Int Arch Occup Environ Health (2012) 85:941–950
DOI 10.1007/s00420-012-0734-z

ORIGINAL ARTICLE

Variation in benchmark dose (BMD) and the 95% lower confidence limit of benchmark dose (BMDL) among general Japanese populations with no anthropogenic exposure to cadmium

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Received: 22 February 2011 / Accepted: 6 January 2012 / Published online: 24 January 2012

Abstract
Background The use of benchmark dose (BMD) and the 95% lower confidence limit of benchmark dose (BMDL) have been gaining popularity not only in experimental studies but also in epidemiological studies including those on toxicology of cadmium (Cd), a ubiquitous hazardous element in the environment. However, the reproducibility of BMD and BMDL values has seldom been examined.
Objectives This study was initiated to determine whether consistent BMD and BMDL values are obtained for similar non-exposed populations, i.e., the populations with no anthropogenic exposure to Cd in a single nation of Japan.
Methods Cd (an exposure marker), α_1-microglobulin (α_1-MG), β_2-microglobulin (β_2-MG) and N-acetyl-β-D-glucosaminidase (NAG) (three effect markers of tubular dysfunction) levels in the urine of adult Japanese women from five previous publications of this study group were examined. Overall, data were available for 17,375 cases (in 16 prefectures) regarding Cd, α_1-MG and β_2-MG, and 6,409 cases (in ten prefectures) regarding NAG. The data were used to calculate BMD and BMDL values taking advantage of the hybrid approach (Budtz-Jørgensen et al. in Biometrics 57:698–706, 2001). It was possible to calculate BMD and BMDL values for α_1-MG and β_2-MG for all of the 16 prefectures with 17,375 cases, whereas the values for NAG were successfully calculated for nine prefectures with 5,843 cases.
Results The application gave BMD values of 1.92, 2.46 and 2.32 μg Cd/g cr for α_1-MG, β_2-MG and NAG, respectively, and BMDL values of 1.83, 2.32 and 2.09 μg Cd/g cr. Large inter-prefectural variations were observed in the BMD and BMDL; there was about fourfold difference both in BMD and in BMDL calculated for α_1-MG and β_2-MG in 16 prefectures, and the variation was greater (i.e., by about sevenfold) in BMD and BMDL for NAG in nine prefectures. A survey of relevant literature revealed variation in BMD and BMDL values of similar folds as observed in the present analyses in five studies of Japanese populations. Multiple regression analyses taking BMD or BMDL as a dependent variable and age, CR concentration and Cd concentration as independent variables showed both BMD and BMDL were significantly influenced by Cd concentration in cases of α_1-MG and β_2-MG, whereas BMD and BMDL for NAG was by CR.
Conclusions Even when the analysis was conducted in a single nation, both BMD and BMDL for the Cd effect markers varied by ca. fourfold when examining α_1-MG or β_2-MG and the values varied by ca. sevenfold for NAG among Cd-non-exposed populations. The most influential factors in the study population may include urine density and Cd levels in the urine.

Keywords Biological monitoring · Benchmark dose · The 95% lower confidence limit of benchmark dose · Cadmium · Japanese women · Urine

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Introduction

The benchmark dose (BMD) approach [including the use of the 95% lower confidence limit of benchmark dose (BMDL)] has gained popularity as a tool for estimating no-effect level in hazard associated with non-cancer responses (Bailer et al. 1997; Crump 2002; Filipsson et al. 2003; Slob et al. 2005; Muri et al. 2009). The application of these methods to epidemiological data has also been recommended (Bailer et al. 1997; Budtz-Jørgensen et al. 2001; Morales and Ryan 2005; Sand et al. 2006).

The application has been expanded from metal toxicology in environmental health [e.g., organic mercury on the central nervous system development (van Wijngaarden et al. 2006), cadmium on renal tubular dysfunction (as to be reviewed in the "Discussion" section), on pancreatic function (Lei et al. 2007) and on osteoporosis (Suwazono et al. 2010a)] to occupational health issues, for example, effects of lead on haematopoiesis (Murata et al. 2003; Karita et al. 2005) and manganese on Parkinsonian syndrome (Park et al. 2006; Santamaria and Sulsky 2010).

The methods have been used also in studies on lifestyle-related factors, such as alcohol consumptions on liver function (Dakeishi et al. 2004, 2006) and working hours on mental and physical fatigue symptoms (Suwazono et al. 2007). Recently, the European Food Safety Authority (2009a, b) employed BMD approach to issue an opinion regarding Cd levels in foods. However, the number of groups of populations analyzed in each of these studies was generally limited, and the stability or reproducibility of the BMD and BMDL values was seldom examined, leading to questions regarding whether the application of the BMD and BMDL methods to similar populations would give consistent values.

For the present study, data were available on Cd and the tubular effect marker levels in urine from more than 17,000 adult women in non-polluted areas in 16 prefectures in Japan. The present study was initiated to investigate whether consistent BMD and BMDL values would be obtained when the same procedures for BMD and BMDL calculation were applied to multiple but similar groups of people who lived in Cd-non-polluted areas in Japan with no occupational exposure to Cd.

Materials and methods

Ethical issues

The study protocol for the BMD and BMDL analyses was approved by the Ethics Committee of the Kyoto Industrial Health Association, Kyoto, Japan. Each of the participating women provided informed consent in writing at the time of each survey.

Data sources and methods of urinalyses

Urine samples were collected from 17,468 adult women in Cd-non-polluted areas in 16 prefectures (Prefectures 1, 2, 4, 5, 6, 14, 15, 16, 17, 18, 20, 26, 34, 39, 40 and 47; see Fig. 1 for locations) all over Japan from the northern-most Prefecture 1 to the southern-most Prefecture 47. Japan is divided into 47 prefectures, primarily by watershed mountain ranges, rivers or seas (see Fig. 1).

For the present study, the data were cited from the six previous publications of Ezaki et al. (2003a), Tsukahara et al. (2003) for Prefectures 1, 4, 14, 15, 20, 26, 34, 39, 40 and 47, Moriguchi et al. (2005a, 2010) for Prefectures 5, 6 and 17, Yamagami et al. (2006) for Prefecture 16 and Ikeda et al. (2011) for Prefectures 2 and 18.

Urine samples were analyzed for Cd, the three renal tubular dysfunction markers of α_1-microglobulin (α_1-MG), β_2-microglobulin (β_2-MG), and N-acetyl-β-D-glucosaminidase (NAG), and creatinine (CR) by graphite furnace atomic absorption spectrometry [0.5 μg/l as the material limit of determination (LOD) for Cd], latex methods (0.6 mg/l for α_1-MG and 1.0 μg/l for β_2-MG,), a NAG test kit from Shionogi Pharmaceuticals, Osaka, Japan (0.01 unit/l for

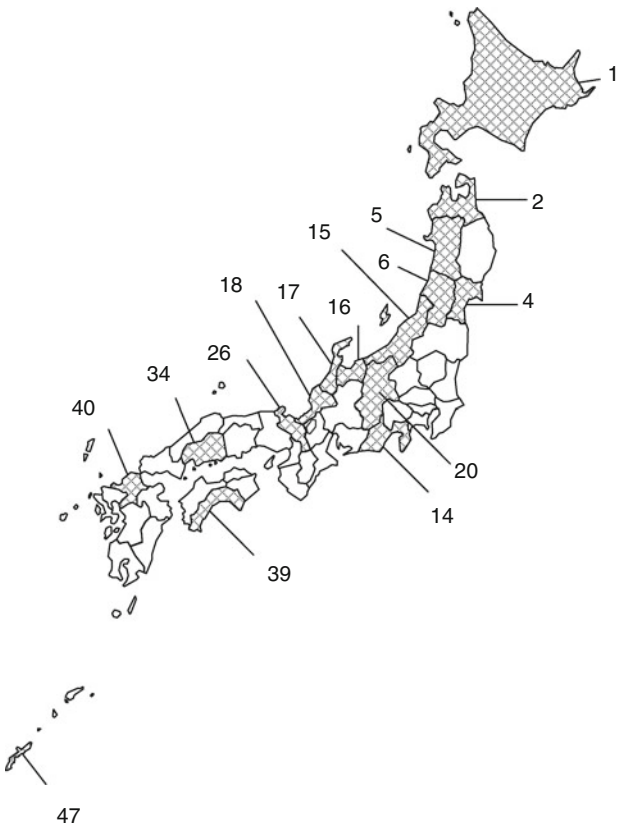

Fig. 1 The locations of the sixteen prefectures where urine samples were collected. The sixteen prefectures of urine sample collection are shown with *shades*. The numbers correspond to the numbers in Table 2. Note that Japan consists of 47 prefectures in total

NAG) and a clinical auto-analyzer method (0.05 mg/l for CR), respectively. The analyses were conducted using the same methods throughout all studies. The results were corrected for CR concentration (Jackson 1966). The quality of Cd determination was certified by Round Robin (German Society of Occupational Medicine and Environmental Medicine, 2001–2009). The qualities of other assays were approved by Japan Medical Association (2001–2009) (Ezaki et al. 2003a, b; Moriguchi et al. 2010).

BMD and BMDL calculations

The hybrid approach by Budtz-Jørgensen et al. (2001) was employed. BMR = 5%, and BMD_{05} and $BMDL_{05}$ (rather than BMD_{10} and $BMDL_{10}$) were used; hereafter, BMD_{05} and $BMDL_{05}$ are described as BMD and BMDL, respectively, unless otherwise specified.

α_1-MG, β_2-MG and NAG were introduced after logarithmic conversion for quasi-normal distribution of the response parameters (van Wijngaarden et al. 2006). For the present study, 93 cases with β_2-MG $\geq$ 1,000 μg/g cr (Ezaki et al. 2003b; Bernard 2008) were deleted, and α_1-MG and β_2-MG data were available for the 17,375 cases in 16 prefectures (to be called 'the total prefecture database'). NAG was measured in 6,409 cases. Nevertheless, preliminary analyses for BMD and BMDL revealed that dose–response relationship was not significant ($p > 0.05$) in Pref. 16 (as to be detailed in the "Results" section), and 566 cases in the prefecture were excluded in further analyses so that 5,843 cases in 9 prefectures were employed as 'the selected prefecture database' with complete sets of three effect markers of α_1-MG, β_2-MG and NAG (Table 1).

Distribution patterns and statistical analysis

Age and CR were distributed normally. A log-normal distribution was assumed for Cd, α_1-MG, β_2-MG and NAG. Accordingly, the distributions of age and CR were presented as arithmetic means and arithmetic standard deviations (i.e., AM ± ASD), whereas the Cd, α_1-MG, β_2-MG and NAG data were presented as geometric means and geometric standard deviations [GM (GSD)]. In calculating GM and GSD, the value below the corresponding LOD was assumed to be half the LOD.

Wilcoxon test and Spearman rank correlation analysis were employed when an assumption of a normal distribution was not applicable to the parameter distribution. Multiple regression analysis was also used. In evaluating correlation coefficients, a value of 0.2 was selected as a cut-off to identify the significance when the number was >100 (Ezaki et al. 2003a).

Results

Populations surveyed

The basic parameters are presented in Table 1 for individual prefectures and the total study population (Table 1) in terms of means (AMs or GMs) and standard deviations (ASDs or GSDs) for age, CR (as a urine density marker), Cd (as an exposure marker), and α_1-MG, β_2-MG and NAG (as the three effect markers). As NAG was measured only in selected prefectures, the numbers of available cases for NAG are shown separately from the numbers of the parameters other than NAG. The parameters are presented for the total prefecture database and for the selected prefecture database ('A' and 'B' in Table 1).

When the total prefecture database was taken as an example, the number of cases by prefecture was not uniform, distributing in a broad range from 650 (Prefecture 16) to 3,081 cases (Prefecture 26). In examining NAG, the fewest cases were observed in Prefecture 4 (104 cases), and the most abundant cases (1,789 cases) were in Prefecture 26. The lowest and highest levels of the exposure marker, Cd, were 0.79 and 2.67 μg/g cr as GM, respectively, with >3-fold difference. The grand GM was 1.34 μg/g cr. Prefectural GM values for α_1-MG, β_2-MG and NAG were distributed in relatively narrow ranges with the minimum and the maximum of 2.06–3.12 mg/g cr for α_1-MG, 94–133 μg/g cr for β_2-MG and 2.89–4.17 units/g cr for NAG. The GSDs by prefecture were mostly <2, but the GSD for NAG was up to 3 in four prefectures out of ten studied.

BMD and BMDL by prefectures

The calculation for BMD and BMDL values was possible for α_1-MG and β_2-MG in all prefectures in the total prefecture database (Table 2). In cases of NAG BMD and BMDL, calculation was not possible in 6 prefectures as no data were available (Table 1). In addition, the calculation results were not reliable in Pref. 16 due to poor dose–response relationship with $p > 0.05$ for the regression coefficient. Thus, the values were available for 9 prefectures with 5,843 cases (the selected prefecture database). BMD and BMDL for α_1-MG and β_2-MG were recalculated for the selected prefectures in parallel with NAG (Table 3).

The BMD and BMDL for the total study population of 17,375 cases were 1.92 and 1.83 μg Cd/g cr, respectively, for α_1-MG, 2.46 and 2.32 μg Cd/g cr for β_2-MG (Table 2). There were variations in the calculated BMD and BMDL values for α_1-MG and β_2-MG among 16 prefectures. For example, the minimum and the maximum BMD were 0.78 and 3.18 μg Cd/g cr, respectively, for α_1-MG, and 1.05 and 4.82 μg Cd/g cr, respectively, for β_2-MG. Similar

Table 1 Basic parameters by prefectures

Prefecture No.[a]	No. of cases studied		Age (AM) (years)		Creatinine (AM) (g/l)		Cd (GM) (μg/g cr)		α_1-MG (GM) (mg/g cr)		β_2-MG (GM) (μg/g cr)		NAG (GM) (units/g cr)
	No.[b]	No.[c]	A[d]	B[e]	A[d]	B[e]	A[d]	B[e]	A[d]	B[e]	A[d]	B[e]	
1	927	0	46.2		1.23		1.22		2.48		102		NC[f]
2	694	694	49.1	49.1	1.04	1.04	1.13	1.13	2.58	2.58	97	97	3.37
4	1,119	104	47.0	44.3	1.05	1.09	1.35	1.03	2.70	2.69	121	128	3.10
5	716	716	52.3	52.3	1.05	1.05	2.10	2.10	3.07	3.07	113	113	3.91
6	728	728	47.7	47.7	1.09	1.09	1.19	1.19	2.30	2.30	106	106	3.44
14	1,034	0	50.1		0.83		1.37		2.06		115		NC[f]
15	1,212	185	49.2	35.2	0.99	1.15	2.67	1.10	2.77	1.82	123	103	3.06
16	650	566	39.6	39.8	1.12	1.13	1.98	1.98	2.40	2.40	103	104	2.90
17	701	701	44.9	44.9	1.17	1.17	1.76	1.76	2.52	2.52	94	94	3.49
18	699	699	43.7	43.7	0.97	0.97	0.94	0.94	2.58	2.58	99	99	3.44
20	1,317	0	46.8		1.03		0.98		2.48		113		NC[f]
26	3,081	1,789	55.1	59.4	0.91	0.89	1.69	1.85	3.12	3.18	133	142	4.17
34	1,129	0	48.7		0.97		1.11		2.22		121		NC[f]
39	1,099	0	47.1		1.20		0.96		2.78		102		NC[f]
40	1,039	0	46.4		1.24		1.14		2.60		105		NC[f]
47	1,230	227	48.3	47.9	0.94	0.90	0.79	0.96	2.08	2.22	114	118	4.17
Total	17,375	6,409[e]	48.7	49.8	1.03	1.02	1.34	1.50	2.58	2.69	114	113	3.63
No. of pref.	16	10	16	16	16	16	16	16	16	16	16	16	10
Min.	650	0	39.6	35.2	0.83	0.90	0.79	0.94	2.06	1.82	94	94	2.89
Max.	3,081	1,789	55.1	59.4	3.83	1.85	2.67	2.10	3.12	3.18	133	142	4.17

[a] Prefecture number for identification (for locations, see Fig. 1)

[b] For α_1-MG and β_2-MG in the prefecture

[c] For NAG in the prefecture

[d] Including cases with no NAG values

[e] Cases with all of α_1-MG, β_2-MG and NAG

[f] Not calculable

variations were observed also in BMDL values for α_1-MG and β_2-MG.

With regard to BMD and BMDL for NAG (Table 3), the values for a total of 5,843 cases in 9 prefectures were 2.32 and 2.09 μg Cd/g cr, respectively. Although the number of prefectures available for NAG BMD and BMDL calculation was limited to nine, the BMD and BMDL values for each of the nine prefectures distributed in a range of 0.70–4.98 μg Cd/g cr for BMD, and 0.53–3.50 μg Cd/g cr for BMDL.

Comparison on BMD and BMDL values for effect markers

Comparison of 16 BMDs for α_1-MG and β_2-MG (Table 2) by Wilcoxon test indicated a significant difference ($p = 0.013$) among the BMDs of the two effect markers. A similar comparison of BMDL values also showed a significant difference ($p = 0.013$). A further comparison of the three pairs of α_1-MG and β_2-MG, α_1-MG and NAG, and β_2-MG and NAG (Table 3), however, detected no significant differences ($p > 0.05$) in any pairs. The absence of the significant differences may be due to limited number ($n = 9$) of available prefectures (Table 3).

Factors possibly influencing BMD or BMDL

In a preliminary analysis, correlation of age (AM in years), CR (AM in g/l) and Cd (GM in μg/g cr) with BMD and BMDL for α_1-MG, β_2-MG and NAG was examined by calculating Spearman rank correlation coefficient. Cd correlated significantly ($p < 0.01$–0.05) with all of BMD and BMDL for α_1-MG, β_2-MG and NAG. In contrast, age and CR did not show significant correlation ($p > 0.05$) with any of BMD or BMDL for the three markers.

Subsequently, multiple regression analyses were conducted taking one of the BMD or BMDL for α_1-MG, β_2-MG or NAG as a dependent variable, and age, CR and

Table 2 BMD and BMDL values[a] for α_1-MG and β_2-MG calculated for 16 prefectures

Pref. No.	No. of cases studied[b]	α_1-MG		β_2-MG	
		BMD	BMDL	BMD	BMDL
1	927	1.08	0.92	1.20	1.01
2	694	2.02	1.47	2.90	1.89
4	1,119	2.17	1.73	2.43	1.90
5	716	2.51	1.97	3.00	2.26
6	728	1.05	0.89	1.20	1.00
14	1,034	1.20	1.03	1.35	1.14
15	1,212	3.18	2.70	4.82	3.82
16	650	1.65	1.42	2.73	2.18
17	701	1.41	1.20	1.69	1.40
18	699	0.78	0.66	1.05	0.86
20	1,317	0.98	0.84	1.41	1.14
26	3,081	2.02	1.78	2.14	1.87
34	1,129	1.34	1.12	1.96	1.53
39	1,099	1.42	1.15	1.50	1.20
40	1,039	1.40	1.13	1.86	1.41
47	1,230	1.38	1.10	1.17	0.96
Total[c]	17,375	1.92	1.83	2.46	2.32
Median		1.40	1.14	1.77	1.40
Minimum		0.78	0.66	1.05	0.86
Maximum		3.18	2.70	4.82	3.82

A significant ($p < 0.05$) difference was observed in BMD and in BMDL between α_1-MG and β_2-MG when examined by Wilcoxon test

[a] In μg/g cr

[b] Including those with no NAG values

[c] For a total of the 16 prefectures

Cd as independent variables (thus calculation of 6 cases). In all of the 6 cases examined (Table 4), the regression coefficient (r) was significant ($p < 0.01$) with R^2 of 0.74–0.96. Among the three independent variables, Cd correlated significantly ($p < 0.01$–0.05) with BMD and BMDL of both α_1-MG and β_2-MG. In addition, significant correlations of age with BMD and BMDL of α_1-MG were observed. In case of NAG, CR showed significant ($p < 0.01$) correlations with both BMD and BMDL.

Discussion

The analysis of 17,375 urine samples from non-exposed adult women for α_1-MG and β_2-MG and 5,843 cases for NAG followed by application of the hybrid approach resulted in calculated BMD values of 1.92, 2.46 and 2.32 μg Cd/g cr for α_1-MG, β_2-MG and NAG, respectively, with the corresponding BMDL values of 1.83, 2.32 and 2.09 μg Cd/g cr (Tables 2, 3). Substantial variations were observed in BMD and BMDL values among prefectures. There was 4.1-fold to 4.6-fold difference in the BMD and BMDL values between the minimum and the maximum for prefectures when they were calculated for α_1-MG and β_2-MG in 16 prefectures, and the variation was even greater (i.e., 6.6-fold to 7.1-fold) for NAG in nine prefectures (Tables 2, 3). Attempts to identify BMD- and BMDL-influencing factors indicated that Cd levels in urine were most influential to BMD and BMDL of α_1-MG and β_2-MG among age, average urine density (in terms of the CR level in the urine) and the Cd concentration (Table 4), but none of them affected both BMD an BMDL of all of the three effect markers. Previously, Kobayashi et al. (2008) observed age-dependent decrease in BMD and BMDL values for β_2-MG. It was not possible in the present analyses to observe such effects (Table 4).

To compare the present study results with the values in literature, studies were sorted for BMD and BMDL values of effect markers among the populations exposed to Cd either occupationally or environmentally, or among the populations with no anthropogenic exposures to Cd. Table 5 summarizes the results of the literature review along with the relevant results of the present study at the top of the table.

Five studies (Kobayashi et al. 2006a, b, 2008; Shimizu et al. 2006; Uno et al. 2005) out of ten (the studies mentioned above plus Hong et al. 2004; Jin et al. 2004; Chen et al. 2006; Shao et al. 2007) studied Japanese populations. α_1-MG was examined in one study (Suwazono et al. 2006), whereas β_2-MG and NAG were measured in 15 and 12 groups of people, respectively. An examination of the reported BMD and BMDL values clearly indicates that the use of the 84% cut-off always gives smaller values than the 97.5% cut-off, as expected. Of particular interest is the range of reported BMD and BMDL values for each of the three effect markers. When studies on Japanese women (with 84% cut-off) were selected to ensure similarity in lifestyles with cases of the present study, the literature BMD and BMDL values for β_2-MG were in ranges of 0.9–3.8 and 0.7–3.2 μg Cd/g cr, respectively, and the values were 0.8–4.7 and 0.6–3.7 μg Cd/g cr for NAG (Table 5). Thus, the minimum and the maximum values reported differ by four to sixfold for BMD and BMDL of β_2-MG and NAG, respectively (the bottom of Table 5). The observation suggests that the variations reported in literature were apparently similar to what was observed in the present study (Tables 2, 3). A similar within-Japan variation was reported in a recent review of four studies in Japan, and one study each in China and Sweden (Suwazono et al. 2010b). As for the potential modifier for BMD and BMDL values, the present analyses suggest that Cd in urine affects BMD and BMDL of both α_1-MG and β_2-MG, age influences BMD and BMDL of α_1-MG and β_2-MG and CR those of NAG (Table 4).

Table 3 BMD and BMDL values[a] for α_1-MG, β_2-MG and NAG calculated for selected nine prefectures[b]

Pref. No.	No. of cases studied[c]	α_1-MG		β_2-MG		NAG	
		BMD	BMDL	BMD	BMDL	BMD	BMDL
2	694	2.02	1.47	2.90	1.89	1.46	1.14
4	104	1.46	0.88	1.32	0.82	1.89	1.02
5	716	2.51	1.97	3.00	2.26	2.04	1.67
6	728	1.05	0.89	1.20	1.00	1.16	0.97
15	185	1.55	1.08	1.65	1.13	2.15	1.35
17	701	1.41	1.20	1.69	1.40	1.47	1.24
18	699	0.78	0.66	1.05	0.86	0.76	0.65
26	1,789	1.63	1.43	1.71	1.49	4.98	3.50
47	227	1.18	0.77	0.82	0.59	0.70	0.53
Total[d]	5,843	1.49	1.39	1.75	1.62	2.32	2.09
Median		1.46	1.08	1.65	1.13	1.47	1.14
Minimum		0.78	0.66	0.82	0.59	0.70	0.53
Maximum		2.51	1.97	3.00	2.26	4.98	3.50

A significant ($p < 0.05$) difference was observed in BMD and in BMDL between α_1-MG and β_2-MG when examined by Wilcoxon test

[a] In μg Cd/g cr

[b] Pref. 16 was deleted because p for the regression coefficients for NAG was >0.05 and thus BMD (28.5) and BMDL values (7.6) were considered not reliable

[c] Only those for which all of α_1-MG, β_2-MG and NAG values were available

[d] For a total of the 9 prefectures

Table 4 Multiple regression analyses

Dependent variable	Independent variables						R^2	r	p for r
	Age		CR		Cd				
	SRC	p	SRC	p	SRC	p			
α_1-MG[a]									
BMD	0.33	*	0.27	ns	0.56	*	0.74	0.86	**
BMDL	0.31	*	0.28	ns	0.60	**	0.82	0.91	**
β_2-MG[a]									
BMD	0.10	ns	0.39	ns	0.55	*	0.76	0.87	**
BMDL	0.10	ns	0.39	*	0.60	**	0.85	0.92	**
NAG[b]									
BMD	−0.01	ns	0.93	**	0.09	ns	0.93	0.96	**
BMDL	0.08	ns	0.83	**	0.20	ns	0.96	0.98	**

Multiple regression analyses were conducted taking one of BMD or BMDL for α_1-MG, β_2-MG or NAG as a dependent variable and age (years), creatinine (CR; g/l) and cadmium (Cd; μg/g cr) as three independent variables

SRC standardized regression coefficient

**, * and ns for $p < 0.01$, $p < 0.05$ and $p \geq 0.05$, respectively

[a] Calculated with data on 16 prefectures (Table 2)

[b] Calculated with data on nine prefectures (Table 3)

It is of practical interest to identify an effect marker that gives the lowest BMD and BMDL among the three effect markers studied. The present analysis indicated that BMD and BMDL for α_1-MG appeared to be lower than the values for and β_2-MG when the total prefecture database was employed (Table 2). However, comparison of NAG with α_1-MG and β_2-MG by use of the selected prefecture database failed to identify any superior marker. Nevertheless, higher sensitivity for α_1-MG in comparison with β_2-MG is consistent with the previous observations by this study group (Moriguchi et al. 2004, 2005b) on better sensitivity of α_1-MG than β_2-MG as an indicator of Cd-induced

Table 5 BMD and BMDL values reported in literature

Population				Parameter in urine						The model; the values indicate cut-off either in % or in creatinine concentration
Reference	No. of cases	Age range (years)	Cd–U_{cr} (GM)[a]	α_1-MG[b]		β_2-MG[c]		NAG[d]		
				BMD^{e}_{05}	$BMDL^{e}_{05}$	BMD^{e}_{05}	$BMDL^{e}_{05}$	BMD^{e}_{05}	$BMDL^{e}_{05}$	
The present study	17,375	48.7 ± 10.1[f]	1.34	1.92	1.83	2.46	2.32			Quantal linear model (For details of database, see Table 2); 95%
	5,843	50.7 ± 12.5	1.46	1.62	1.51	1.97	1.82	3.26	2.88	Quantal linear model (For details of database, see Table 3); 95%
Occupationally exposed										
Chen et al. (2006)	85 exposed + 29 non-exposed	Unknown	1.14[g]–3.53[g]			4.6[h]	3.6[h]	3.6[h]	2.7[h]	Logistic model
Shao et al. (2007)	150 exposed + 46 non-exposed	Unknown	Up to >10[i] (the range)			4.9[h]	3.6[h]	2.9[h]	2.1[h]	Logistic model; 360 μg/g cr for β_2-MG and 9.4 units/g cr for NAG
Ibid.	58 exposed + 101 non-exposed	Unknown	Up to >20[i] (the range)			5.1[h]	4.2[h]	3.2[h]	2.6[h]	Logistic model; 500 μg/g cr for β_2-MG and 12.0 units/g cr for NAG
Environmentally exposed										
Hong et al. (2004)	122 exposed + 123 non-exposed	Unknown	Up to >18[i] (the range)			8.4[h]	7.3[h]	6.7[h]	5.9[h]	Probit model; Co-exposed to cadmium and arsenic; arsenic exposure by use of arsenic-rich coal
Jin et al. (2004)	790 residents of both sexes	Unknown	Up to >20[i] (the range)			8.4	7.3	6.7	5.9	Logistic model
Kobayashi et al. (2008)	2,578 men	50–70+	3.0			3.0[j]	2.7[j]			Logistic model; 84%
						4.9[j]	4.5[j]			Logistic model; 97.5%
	3,454 women	50–70+	4.2			3.4[j]	3.2[j]			Logistic model; 84%
						5.9[j]	5.6[j]			Logistic model; 97.5%
										Those in Cd-polluted and non-polluted areas
Shimizu et al. (2006)	1,527 men	50–80+	Up to ≤12.0[i]			3.7	2.9			Log-logistic model; 84%
						4.8	3.9			Log-logistic model; 97.5%
	1,865 women	50–80+	Up to ≤15.0[i]			2.6	1.5			Log-logistic model; 84%
						4.4	3.2			Log-logistic model; 97.5%
Non-exposed										
Kobayashi et al. (2006a)	1,114 men	50–80+	Up to ≥7[i]			2.9	2.4	4.8	3.3	Log-logistic model; 84%
						6.4	4.5	12.0	7.7	Log-logistic model; 97.5%
	1,664 women	50–80+	Up to ≥7[i]			3.8	3.3	4.7	3.7	Log-logistic model; 84%
						8.7	7.3	10.8	8.5	Log-logistic model; 97.5%
Kobayashi et al. (2006b)	547 men	50–80+	Up to ≥7[i]			2.6	2.0	3.6	2.5	Logistic model; 84%
	723 women	50–80+	Up to ≥7[i]			1.9	1.6	3.1	2.2	Logistic model; 84%

Table 5 continued

Population				Parameter in urine						The model; the values indicate cut-off either in % or in creatinine concentration
Reference	No. of cases	Age range (years)	Cd–U_{cr} (GM)[a]	α_1-MG[b]		β_2-MG[c]		NAG[d]		
				BMD^{e}_{05}	$BMDL^{e}_{05}$	BMD^{e}_{05}	$BMDL^{e}_{05}$	BMD^{e}_{05}	$BMDL^{e}_{05}$	
Suwazono et al. (2006)	820 women	53–64	0.76 ± 0.42[k]	0.63	0.49			0.64	0.5	Logistic model; 3.6 unit NAG/g cr
Uno et al. (2005)	410 men	40–59	0.8[l]			0.5	0.4	0.3	0.3	Quantal linear model; 84%
	418 women	40–59	1.8[l]			0.9	0.7	0.8	0.6	Quantal linear model; 84%
Japanese women (with 84% cut-off) only[m]										
Min.						0.9	0.7	0.8	0.6	
Max.						3.8	3.2	4.7	3.7	

[a] Geometric mean (arithmetic mean ± arithmetic standard deviation (μg/g cr))

[b] α_1-MG; α_1-microglobulin (mg/g cr)

[c] β_2-MG; β_2-microglobulin (μg/g cr)

[d] NAG; N-acetyl-β-D-glucosaminidase (unit/g cr)

[e] Values are in the unit of μg Cd/g cr in urine

[f] Arithmetic mean ± arithmetic standard deviation (years)

[g] Non-exposed non-smokers (1.14 μg/g cr) and exposed smokers (3.53 μg/g cr)

[h] BMD_{10} and $BMDL_{10}$, respectively

[i] Individual values

[j] Both BMD and BMDL values decreased as a reverse function of age

[k] Arithmetic mean ± arithmetic standard deviation (μg/g cr)

[l] Median

[m] Kobayashi et al. (2006a, b, 2008); Shimizu et al. (2006); Uno et al. (2005)

effects on the renal tubules. Overall, published data on α_1-MG-based BMD and BMDL values are still limited (Table 5) to examine whether α_1-MG is the best marker of Cd-induced health effects.

An overall evaluation of the results of the present analysis in combination with findings in the literature suggests that both BMD and BMDL values vary substantially depending on the populations studied. Such was the case even when all data are from non-exposed adult women in a single nation.

Acknowledgments The authors are grateful to the administration and staff of the Kyoto Industrial Health Association, Kyoto, Japan, for their interest in and support for this study.

Conflicts of interest The authors declare that they have no conflicts of interest.

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