed with the 3178 inhabitants (1424 men and 1754 women), amounting to 91% of all residents aged ≥ 50 years old of the 23 hamlets in Kakehashi River basin defined by measurements of Cd in rice ($\geq 0.4 \text{ mg/kg}$) and/or soil of paddy fields ($\geq 1.0 \text{ mg/kg}$). The survival status (living or deceased) and place of residence (still residing in the target area or not), were determined, and the date of death and individual causes of death ascertained from the death certificates, with the cooperation of the Prefecture Public Health Office and City Municipal Office. Individual causes of death were classified according to the International Classification of Diseases, Ninth Revision (ICD-9).

The standardised mortality ratios (SMRs) with 95% confidence intervals (95% CIs) of the subjects with urinary $\beta 2$ -MG $\geq 1000 \mu\text{g/gCr}$ and subjects with urinary $\beta 2$ -MG $<1000 \mu\text{g/gCr}$ were computed using the person-years method. They were estimated with the expected number of deaths calculated using age, sex, cause, and period specific mortality in five year age groups of the general Japanese population, during the observation period. Geometrical mean of urinary Cd in 1981-82, total person-years, and the mean number of observation years per person of the subjects with

urinary $\beta 2$ -MG $\geq 1000 \mu\text{g/gCr}$ and the subjects with $<1000 \mu\text{g/gCr}$ are shown in table 1. A clear dose-response relationship among these subjects has been clarified between urinary Cd and the urinary $\beta 2$ -MG positive rate by Ishizaki *et al.*¹⁷

To compare the mortality for all causes, and the major specific causes of death, between the subjects with and without $\beta 2$ -MG $\geq 1000 \mu\text{g/gCr}$ after adjustment for age, the risk ratios of mortality from the main causes of death were investigated after adjustment for age group (50-59, 60-69, 70-79, 80-89, ≥ 90 years old) using Cox's proportional hazard model. In the same way as for the analysis covering the total 15 year observation period, risk analysis of mortality for five years from the baseline in 1981 to December 1986, and for 10 years from the baseline to December 1991 of the subjects with urinary $\beta 2$ -MG $\geq 1000 \mu\text{g/gCr}$ compared with subjects $<1000 \mu\text{g/gCr}$, was performed to investigate changes in mortality during the 15 year observation period.

For analysis of the relationships between the degree of renal tubular dysfunction and mortality, the subjects were divided into four groups according to the amount of urinary $\beta 2$ -MG (<300 , 300-1000, 1000-10000, $\geq 10000 \mu\text{g/gCr}$). The

Table 2 Causes of deaths during all observation period in $\beta 2$ -microglobulin positive and negative subjects

	ICD code	Men						Women					
		$\beta 2$ -MG(-) (n = 1219)			$\beta 2$ -MG(+) (n = 205)			$\beta 2$ -MG(-) (n = 1425)			$\beta 2$ -MG(+) (n = 329)		
		Obs	SMR	(95% CI)	Obs	SMR	(95% CI)	Obs	SMR	(95% CI)	Obs	SMR	(95% CI)
All causes	001-999	367	83	(74-91)	140	127	(106-148)	271	82	(71-91)	199	146	(126-167)
Malignant neoplasms	140-208	104	75	(60-89)	24	93	(54-133)	59	71	(53-89)	24	106	(61-151)
Oesophagus	150	1	16	(0-221)	1	96	(0-1323)	0	0		3	709	(0-2470)
Stomach	151	21	64	(35-93)	5	77	(0-173)	14	85	(36-133)	4	79	(0-203)
Colon, rectum	153,154	14	106	(45-167)	4	162	(0-420)	8	77	(13-140)	3	101	(0-351)
Liver	155	6	37	(0-75)	1	43	(0-593)	4	62	(0-160)	0	0	
Pancreas	157	9	117	(27-208)	2	150	(0-1500)	11	187	(62-318)	1	63	(0-862)
Lung	162	25	82	(48-115)	8	142	(24-260)	6	61	(0-126)	4	146	(0-379)
Breast	174	-	-		-	-		2	53	(0-528)	3	456	(0-1588)
Uterus	180	-	-		-	-		1	24	(0-324)	0	0	
Prostate	185	3	68	(0-237)	1	90	(0-1235)	-	-		-	-	
Bladder	188	1	41	(0-563)	1	170	(0-2333)	0	0		2	548	(0-5475)
Hypertensive diseases	401-405	1	24	(0-71)	0	0		2	36	(0-361)	2	62	(0-614)
Ishaemic heart diseases	410-414	17	54	(26-82)	3	38	(0-132)	14	59	(28-87)	10	98	(28-168)
Heart failure	428	38	93	(63-122)	22	179	(99-258)	41	104	(72-136)	46	248	(177-320)
Cerebrovascular diseases	430-438	50	76	(55-97)	32	166	(109-224)	47	71	(51-92)	39	135	(93-178)
Cerebral haemorrhage	430-432	14	79	(33-125)	4	99	(0-257)	14	88	(37-139)	3	51	(0-179)
Cerebral infarction	433,34,37	31	69	(45-93)	28	160	(98-221)	23	66	(38-95)	31	174	(110-237)
Pneumonia and bronchitis	480-487	34	83	(55-111)	8	65	(11-120)	21	80	(43-116)	13	113	(45-182)
Digestive diseases	520-579	17	83	(40-125)	8	180	(30-330)	18	113	(57-169)	14	238	(114-363)
Kidney and urinary diseases	580-599	8	81	(13-148)	10	357	(102-612)	7	75	(6-144)	9	230	(53-407)
Nephritis and nephrosis	580-589	7	79	(21-138)	10	420	(160-681)	3	37	(0-80)	8	247	(76-419)

$\beta 2$ -MG(-), urinary $\beta 2$ -microglobulin $<1000 \mu\text{g/gCr}$; $\beta 2$ -MG(+), urinary $\beta 2$ -microglobulin $\geq 1000 \mu\text{g/gCr}$; Obs, observed number of death; SMR, standardised mortality ratio; 95% CI, 95% confidence interval.

Table 3 Changes of mortality for special causes of death in β 2-microglobulin positive and negative subjects

	Men			Women		
	β 2-MG	Death	Hazard ratio (95% CI)	Death	Hazard ratio (95% CI)	
<i>All causes</i>						
5 years (-1986)	-	86	1	64	1	
	+	58	1.83 (1.27-2.62)***	66	1.79 (1.23-2.61)**	
10 years (-1991)	-	216	1	164	1	
	+	104	1.61 (1.25-2.07)***	145	1.82 (1.43-2.33)***	
15 years (-1996)	-	367	1	271	1	
	+	140	1.56 (1.27-1.92)***	199	1.86 (1.53-2.27)***	
<i>Malignant neoplasms</i>						
5 years (-1986)	-	24	1	14	1	
	+	7	0.95 (0.39-2.33) NS	10	2.57 (1.03-6.43)*	
10 years (-1991)	-	63	1	27	1	
	+	14	0.84 (0.46-1.55) NS	21	2.89 (1.52-5.48)**	
15 years (-1996)	-	103	1	59	1	
	+	24	1.12 (0.75-1.92) NS	24	1.63 (0.97-2.74) NS	
<i>Heart failure</i>						
5 years (-1986)	-	7	1	7	1	
	+	8	2.16 (0.64-6.34) NS	14	2.4 (0.8-6.58) NS	
10 years (-1991)	-	22	1	30	1	
	+	20	2.7 (1.41-5.15)**	34	1.83 (1.08-3.08)*	
15 years (-1996)	-	38	1	41	1	
	+	22	1.92 (1.10-3.35)*	46	2.16 (1.88-3.37)**	
<i>Cerebral infarction</i>						
5 years (-1986)	-	8	1	7	1	
	+	11	2.78 (1.02-7.60)*	12	2.4 (0.87-6.58) NS	
10 years (-1991)	-	22	1	15	1	
	+	20	3.66 (1.36-9.88)*	23	2.42 (1.20-4.87)*	
15 years (-1996)	-	31	1	23	1	
	+	28	3.34 (1.92-5.80)***	31	2.64 (1.48-4.71)**	
<i>Digestive diseases</i>						
5 years (-1986)	-	7	1	4	1	
	+	5	2.31 (0.66-8.15) NS	3	0.91 (0.19-4.48) NS	
10 years (-1991)	-	12	1	11	1	
	+	7	2.45 (0.88-6.80)*	10	1.62 (0.64-4.06) NS	
15 years (-1996)	-	17	1	18	1	
	+	8	2.6 (1.04-6.51)*	14	1.88 (0.89-3.99) NS	
<i>Nephritis and nephrosis</i>						
5 years (-1986)	-	0	-	1	-	-
	+	3	-	0	-	-
10 years (-1991)	-	4	1	2	1	
	+	5	3.29 (0.82-13.3)*	3	2.63 (0.39-17.8) NS	
15 years (-1996)	-	7	1	3	1	
	+	10	5.66 (2.01-16.0)**	8	7.31 (1.78-30.1)***	

β 2-MG(-), urinary β 2-microglobulin <1000 μ g/gCr; β 2-MG(+), urinary β 2-microglobulin $\geq$ 1000 μ g/gCr; NS, not significant.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

risk ratios of mortality from the major causes of death of the three groups with urinary β 2-MG $\geq$ 300 μ g/gCr were compared with the subjects with <300 μ g/gCr after adjustment for age group using Cox's proportional hazard model.

RESULTS

Among the subjects with urinary β 2-MG $\geq$ 1000 μ g/gCr, 140 men (68.3%) and 199 women (60.5%) died during the total 15 year observation period. The SMRs for all causes were 127 for men and 146 for women, with these values both being significantly higher than expected mortality (table 2). In contrast, the SMRs for all causes of the subjects with urinary β 2-MG <1000 μ g/gCr were significantly lower in both sexes, with decreases in mortality for almost of all special causes of death. These facts suggested big differences in mortality between the urinary β 2-MG $\geq$ 1000 μ g/gCr and <1000 μ g/gCr subjects (table 2). Although the SMR of the subjects with urinary β 2-MG $\geq$ 1000 μ g/gCr for total malignant neoplasms was higher only in women, the excess was not significant. The SMRs of the subjects with urinary β 2-MG $\geq$ 1000 μ g/gCr for oesophagus, lung, and breast cancer in women, were greater than 100, but were not significantly higher due to the small number of deaths (table 2).

The most frequent cause of death in men with urinary β 2-MG $\geq$ 1000 μ g/gCr was cerebrovascular diseases, for which excess of mortality was significantly higher. An excess of mortality for heart failure of borderline significance was also observed in men (table 2). In the women with urinary β 2-MG $\geq$ 1000 μ g/gCr, the most frequent cause of death was heart failure, at 46 deaths (23% of all deaths), for which the SMR was 248, with significant excess of mortality. Although the excess of mortality for total cardiovascular diseases in the women with urinary β 2-MG $\geq$ 1000 μ g/gCr was not significant, the excess of mortality for cerebral infarction was significant. Also, a significant increase in the SMR for digestive diseases was found in the women with urinary β 2-MG $\geq$ 1000 μ g/g (table 2). The SMR for nephritis and nephrosis was significantly higher in men, as well as the SMR for kidney and urinary diseases. In women with urinary β 2-MG $\geq$ 1000 μ g/gCr, the SMR for nephritis and nephrosis was 247, but this increase in SMR was not significant (table 2).

Changes in mortality for all causes and special causes for which excess of mortality was observed were then investigated. The mortality risks of subjects with urinary β 2-MG $\geq$ 1000 μ g/gCr over the first five years (from the baseline to

Table 4 Mortality risk ratios for the special causes of deaths in proportion to urinary β 2-MG concentration

β 2-MG	Men			Women		
	n	Obs	Hazard ratio (95% CI)	n	Obs	Hazard ratio (95% CI)
<i>Malignant neoplasms</i>						
<300	1005	86	1	1094	40	1
300–1000	207	17	0.79 (0.46–1.34)	327	19	1.46 (0.83–2.56)
1000–10000	161	21	1.21 (0.73–2.00)	242	21	2.15 (1.22–3.80)
≥ 10000	43	3	0.78 (0.24–2.52)	87	3	0.89 (0.26–3.03)
<i>Heart failure</i>						
<300	1005	29	1	1094	16	1
300–1000	207	9	0.88 (0.41–1.89)	327	25	1.94 (1.08–3.48)
1000–10000	161	14	1.45 (0.74–2.84)	242	26	3.05 (1.73–5.35)
≥ 10000	43	8	3.69 (1.62–8.39)	87	20	3.19 (1.19–5.52)
<i>Cerebral infarction</i>						
<300	1005	18	1	1094	12	1
300–1000	207	13	2.4 (1.15–4.98)	327	11	1.88 (0.82–4.29)
1000–10000	161	22	4.48 (2.29–8.78)	242	21	3.58 (1.71–7.51)
≥ 10000	43	6	5.36 (2.04–8.78)	87	10	3.19 (1.29–7.88)
<i>Digestive diseases</i>						
<300	1005	9	1	1094	10	1
300–1000	207	8	4.19 (1.57–11.2)	327	8	1.86 (0.72–4.78)
1000–10000	161	7	4.89 (1.69–14.1)	242	7	1.85 (0.67–5.09)
≥ 10000	43	1	2.99 (0.36–24.9)	87	7	3.97 (1.35–11.7)
<i>Nephritis and nephrosis</i>						
<300	1005	4	1	1094	1	1
300–1000	207	3	2.44 (0.53–11.2)	327	2	5.43 (0.48–61.5)
1000–10000	161	6	5.67 (1.47–12.8)	242	2	6.94 (0.59–81.7)
≥ 10000	43	4	18.15 (4.24–77.6)	87	6	54.98 (5.41–558.5)

β 2-MG, urinary β 2-microglobulin concentration ($\mu\text{g/gCr}$); n, number of subjects; Obs, observed number of deaths; 95% CI, 95% confidence interval.

1986), 10 years (from the baseline to 1991), and the total 15 years are shown in table 3. For all causes, the mortality risk ratios for the five year, 10 year, and 15 year observation periods of subjects with urinary β 2-MG $\geq 1000 \mu\text{g/gCr}$ were all significantly increased in both sexes compared with urinary β 2-MG < 1000 subjects. However, the risk ratios of the subjects with urinary β 2-MG $\geq 1000 \mu\text{g/gCr}$ decreased in men, and increased in women, as the observation period became longer, with the highest risk ratio being 1.83 for the five year observation in men, and 1.86 for the 15 year observation period in women (table 3).

For malignant neoplasms, no significant increase in mortality risk ratio was observed in any of the analyses of different observation periods for men. However, significantly higher mortality risk ratios for malignant neoplasms were observed for the five and 10 year observation periods in women. The mortality risk ratio for heart failure of the subjects with urinary β 2-MG $\geq 1000 \mu\text{g/gCr}$ was significantly higher for the 10 year and 15 year observation period in both sexes. For cerebral infarction, significant increases in the risk ratios of the subjects with urinary β 2-MG $\geq 1000 \mu\text{g/gCr}$ were found for all three observation periods in men, but were only noted in the 10 and 15 year observation periods in women (table 3). For the 15 year observation period, the risk ratios for digestive diseases of the subjects with urinary β 2-MG $\geq 1000 \mu\text{g/gCr}$ were significantly higher compared with β 2-MG < 1000 subjects, but only in men. The number of deaths due to nephritis and nephrosis over the five years to 1986 was so small that the risk ratio could not be computed for either

sex. However, a significantly increased mortality risk ratio in β 2-MG $\geq 1000 \mu\text{g/gCr}$ subjects was observed for the 15 year observation period, for both sexes (table 3).

To investigate the relationships between the degree of renal tubular dysfunction and mortality, we analysed the risk ratios of mortality over the 15 years due to the major causes of death of the subjects with 300–1000, 1000–10000, or $\geq 10000 \mu\text{g/gCr}$ urinary β 2-MG, with the hazard ratio of the subjects with $< 300 \mu\text{g/gCr}$ set at 1 (table 4). Geometrical means of urinary Cd in each category of urinary β 2-MG are shown in table 5. The risk ratio for malignant neoplasms was significantly increased only in the category of 1000–10000 $\mu\text{g/gCr}$ in women, and no increased mortality risk ratio in proportion to urinary β 2-MG was observed in either sex. For heart failure, the risk ratios of the 300–1000, 1000–10000, and $\geq 10000 \mu\text{g/gCr}$ categories were 1.94, 3.05, and 3.19, respectively, in women, whereas in men a significantly increased hazard ratio was found only in the highest concentration category. Significantly increased mortality risk ratios for cerebral infarction were found in all categories $\geq 300 \mu\text{g/gCr}$, compared with $< 300 \mu\text{g/gCr}$ in men, and for women, the 1000–10000 and $\geq 10000 \mu\text{g/gCr}$ categories were significantly related to mortality. In men, the risk ratio for digestive diseases was significantly increased in the 300–1000 and 1000–10000 $\mu\text{g/gCr}$ categories, but only in the $\geq 10000 \mu\text{g/gCr}$ category in women. For nephritis and nephrosis, the risk ratios increased with the increase in β 2-MG concentration, and a significant increase was observed in the 1000–10000, and $\geq 10000 \mu\text{g/gCr}$ categories. At this time in women, the risk ratio was significantly increased in the $\geq 10000 \mu\text{g/gCr}$ category.

Table 5 Geometrical means (geometrical standard deviation) of urinary Cd ($\mu\text{g/gCr}$)

β 2-MG ($\mu\text{g/gCr}$)	<300	300–1000	1000–10000	≥ 10000
Men	4.0 (1.8)	5.4 (1.8)	7.3 (1.9)	10.0 (1.7)
Women	6.2 (1.8)	7.6 (1.6)	10.2 (1.7)	12.7 (1.9)

DISCUSSION

In a 15 year follow up study of targeted participants in a 1974–75 health impact survey in Kakehashi River basin, we found increased SMRs for heart failure and kidney and urinary tract diseases, in particular nephritis and nephrosis of urinary RBP positive ($\geq 4 \text{ mg/l}$) subjects in both sexes.⁵ We also conducted a nine year follow up survey of subjects whose

urinary β 2-MG was examined in 1981–82, and found excess mortality from heart failure and cerebrovascular diseases in the subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$ in both sexes.⁴ In the present study, we confirmed the excess of mortality for heart failure and cardiovascular diseases in men, and heart failure and cerebral infarction in women with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$, and found significantly increased mortality risk for heart failure and cerebral infarction in the subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$, as compared with <1000 $\mu\text{g/gCr}$ subjects in both sexes during observation for more than 10 years. However, increased risk of mortality from cerebral infarction in men with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$ was observed early, even in the first five years before 1986. Moreover, increased mortality risk from cerebral infarction in men was found even in the urinary category with β 2-MG 300–1000 $\mu\text{g/gCr}$ during observation for 15 years. Therefore, the increase of mortality from cerebral infarction may contribute to the increase of mortality for men exposed to Cd.

Elliott *et al*¹⁸ extended to 1997 the follow up of the Shipham cohort in the UK analysed by Inskip *et al*,¹⁶ and reported an excess in mortality from hypertension and cerebrovascular diseases of borderline significance; however they were unable to find excess mortality from cerebrovascular disease in their geographical study. The apparent discrepancy between their results and those of the present study may be due to the difference in risk factors of cardiovascular disease of the subjects, as the SMRs from hypertensive diseases and cerebral hemorrhage strongly related to hypertension were low in our subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$. Staessen *et al* reviewed epidemiological studies targeting inhabitants environmentally exposed to Cd in Belgium, but also found no excess mortality for cardiovascular disease.¹⁹ Recently, Navas-Acien *et al* reported an association between blood and urinary Cd and peripheral arterial diseases based on the results of the general population examined in the 1999–2000 National Health and Nutritional Survey (NHANES) in the USA.^{20–21} However, the maximum level of urinary Cd of their subjects was under 1.5 $\mu\text{g/gCr}$, a much lower level than the urinary Cd in the β 2-MG <300 $\mu\text{g/gCr}$ subjects, of which geometrical mean was 4.0 $\mu\text{g/gCr}$ for men and 6.2 $\mu\text{g/gCr}$ for women in the present study.

Ever since Lauwerys and De Wals suggested high mortality from renal disease was caused by exposure to environmental Cd in Belgium,¹⁴ increased mortality from renal disease in patients with renal tubular dysfunction has been of huge concern among inhabitants living in Cd polluted areas. In the present study, increased mortality from nephritis and nephrosis, which in the ICD-9 is included in renal diseases in addition to renal failure, was observed after 10 years in men with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$, and became statistically significant with a high risk ratio for the 15 year observation period. In women, a significantly higher risk ratio of mortality was identified, particularly in the subjects in the highest β 2-MG category, ≥ 10000 $\mu\text{g/gCr}$, for the 15 year observation period. This late development of increased mortality, occurring 10 years after the restoration of the paddy fields, suggests that Cd stored in the body affects the health of residents even after Cd intake appears to markedly decrease. In a 15 year follow up survey from 1974–75 to 1990 in this area, we found excess mortality from nephritis and nephrosis in urinary RBP positive subjects, including severe renal tubular dysfunction cases, more frequently than in subjects with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$.⁵ Elliott *et al* also reported excess mortality from urogenital diseases of borderline significance in Shipham residents, which might be associated with nephritis and nephrosis, as they were unable to categorise the diagnoses due to changes in the ICD classifications over the last

60 years.¹⁸ Moreover, in nickel-cadmium battery workers exposed to Cd hydroxide dust and followed for the period from 1947 to 2000, Sorahan *et al* reported significantly increased SMR for the genitourinary system and suggested the late effects of kidney damage.²²

Although an excess of mortality for digestive diseases was significant in women, and not significant in men with urinary β 2-MG ≥ 1000 $\mu\text{g/gCr}$, significant increases in mortality risk ratios of β 2-MG ≥ 1000 $\mu\text{g/gCr}$ subjects, as compared with β 2-MG <1000 subjects, were observed in men and not in women. In addition, the increase of mortality risk ratio in proportion to urinary β 2-MG was not clear in men. We need longer follow up for a greater number of deaths to reach conclusions on the effects on mortality from digestive diseases.

Among industrial workers exposed to Cd at a higher level than that of the general population in European countries, several studies on mortality have documented excess deaths from prostate and lung cancer.^{10–13} However, Verougstraete *et al* reviewed a cohort of workers exposed to Cd and observations of tumours in animals caused by Cd compounds, and found no clear evidence of increased risk of lung or prostate cancer.²³ Sorahan *et al* investigated mortality for lung cancer in nickel-cadmium battery workers exposed to Cd, but were unable to detect a significant increase in the SMR and positive relationships between estimated cumulative Cd exposure and lung cancer risks.²² In the present study, as well as our previous nine year follow up study,⁴ no significant increases were observed in the SMRs for lung cancer and prostate cancer of urinary β 2-MG positive subjects, and nor for other malignant diseases. However, a comparison of mortality between β 2-MG ≥ 1000 $\mu\text{g/gCr}$ and <1000 $\mu\text{g/gCr}$ subjects revealed that the risk of mortality from malignant neoplasms, including oesophagus and breast cancer, was increased in the five and 10 year observation periods in women, but not in men. Thus, cancer mortality might have been affected by Cd exposure during the relatively early period of exposure, especially that from oesophagus and breast in women. Quite recently, in Belgian residents environmentally exposed to airborne Cd which zinc smelter emitted in past for around 100 years, Nawrot *et al* reported the association between lung cancer risk and Cd exposure.¹⁵ They suggested that Cd exposure by aspiration of house dust with particles contaminated by Cd in soil caused by past emissions might be related to the increase of lung cancer. By contrast, Cd exposure of the residents in the present study was caused by contaminated water and food due to outflow containing Cd from a mining site into a river irrigating a residential area. The difference of exposure between residents of the Belgium study and our study might be the cause of inconsistent results of lung cancer risk. Moreover, Nawrot *et al* targeted younger subjects (19–49 years old) than ours, and investigated not only dead cases but also non-fatal cases. Therefore, a future study on cancer incidence will be necessary among the residents in our area as well as mortality of a bigger cohort including younger residents, particularly women.

CONCLUSION

The prognosis of inhabitants with renal tubular dysfunction induced by Cd is unfavourable, with higher mortality rates due to heart failure and cerebrovascular infarction—despite rice paddy restoration being completed many years previously. An increase in mortality from renal disease was observed in subjects with severe renal tubular dysfunction. Increased mortality in women from cancer appeared to occur only in the early periods of the study, when contamination was ongoing.

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