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Global burden of late-stage chronic kidney disease resulting from dietary exposure to cadmium, 2015

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ABSTRACT

Chronic exposures to cadmium (Cd) are associated with reduced glomerular filtration rate (GFR), increasing the risk of chronic kidney disease (CKD). In support of the World Health Organization (WHO)'s initiative to estimate the global burden of foodborne diseases, a risk assessment was performed to estimate the Disability-Adjusted Life Years (DALYs) due to late-stage CKD associated with dietary exposures to cadmium. Using the distribution of population GFRs, the prevalence of CKD was calculated as the proportion of humans whose GFR fall in the ranges corresponding to Stage 4 or Stage 5 CKD. The increase in the CKD prevalence due to cadmium exposure was simulated based on a previously reported pharmacokinetic model describing the relationship between dietary cadmium intake and urinary cadmium (UCd), as well as a previously published dose-response relationship between UCd and GFR. Cadmium-related incidence rate, calculated as the change in the prevalence during a one-year period, were used to compute the mortality and DALY in all WHO regions. It is estimated that dietary cadmium would result in a median of 12,224 stage 4 and stage 5 new CKD cases per year worldwide, resulting in 2064 global deaths and 70,513 DALYs. These data translate into a median global burden of 1.0 DALY per 100,000 population, which account for 0.2% of the global DALYs of CKD. While these results suggest that the overall impact of dietary cadmium exposure on global CKD is low, they do indicate that reasonable efforts to reduce dietary exposure will result a positive public health impact. This would be particularly the case in areas with elevated levels of dietary cadmium.

1. Introduction

Foodborne diseases constitute a serious public threat worldwide. In the efforts to control foodborne diseases, assessments of their public health impact serve as the scientific basis for risk-based management decisions and regulatory actions. This endeavor, however, has been impeded by the lack of a reliable estimate of foodborne burden of disease. In collaboration with multiple external and internal partners, the Department of Food Safety and Zoonoses at the World Health Organization (WHO) launched the initiative to estimate the global burden of foodborne diseases. The Foodborne Disease Burden Epidemiology Reference Group (FERG) was convened to assist with this task. The current study is among the efforts undertaken by the Chemicals and Toxins Task Force (CTTF) of FERG to estimate the global burden of diseases from dietary exposure to chemical contaminants and toxins in food, including cadmium (Havelaar et al., 2015).

Cadmium is a naturally occurring metallic element found in the earth's crust and a widely used industrial material, especially between the 1930s and 1970s (United Nations Environment Programme, 2010). It is released into the environment through natural emissions and human activities such as mining and smelting. The cadmium staying in water and soil can be taken up by plants, fish and animals and bioaccumulates in these organisms, eventually entering the food supplies for humans (Faroon et al., 2012). In the non-occupational general

Abbreviations: CKD, Chronic kidney disease; CTTF, Chemicals and Toxins Task Force; DALY, Disability-adjusted life year; FERG, Foodborne Disease Burden Epidemiology Reference Group; GBD, Global burden of disease; GFR, Glomerular filtration rate; JECFA, Joint FAO/WHO Expert Committee on Food Additives; RR, Relative risk; SD, Standard deviation; UCd, Urinary cadmium; WHO, World Health Organization; YLD, Years lived with disability; YLL, Year of life lost

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population, food is the major source of cadmium exposure (Jarup, 2003). Smoking increases cadmium exposure, and heavy smokers typically have cadmium body burdens that are more than double that of non-smokers (Waalkes, 2003). Concentrations of cadmium in food vary widely among food categories and geographic regions, ranging from < 0.0001 to 0.04 mg/kg (ppm (parts per million)) in most food categories. Higher concentrations ranging from 0.1 to 4.8 mg/kg have been reported in certain foods that accumulate relatively high levels of cadmium, such as shellfish/mollusks, animal offal, oilseeds, mushrooms and vegetables (JECFA, 2010).

With no known biological function in mammals, cadmium undergoes very little metabolism and excretion in humans, resulting in an extremely long half-life of up to 10–30 years. The kidneys are among the major target organs of cadmium toxicity in humans (Faroon et al., 2012). Cadmium-induced renal toxicity is characterized by tubular proteinuria, a condition marked by the elevated excretion of low molecular weight proteins, such as beta-2-microglobulin and retinol binding protein, due to the damage to the renal tubules. In some cases, glomerular damage may also occur, manifested by albuminuria and reduced glomerular filtration rate (GFR). Unlike tubular proteinuria, which alone usually shows no symptoms, glomerular damage can be more clinically relevant (Bernard, 2004). Cadmium-induced glomerular damage was evident in both in vivo (rats) and in vitro (cultured rodent and human glomerular cells) toxicological studies (Barrouillet et al., 1999; Brzoska et al., 2003; Hirano et al., 2005; L'Azou et al., 2007). However, epidemiological investigations of the association between cadmium exposure and impaired renal function have generated inconsistent results. Some studies suggested that cadmium exposure is related to albuminuria or reduced GFR. These studies include those conducted in occupational workers (Jarup et al., 1993, 1995; Piscator, 1984), among residents in heavy polluted areas (Kobayashi et al., 2008; Limpatanachote et al., 2009; Nakano et al., 1987; Trzcinka-Ochocka et al., 2010), and in the general population (Akesson et al., 2005; Grau-Perez et al., 2017; Hellstrom et al., 2001; Hwangbo et al., 2011; Kim et al., 2015; Navas-Acien et al., 2009). However, there are other epidemiological studies that do not support this association (Buser et al., 2016; Byber et al., 2016; Thomas et al., 2014; Wang et al., 2016). Such inconsistency could be explained by the differences in the study designs, the co-exposure to other toxic metals and other risk factors, the selection of biomarkers for cadmium exposure and renal damage, etc. Importantly, the association between cadmium exposure and renal function may be highly related to the level of exposure (Akesson et al., 2014; Bernard, 2016). When the exposure is low, urinary cadmium (UCd), an exposure biomarker commonly used in epidemiological studies, may be influenced by renal physiology and factors unrelated to cadmium body burden (Bernard, 2016). In fact, all the epidemiological studies suggesting no association were conducted with study populations with a median/mean UCd of lower than 0.5 μg/g creatinine. On the other hand, an analysis of NHANES data (1999–2006) demonstrated that moderately high level of UCd (≥1 μg/g creatinine) was associated with higher incidence of albuminuria, a well-known biomarker of renal dysfunction (Ferraro et al., 2010). In addition, for itai-itai disease patients who typically had UCd as high as 20–30 μg/g creatinine, renal disease is a significant mortality risk (Nishijo et al., 2017).

In summary, although the renal effects at low cadmium exposure remains to be clarified, based on the current available scientific data, the overall weight of evidence supports the causal role of cadmium at high exposure levels in renal tubular dysfunction (presenting as tubular proteinuria) and glomerular dysfunction (presenting as albuminuria and/or reduced GFR). Since clinical symptoms usually do not present in individuals with only tubular dysfunction, it is not suitable to use tubular dysfunction as an endpoint for estimating the global burden of disease (GBD). In contrast, progressive glomerular dysfunction, as seen in CKD, is a global threat to public health (Zhang and Rothenbacher, 2008). CKD is categorized in five stages that are mainly based on the GFR according to the National Kidney Foundation guideline that has been accepted worldwide (National Kidney Foundation, 2002). The early stages (stages 1–3) of CKD usually do not show clinical symptoms, however, the late stage CKD (stage 4–5), characterized by severe decreases in the GFR (stage 4: 15–30 ml/min/1.73 m^2; stage 5: < 15 ml/min/1.73 m^2) requires clinical interventions such as dialysis or a kidney transplant. Late stage CKD constitutes a large, world-wide public health burden, particularly in those parts of the world with limited dialysis and kidney transplant infrastructures. The computation of disease burden in this study was only derived from the estimated incidence of late-stage (stage 4 and 5) CKD that need hospital visits and medical procedures, which is in accordance with the health states defined in the GBD studies (Salomon et al., 2015).

This current assessment utilizes an exposure-based quantitative risk assessment method that can be used to estimate the burden of disease due to dietary consumption of a chemical contaminant. Traditionally, estimating the burden of disease from a foodborne contaminant (such as a microbial pathogen) can be imputed based on relevant case reports (Devleesschauwer et al., 2015). However, such information is almost always not available for chronic diseases related to chemical contaminants. Therefore, an exposure-based approach that had been used previously to estimate the global burden of disease for lead (Fewtrell et al., 2004) was adapted in this assessment. This exposure-based approach can make use of a quantitatively described dose-response relationship between the exposure to a specific chemical and corresponding health endpoints. The disease frequency can then be derived from estimated exposure levels. For cadmium, a negative association between UCd and GFR was observed by Akesson et al. (2005). Recently, a dose-response relationship was derived and published (Ginsberg, 2012), which served as our basis of estimating the burden of late-stage CKD attributable to from cadmium exposures from food consumption.

2. Materials and methods

2.1. Modeling CKD prevalence

2.1.1. Deriving CKD prevalence using GFR

In this assessment, stage 4 and stage 5 CKD are defined according to the National Kidney Foundation's guideline as conditions with GFR 15–30 ml/min/1.73 m^2 and < 15 ml/min/1.73 m^2, respectively (National Kidney Foundation, 2002). Since GFR generally follows a normal distribution in the general human population (Glassock and Winearls, 2009), the prevalence of stage 4 and stage 5 CKD can be modeled using the cumulative density function from a normal distribution given the mean and the standard deviation (SD). Fig. 1 gives an example of such calculation for a hypothetical population in which the GFR is 91.1 ± 22.2 (mean ± SD) ml/min/1.73 m^2. The area under the distribution curve from 15 to 30 ml/min/1.73 m^2 represents the

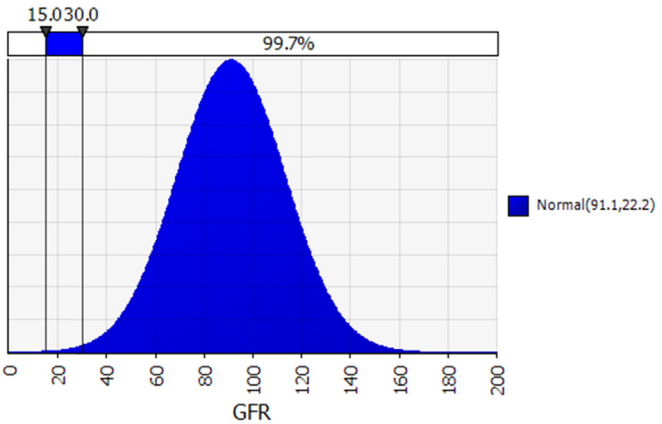

Fig. 1. The calculation of the prevalence of Stage 4 and stage 5 CKD based on a hypothetical GFR normal distribution.

prevalence of stage 4 CKD (around 0.30% in this population) and similarly, the area under the curve to the left side of the 15 ml/min/1.73 m^2 represents the prevalence of stage 5 CKD (around 0.03% in this population).

2.1.2. Deriving age-specific CKD prevalence

A literature search for the GFR baseline data in the general, healthy population was conducted for all WHO member states. GFR values reported among a population with certain health conditions or a population living in areas with known cadmium pollution were deemed not representative of the member states. For each member state with eligible GFR data, three pieces of raw information were recorded: the mean (x) and the standard deviation (δ) of the published GFR, and the mean or median age of the population from which the GFR data was collected (α). The age information was collected because age-related GFR decreases, as a physiological process, should be considered in the risk assessment. In general, after age 30–40, GFR declines by about 0.8 ml/min/1.73 m^2 per year in healthy populations (Glassock and Winearls, 2009). Assuming that this rate of decline is consistent through life after 40 years old and using a published mean GFR (x_α) obtained for a population with an average age of α, the mean GFR for an older population of the same geographic area ($x_{\alpha+n}$) can be modeled using Eq. (1) below:

$$x_{\alpha+n} = x_\alpha - 0.8n \quad (1)$$

where n is the number of years the calculated population is older than the published population.

Assuming that the standard deviation δ remains the same for the population of all age groups in a given geographic area, the increase of n years of age would make the GFR distribution curve shift left, leading to an increase in the area below the GFR threshold values, i.e., prevalence of stage 4 and stage 5 CKD (Fig. 2), thus an increase in the disease prevalence. The increased prevalence could be modeled mathematically using the normal distribution's cumulative distribution function. Fig. 2 shows an example of the shift of the GFR distribution curve resulting from the aging of this population for about 20 years.

2.1.3. Deriving cadmium-related CKD prevalence based on cadmium exposure in conjunction with aging

UCd has been commonly used to reflect cadmium body burden from long term cadmium exposure. Based on published epidemiological data, a dose-response analysis showed that cadmium exposure was associated with reduced GFR at a rate of 7.8% per unit (μg/L) UCd (Akesson et al., 2005; Gingsberg, 2012). Note that the same unit change also applies to another commonly-used unit of UCd: μg/g creatinine, assuming a 1.5 L/day urine production and 1.5 g/day creatinine excretion.

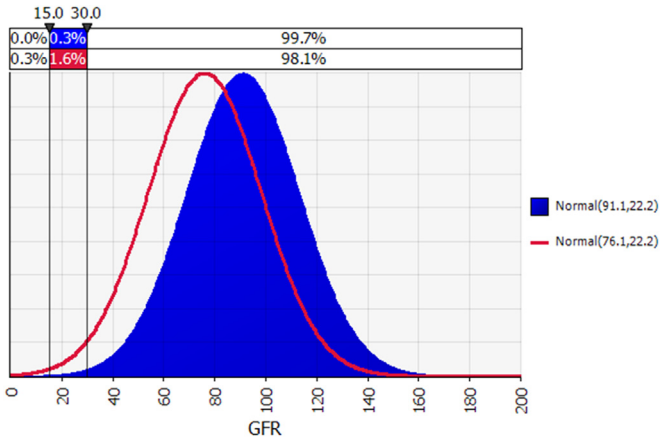

Fig. 2. The shift of GFR distribution curve due to aging (the red curve). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Given that cadmium is ubiquitously present in foods, a threshold cadmium exposure can be identified below which no clinically significant adverse effects are likely to occur. Based on the epidemiological data, UCd at 1.0 μg/g creatinine was used as the threshold for an adverse outcome estimation based on the Ferraro et al. (2010) study. Hence if the mean baseline GFR for a reference population (x) is known, the mean GFR for a population with given cadmium exposure (measured by UCd) can be described as:

$$x_{cd} = x(1 - 0.078(UCd - 1.0)) \quad (2)$$

UCd is modeled from dietary exposure which is described in the next section. In cases where UCd is less than 1.0 μg/g creatinine, $(UCd - 1.0)$ is returned to zero in the simulation.

Based on Eqs. (1) and (2), the mean GFR for a population under the influence of aging and cadmium combined can be described as

$$x_{\alpha+n,cd} = (x_\alpha - 0.8n)(1 - 0.078(UCd - 1.0)) \quad (3)$$

Assuming that aging and cadmium exposure will not change the standard deviation of the population GFR, the combined effect of aging and cadmium on GFR can also be illustrated on the GFR distribution curve (Fig. 3). As shown in the figure, in addition to the influence of aging, cadmium exposure makes the GFR distribution curve shift further to the left, leading to a further increase in the prevalence of CKD.

2.1.4. Estimating UCd from dietary cadmium exposure

The dietary cadmium exposure data from some countries were obtained from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) publication (JECFA, 2010). These exposure estimates were based on market-basket-based surveys and represented a population-level exposure. Originally expressed as μg/kg bw/month, these data were converted into a daily basis, by dividing by 30, to calculate the corresponding UCd change.

For countries that had no direct market-basket-based intake data, a literature search was conducted. In the cases when published data were unavailable, a surrogate daily exposure of 0.5 μg/kg bw was used. The surrogate dietary exposure was based on the exposure data from all available countries/regions at JECFA (2010). Specifically, global cadmium exposure was assumed to follow a triangular distribution. The minimal, maximum, and the most likely value of this triangular distribution were assumed to be the lowest (0.5 μg/kg/month, Ningxia, China), highest (36.5 μg/kg/month, Sichuan, China), and the mean of the rest countries (8.6 μg/kg/month), respectively. The mean of this

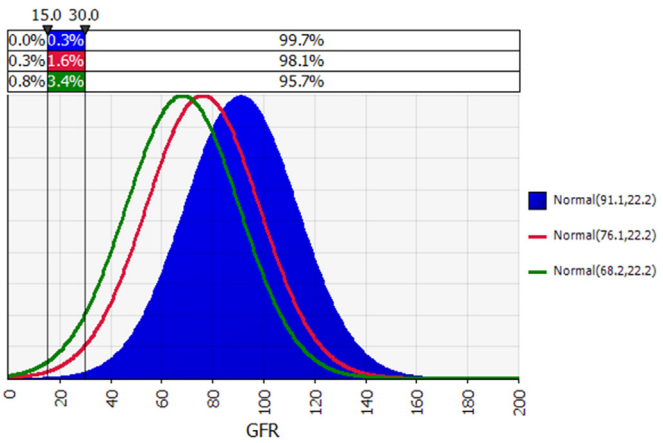

Fig. 3. The shift of GFR distribution curve resulting from aging alone (the red curve) and resulting from aging and cadmium exposure together (the green curve). The prevalence of Stage 5 CKD from exposure to cadmium, for example, can be calculated as the area under the green curve minus the area under the red curve to the left side of the 15 ml/min/1.73 m^2 threshold line. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

distribution, 15.2 μg/kg bw/month, was used to represent the surrogate dietary exposure, which was then converted to 0.51 μg/kg bw/day.

UCd was estimated based on dietary cadmium exposure estimated using a toxicokinetic model that describes the relationship between daily cadmium exposure and UCd (Amzal et al., 2009). In this toxicokinetic model, cadmium exposure on a body weight basis is assumed to be constant over the lifetime, and the UCd at a given age is a lognormal function of daily exposure (d), age, half-life ($t_{1/2}$), an aggregated physiological parameter (f_k), and an elimination factor (f_u):

$$UCd(age) = \frac{f_k * f_u}{\log(2)} * d * t_{1/2} \frac{\left[1-\exp\left(-\frac{\log(2) * age}{t_{1/2}}\right)\right]}{\left[1-\exp\left(-\frac{\log(2)}{t_{1/2}}\right)\right]} \quad (4)$$

By fitting the model with individual data from the Swedish women's study, Amzal et al. (2009) estimated the model parameters using a Bayesian approach and reported the cadmium $t_{1/2}$ as 11.6 ± 3.0 yrs, and the mean of $f_k * f_u$ as 0.005. Using these parameters, we simulated the annual change of UCd for each country, based on the respective daily dietary cadmium exposure, assuming that these pharmacokinetic parameters are the same across all populations. The simulations were performed in R using 1,000,000 iterations. The half-life ($t_{1/2}$) was modeled as a lognormal variable (mean = 11.6 year, sd = 3.0 year, truncated 3–35 year), while age, intake, and $f_k * f_u$ were modeled as constants.

2.2. Simulation of CKD incidence from prevalence

To calculate the cadmium-attributable disease burden, an estimate of the increased incidence due to cadmium exposure is necessary. The incidence rate of CKD for each age group, expressed as the number of new cases per 100,000 population per year, was imputed as the difference between the two mid-point prevalence estimates in a one-year period, assuming the size of the population remains the same. Since the increase of UCd from cadmium exposure is not linear throughout the life (see Eq. (4)), the at-risk population (40 years and older) was divided into six different age groups, i.e. 35–44 yr, 45–54 yr, 55–64 yr, 65–74 yr, 75–84 yr, 85–94 yr and modeled separately.

Using the 65–74 yr age group as an example, we simulated the CKD prevalence for population at 70 ± 0.5 yrs of age (i.e., 69.5 yr and 70.5 yr respectively), and the difference between these two simulated results was used to represent the new CKD cases on a yearly basis for the whole 65–74 age group. The simulation was performed using both Eqs. (1) and (3), representing the CKD incidence rates resulting from aging only and from aging and cadmium combined, respectively. The cadmium-attributable incidence rate was simulated as the difference between the two incidence rates so that the CKD incidence due to normal aging could be deducted from the combined effect. The simulated result was used to represent the incidence rate for the entire population of 65–74 yrs.

2.3. Imputation of CKD incidence rates for countries without GFR data

Based on the availability of country-specific GFR data, cadmium-attributable CKD incidence rates could be estimated for 34 countries using the respective dietary cadmium exposure estimates. To impute incidence rates for the remaining countries, we adopted the imputation approach developed and applied by the Child Health Epidemiology Reference Group (Devleesschauwer et al., 2015; Pires et al., 2015). In this approach, countries are clustered according to 14 subregions, based on the six WHO regions and a further sub-classification into five levels (A–E) according to child and adult mortality rates (Ezzati et al., 2002). For each country with incidence estimates, a Gamma distribution was fitted to represent the uncertainty in the country-specific estimate. Then, the median incidence rate with corresponding uncertainty was obtained for each subregion, by simulating random Gamma deviates per country and obtaining the iteration-wise median. Likewise, a global median with corresponding uncertainty was obtained by taking the iteration-wise median of subregional incidence rates. Finally, the cadmium-attributable CKD incidence rates of countries without estimates, but for which at least one other country in the same subregion had estimates, was imputed as the subregional median and corresponding uncertainty; for countries without data in a subregion where none of the country had estimates, it was imputed as the global median and corresponding uncertainty.

2.4. Estimation of CKD mortality and disability-adjusted life years

In a final step, the cadmium-attributable CKD incidence rates were translated into deaths and DALYs. The DALY is a summary measure of population health that combines Years Lived with Disability (YLDs) due to living with disease with Years of Life Lost (YLLs) due to premature death. For comparability with the other FERG estimates, DALYs were calculated from an incidence perspective, without applying age weighting or time discounting (Devleesschauwer et al., 2015). For stage 4 CKD, we assumed no excess mortality. Stage 4 CKD DALYs were therefore given by the YLD component, obtained by multiplying the incidence rates with the stage 4 CKD duration and disability weight. We applied a lifelong duration, corresponding to the age group specific national life expectancy, which was derived from the 2015 revision of the United Nations World Population Prospects (available at: https://esa.un.org/unpd/wpp/Download/Standard/Population/). The stage 4 CKD disability was 0.104, in accordance to the GBD studies (Salomon et al., 2015). For stage 5 CKD (end-stage renal disease), assumed a 20% case fatality ratio in low mortality regions (i.e., the A subregions of the WHO American, European and Western Pacific regions), and a 100% case fatality ratio in the remaining regions (Kirk et al., 2015). YLLs were calculated by multiplying the number of deaths with the age group specific residual life expectancy. In accordance with the FERG and WHO Global Health Estimates, we used the highest projected life expectancy for 2050 as the normative life expectancy table (Devleesschauwer et al., 2015; World Health Organization, 2017). For stage 5 CKD cases that were projected to survive, we estimated YLDs by multiplying the number of surviving cases with the age group specific national life expectancy and a disability weight of 0.571 (Salomon et al., 2015).

Uncertainty in input parameters was propagated using 10,000 Monte Carlo simulations. The resulting uncertainty distribution were summarized by their median and a 95% uncertainty interval (UI) defined as the 2.5th and 97.5th percentile. The reference year for the calculation of absolute numbers was 2015, with population estimates obtained from the 2015 revision of the United Nations World Population Prospects.

3. Results

3.1. Parameters used for disease incidence modeling

3.1.1. Country-specific GFR and dietary cadmium exposure data from literature

In the general population, GFR can be assumed to follow a normal distribution (Gilbert et al., 2014). Country-specific information on the mean and the standard deviation of GFR, as well as the mean age of the population were recorded and listed in Table 1. The country-specific dietary cadmium exposures are also listed in Table 1.

3.2. Disease burden of cadmium-related stage 4 and stage 5 chronic kidney disease

The incidence of CKD stage 4 and stage 5, deaths from CKD stage 5, and resulting DALYs are summarized in Table 2.

Table 1
Input data for simulation of incidence and death.

WHO member state	WHO region	GFR (mean (SD) ml/min/ 1.73 m^2)	Age (mean)	GFR Reference[a]	Cd dietary intake (μg/kg bw/d)	Cd intake Reference[a]
Argentina	AMR B	85.15 (18.49)	42	Salazar et al., 2009	0.51	Surrogate
Australia	WPR A	78.9 (15.2)	51.5	White et al., 2010	0.23	JECFA, 2010
Austria	EUR A	93.8 (13.5)	41.9	Obermayr et al., 2008	0.3	JECFA, 2010
Belgium	EUR A	91.6 (24.4)	48.1	Van Biesen et al., 2007	0.31	JECFA, 2010
Brazil	AMR B	106 (18)	41	Soares et al., 2013	0.03	Santos et al., 2004
Chile	AMR B	77.1 (16.3)	55	Zuniga et al., 2011	0.3	JECFA, 2010
China	WPR B	101.2 (27.4)	49.6	Zhang et al., 2012	0.33	JECFA, 2010
France	EUR A	71 (15)	68.3	Bacchetta et al., 2010	0.3	JECFA, 2010
Germany	EUR A	90.9 (18.2)	56.1	Goek et al., 2012	0.39	JECFA, 2010
Ghana	AFR D	103.1 (18.5)	54.7	Eastwood et al., 2010	0.51	Surrogate
Greece	EUR A	87.9 (9.9)	59.5	Liberopoulos et al., 2004	0.74	JECFA, 2004
Iran (Islamic Republic of)	EMR B	68.4 (11.0)	47.4	Hosseinpanah et al., 2012	0.6	Rahmedel et al., 2015
Italy	EUR A	88.0 (13.4)	40.1	Menzaghi et al., 2012;	0.27	JECFA, 2010
Japan	WPR A	75.0 (16.2)	63.6	Iseki et al., 2012	0.4	JECFA, 2010
Kuwait	EMR B	94 (19)	40.9	Mojiminiyi et al., 2008	0.51	Surrogate
Malaysia	WPR B	107.3 (22.4)	45.1	Jayapalan et al., 2010	0.12	Moon et al., 1996
Netherlands	EUR A	84 (16)	49	Smink et al., 2012	0.3	JECFA, 2010
Nicaragua	AMR D	93.1 (32.1)	38.5	O'Donnell et al., 2011	0.51	Surrogate
Norway	EUR A	94.2 (21.5)	50.1	Hallan et al., 2009	0.31	JECFA, 2010
Republic of Korea	WPR B	76.4 (12.2)	46.5	Lee et al., 2012	0.26	JECFA, 2010
Rwanda	AFR E	94.5 (19.9)	43	Wyatt et al., 2011	0.51	Surrogate
Saudi Arabia	EMR B	107.8 (24.0)	37.4	Alsuwaida, et al., 2010	0.51	Surrogate
Singapore	WPR A	90.2 (18.5)	45.4	Teo et al., 2009	0.51	Surrogate
South Africa	AFR E	97.3 (27.8)	52.9	Matsha et al., 2013	0.51	Surrogate
Spain	EUR A	84.6 (36.7)	49.5	Otero et al., 2010	0.3	JECFA, 2010
Sweden	EUR A	107 (19)	49.6	Soveri et al., 2009	0.31	JECFA, 2010
Switzerland	EUR A	85.9 (20.0)	79.3	Marti et al., 2011	0.3	JECFA, 2010
Turkey	EUR B	91.8 (20.9)	40.5	Süleymanlar et al., 2011	0.51	Surrogate
Uganda	AFR E	127 (29.7)	28	Wyatt et al., 2011	0.51	Surrogate
United Kingdom	EUR A	97.1 (15.1)	51.2	Goek et al., 2012	0.29	JECFA, 2010
United States of America	AMR A	76.2 (18.7)	62.1	Shankar et al., 2010	0.15	JECFA, 2010
Venezuela	AMR B	101 (16.9)	25.3	Herrera et al., 2002	0.51	Surrogate

[a] References in this table are provided in Appendix.

Table 2
Estimated incidence of chronic kidney disease (CKD) stage 4 and 5, deaths, and disability-adjusted life years (DALYs) from different World Health Organization (WHO) regions (median and 95% uncertainty interval).

WHO region	Case incidence			Deaths	DALY		
	CKD/4	*CKD/5*	*Total*	*CKD/5*	*CKD/4*	*CKD/5*	*Total*
Africa (AFR)	660 (57–8267)	203 (21–2010)	912 (115–10,143)	203 (21–2010)	945 (73–12,703)	5196 (477–57,351)	6425 (737–68,368)
AFR D	104 (9–2869)	15 (2–244)	119 (12–3115)	15 (2–244)	130 (15–2865)	334 (56–4487)	458 (78–7342)
AFR E	499 (30–5772)	182 (15–1851)	734 (73–7326)	182 (15–1851)	737 (35–10,698)	4694 (326–54,569)	5788 (528–63,682)
America (AMR)	1286 (107–13,829)	481 (47–7244)	1878 (247–20,826)	481 (47–7244)	2431 (182–33,382)	12,148 (1129–242,674)	15,267 (1996–274,776)
AMR A	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
AMR B	833 (48–7281)	219 (12–2031)	1214 (122–8296)	219 (12–2031)	1390 (68–14,211)	4512 (226–43,129)	6998 (635–50,192)
AMR D	198 (7–9511)	143 (6–6442)	341 (20–15,946)	143 (6–6442)	484 (14–26,500)	4598 (165–227,595)	5048 (224–253,934)
Eastern Mediterranean (EMR)	2180 (166–15,586)	301 (29–2146)	2709 (355–16,146)	65 (8–437)	3339 (245–24,385)	2584 (291–15,505)	7143 (1204–32,695)
EMR B	2086 (137–15,159)	295 (26–2133)	2596 (318–15,760)	59 (5–427)	3258 (213–23,997)	2515 (245–15,378)	6995 (1130–32,262)
EMR D	46 (3–779)	4 (1–21)	50 (5–800)	4 (1–21)	37 (4–565)	62 (19–268)	100 (27–828)
Europe (EUR)	2163 (274–36,698)	670 (73–11,280)	2939 (446–47,415)	593 (36–11,179)	3253 (325–64,077)	13,685 (927–260,582)	18,078 (1710–322,569)
EUR A	232 (102–4061)	51 (24–677)	286 (143–4725)	10 (5–135)	245 (132–4725)	425 (228–4713)	681 (412–9462)
EUR B	1714 (71–34,761)	563 (25–11,148)	2418 (177–45,925)	563 (25–11,148)	2840 (103–61,911)	12,844 (505–259,749)	16,866 (1033–321,517)
EUR C	12 (3–59)	3 (0.7–12)	14 (3–72)	3 (0.7–12)	11 (2–61)	44 (12–183)	55 (15–244)
Southeast Asia (SEAR)	38 (8–216)	8 (2–34)	46 (10–250)	8 (2–34)	38 (7–235)	150 (45–561)	188 (52–795)
SEAR B	8 (2–43)	2 (0.5–7)	9 (2–50)	2 (0.5–7)	8 (1–47)	30 (9–113)	38 (10–160)
SEAR D	30 (6–173)	6 (2–27)	37 (8–200)	6 (2–27)	30 (6–188)	120 (36–448)	150 (42–635)
Western Pacific (WPR)	637 (119–25,542)	205 (43–6836)	1027 (245–30,415)	176 (37–5437)	1630 (317–32,865)	6644 (1551–124,666)	9252 (2661–148,337)
WPR A	74 (0.3–14,143)	15 (0.1–2593)	103 (3–16,729)	3 (0.03–519)	132 (0.6–19,245)	157 (2–19,460)	381 (13–38,734)
WPR B	494 (84–12,772)	170 (34–4970)	840 (186–15,553)	170 (34–4970)	1334 (238–17,792)	6261 (1389–108,019)	8485 (2338–119,491)
GLOBAL	9434 (2189–90,257)	2576 (581–25,851)	12,224 (3330–114,626)	2064 (403–22,641)	15,787 (3574–150,918)	53,728 (12,046–604,382)	70,513 (19,113–742,340)
Global rate (per 100,000)	**0.1 (0.03–1)**	**0.04 (0.008–0.4)**	**0.2 (0.05–2)**	**0.03 (0.005–0.3)**	**0.2 (0.05–2)**	**0.7 (0.2–8)**	**1.0 (0.3–10)**

4. Discussion

The current study is aimed to investigate the impact of dietary cadmium intake in the general population on the global burden of late-stage CKD. Ideally, the CKD disease burden from cadmium exposure should be calculated from population-attributable risk percent (PAR) of cadmium, which is derived from the relative risk (RR) of stage 4–5 CKD between the exposed and unexposed population. However, since CKD is a multifactorial disorder, obtaining a reliable PAR of cadmium requires appropriate adjustment of other acquired and genetic risk factors. In addition, as the toxicological effect of cadmium is dose-dependent, and the dietary cadmium exposure varies largely by geographic regions over the world, the PAR of cadmium can be different for different populations. Unfortunately, such information is not contained in any of the currently-available epidemiological studies. Therefore, the traditional way of calculating disease burden using PAR and disease registry data was not applicable to this task.

On the other hand, the dose-response relationship between UCd (an indication of kidney body burden) and GFR (a measurement of kidney function and the indication of stage 4–5 CKD) is available, and the magnitude of GFR reduction with increased UCd has been quantified based on this dose-response relationship. However, the direct use of published UCd to derive the change of GFR is limited by the fact that UCd reflects the overall cadmium exposure, including both from food and other sources, such as cigarette smoking. To deal with this problem, a published pharmacokinetic model that links daily dietary intake of cadmium with UCd and age (Amzal et al., 2009) was used to model the yearly change of UCd at different dietary exposure levels. The dietary exposure-based approach is the most defensible and plausible approach to provide the incidence of CKD attributable to dietary cadmium exposure, which serves as the basis to compute the foodborne disease burden.

The main causes of chronic kidney disease are diabetes and high blood pressure, which are responsible for up to two-thirds of known cases. Genetic and environmental risk factors apart from those clearly associated with the development of diabetes and cardiovascular disease (e.g., high blood pressure) also play important roles in the development and progression of CKD. According to the Global Burden of Disease 2016 study, the median global mortality rate of CKD was 15.9 per 100,000 in 2015. Of the 15.9 CKD deaths (per 100,000 per year), 6.7, 4.0 and 2.0 (per 100,000 per year) were attributable to diabetes, hypertension and glomerulonephritis, respectively, and 3.2 (per 100,000 per year) can be due to other causes (GBD 2016 Causes of Death Collaborators, 2017). The current study estimates that the median global death rate of CKD due to dietary cadmium exposure is 0.03 (95% UI 0.005–0.3) per 100,000 per year, which accounts for nearly 0.2% of total CKD deaths. The median DALY of stage 4 and 5 CKD due to dietary cadmium (70,513, corresponding to 1.0 DALY per 100,000 population) also accounts for only 0.2% of all age DALY of CKD estimated by the Global Burden of Disease 2016 study (34,388,881; corresponding to 470.2 per 100,000 population) (GBD 2016 DALYs and HALE Collaborators, 2017). These results agree with the findings from a recently published population-based prospective cohort study with 13 years of follow-up, which shows no indication of a strong association between low-level dietary cadmium exposure and CKD. Our results suggest that low dietary cadmium exposure in the general population not likely to have a significant impact on the burden of CKD with clinical presentation.

As with any risk assessment there are some uncertainties in the current assessment. We were unable to estimate the CKD incidence for every country because GFR data are unavailable for many countries outside of Europe. We started with 32 countries with available GFR data for the general population and modeled the incidence rates of stage 4 and stage 5 CKD for these countries, based on the published or surrogate dietary cadmium exposure. In order to provide the disease burden estimates for countries in all WHO regions, the CHERG imputation model was applied to the incidence rate of the above 32 countries to impute the incidence for the remaining countries. As a result, the CKD incidence rates and the DALYs were only estimated for the general population in the current assessment. The actual burden of late-stage CKD may very well be underestimated for two reasons. First, some studies have suggested that cadmium may potentiate or synergize glomerular damage related to diabetes. However, we were unable to model the cadmium-attributable disease incidence in diabetics due to the lack of dose-response information in this special at-risk population. Second, the dietary cadmium exposures in heavily polluted areas are much higher than in non-polluted areas. We were unable to estimate the disease burden for those highly contaminated “hot spot” areas due to the lack of a good estimate of the size of the population affected.

In addition to the renal damage, dietary cadmium exposure has been associated with adverse effects on the bone. Although the well-known itai-itai disease is rarely seen now due to improved pollution control measures and improvements in nutrition, recent studies have reported the association of cadmium exposure with increased risk of osteoporosis and fracture. It would be highly valuable to have an estimate of the disease burden of these conditions, once the relevant data becomes available.

5. Conclusion

In summary, using dietary cadmium exposure data, the case incidence, deaths and DALY of cadmium-attributable late-stage CKD in the general population were imputed for different WHO regions. The current study estimates that the median global burden of CKD due to dietary cadmium exposure is 1.0 DALY per 100,000 population, which accounts for 0.2% of the total global burden of CKD. While these results suggest that the overall impact of dietary cadmium exposure on global CKD is low, they do indicate that reasonable efforts to reduce dietary cadmium exposure will result a positive public health impact. This would be particularly the case in areas with elevated levels of dietary cadmium. The burden of non-renal diseases from dietary cadmium exposure urges further investigation.

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Competing interests

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.10.005.

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