Association of pesticides and kidney function among adults in the US population 2001-2010

En-Tzu Wan (entzu.wan@uq.net.au)
The University of Queensland
Darsy Darssan
The University of Queensland
Shamshad Karatela
The University of Queensland
Simon Reid
The University of Queensland
Nicholas Osborne
The University of Queensland

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Abstract

Background

Chronic kidney disease with unknown cause (CKDu) is prevalent in tropical and agricultural communities, however, its aetiology remains unclear. The objective of this study was to examine the association between pesticide exposures and the risk of kidney function loss using four waves of the National Health and Nutrition Examination Survey (NHANES) to identify a pathological pathway.

Methods

We pooled data from four cross-sectional waves of NHANES, providing 41,847 participants in total. Sub-population analyses for 2,4-dichlorophenoxyacetic acid (2,4-D), 3,5,6- trichloropyridinol, 3-phenoxybenzoic acid (3-PBA) and Malathion were conducted using. Logistic regression to estimate the odds ratios (ORs) and 95% CIs of the association between log-pesticide levels and kidney function.

Results

We found that Malathion acid increased the risk of low kidney function among the Malathion sub-population (aOR = 1.26, 95% CI = 1.01–1.56) in the adjusted model. Significantly increased risk of low kidney function was not found among the 2,4-D (aOR = 0.88, 95% CI = 0.72–1.09), 3,5,6-trichloropyridinol (aOR = 0.96, 95% CI = 0.83–1.12) and 3-PBA (aOR = 1.03, 95% CI = 0.94–1.13) subpopulations.

Conclusions

Our findings provide evidence of altered kidney function in people exposed to Malathion, highlighting the need to focus on Malathion acid as a potential cause of renal injury or chronic kidney disease.

Introduction

Chronic kidney disease (CKD) is a condition of permanent nephron damaging and renal function loss (Levey and Coresh 2012). Classic risk factors of CKD, such as hypertension (HTN) and diabetes (DM) account for most of the CKD burden in high income countries (Levey and Coresh 2012). However, numerous cases of CKD have emerged with unknown aetiology (CKDu, definition of exclusion ie no HTN or DM or other) in tropical countries, as most of the affected patients are asymptomatic or with mild symptoms of elevated serum creatinine levels, low-grade or no proteinuria, or chronic interstitial nephritis with variable glomerulosclerosis (Jayasumana et al. 2017; Nanayakkara et al. 2012).

Chronic kidney disease with unknown cause (CKDu) has recently been reports in people from poor communities in Meso-America (Garcia-Trabanino et al. 2015), Sri Lanka (Chandrajith et al. 2011;

Jayasumana et al. 2015) and India (Ganguli 2016). Initially CKDu was suspected to be an occupational disease associated with exposures in the agricultural workplace, such as heat stress and dehydration (Garcia-Trabanino et al. 2015), pesticide spraying (Rajapakse et al. 2016), heavy metals and agrochemicals (Soderland et al. 2010) or use of NSAIDs (Gooch et al. 2007). Non-agricultural workers and other community members could also be at risk of CKDu, as environmental contamination from heavy metals and pesticides residues (Agampodi et al. 2018; Soderland et al. 2010) or use of folk medicines containing heavy metals or aristolochic acid (Debelle et al. 2008) may be contributing to the disease. Spraying pesticides without personal protective equipment (PPE) or working with contaminated soil have been suggested as likely exposure pathways for pesticides (Jayasumana et al. 2017).

Organophosphate and pyrethroid group of insecticide are the most commonly used in agricultural and domestic settings. Multiple adverse effects of pesticide exposure on kidney function and structure have been identified in animal studies. Mesnage et al. (2015) demonstrated the nephrotoxicity of pesticides, which triggered epigenetic effects and pathophysiological changes in kidney function (Mesnage et al. 2015). In addition, pyrethroid exposure in rats cause oxidative stress that induces tissue damage (Nasuti et al. 2003). Whilst chlorpyrifos, accumulates in adipose tissues and in liver and kidney where it disrupts plasma membranes, leading to tissue damage and loss of enzyme activity (Tanvir et al. 2016).

Several epidemiological studies have been conducted to explore chronic pesticide exposure leads to kidney function loss in human beings. A prospective study of people in the USA found the long-term exposure to herbicides, such as paraquat, increased the risk of end-stage renal disease (ESRD) among commercial pesticide applicators (adjusted HR = 2.15, 95% CI = 1.11–4.15 (Lebov et al. 2016). However, this study was not able to recognise the mechanism leading to ESRD since it did not take pesticide ingredient into account. Studies conducted in Sri Lanka had conflicting results due to the high disparity of study designs (2016). Although self-report questionnaire is the main approach to assess pesticide exposure and other information, misclassification of participants and the lack of strategies to consider confounding factors vary the findings (Athuraliya et al. 2011; Wanigasuriya et al. 2007).

The aetiology of CKDu remains unclear with the current evidence provided by studies. The objective of this study was to examine the association between pesticide exposures and the risk of kidney function loss using four waves of the National Health and Nutrition Examination Survey (NHANES) to elucidate a potential pathological pathway. The NHANES is a program of studies that aims to assess the health and nutritional status of adults and children in the United States (Zipf et al. 2013). It uses a multistage, probability sampling design to select nationally representative civilian and non-institutionalised US residents (Zipf et al. 2013). Data from individuals who participated in the NHANES study are collected through physical examination, computer-based questionnaires, and laboratory analyses of biomarkers such as cholesterol level, creatinine level, C-reactive protein and environmental exposures to heavy metals and pesticides from blood and urine samples.

Material And Methods

Study population

We pooled data from four independent NHANES study waves (2001-02, 2003-04, 2007-08, and 2009-10). The NHANES 2005-06 study was not included because measurements of several pesticides of our interest were not available in this study period.

We included every participant from NHANES 2001–2004 and 2007–2010. We conducted several sub-population analyses for 2,4-dichlorophenoxyacetic acid (2,4-D), 3,5,6- trichloropyridinol, 3-phenoxybenzoic acid (3-PBA) and Malathion by only including participants from age 20 to 80, as well as those who did not have missing pesticide and serum creatinine measurements. Participants over 80 years old were excluded in order to reduce biases from older adults who were more likely to have been institutionalised. All participants provided written informed consent during recruitment as part of the NHANES study protocol (Zipf et al. 2013).

Kidney function data

Serum creatinine concentration available for each participant in NHANES. We calculate the estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (Levey et al. 2009) (Eq. 1).

$$\text{eGFR} = 141 \times \min(\text{Scr}/\kappa, 1)\,\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993\,\text{Age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black}) \text{ mL/min/1.73 m}^2 \quad \textbf{(1)}$$

Kidney function was classified into five stages on the basis of eGFR level: more than 90 mL/min per 1.73 m² (stage 1), 60–89 mL/min per 1.73 m² (stage 2), 30–59 mL/min per 1.73 m² (stage 3), 15–29 mL/min per 1.73 m² (stage 4), and less than 15 mL/min per 1.73 m² (stage 5) (Levey and Coresh 2012). Participants in this study were considered to have CKD if their eGFR level was in stage 3 or stage 4.

Measurement of pesticides

The NHANES study measured various types of pesticide metabolite in urine specimens from a one-third subsample or participants that were randomly selected from the total participants in each wave. Analysis methods details are documented at the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes). Data on the concentration of the following herbicide and pesticides, or their metabolites, was available for analysis: 2,4-D herbicide, organophosphate insecticides 3,5,6- trichloropyridinol (chlorpyrifos metabolite) and Malathion, and pyrethroid insecticide metabolite 3-PBA. The target analytes were extracted and concentrated from the urine matrix using an automated solid-phase extraction system, and there was no major change of laboratory methodology in different NHANES waves (Zipf et al. 2013).

The limit of detection (LOD) varied among pesticide metabolites and heavy metals across each study wave. Therefore, we applied the maximum limit of detection (LODmax) to distinguish between non-detectable and detectable measurements from the laboratory. We assigned a substitution to all pesticides

and heavy metal levels below the LODmax with the value of LODmax divided by the square root of two (Barr et al. 2005).

Other variables

The following data were available from the NHANES dataset. Age, sex, race/ethnicity and poverty income ratio (PIR, a proxy of household social-economic status), smoking and alcohol consumption behaviours are collected via self-reported questionnaires. PIR is a ratio of self-report family income to the appropriate poverty threshold of a family, and this index is comparable across NHANES waves. A PIR less than 1.0 indicated those below the official poverty threshold, and PIR values of 1.00 or greater represented people are above the poverty threshold.

People who reported smoking at least 100 cigarettes during their lifetime and who, at the time they participated in the survey, reported smoking every day or some days from the self-report questionnaire were defined as current smokers. Former smokers are those who reported smoking at least 100 cigarettes but are not smoking at the time participating in the survey. Current drinkers are those who self-reported of drinking at least 12 alcohol in their lifetime; abstinence is vice versa.

The health status of each participant was measured directly using the waist circumference (WC), systolic blood pressure (DBP), diastolic blood pressure (DBP) and fasting blood glucose levels. Hypertension was defined according to the JNC7 report, as either systolic blood pressure (SBP) over 140 mmHg or diastolic blood pressure (DBP) over 90 mmHg, or had ever taken anti-hypertensive medications (Chobanian et al. 2003). Diabetes was defined according to the definition of the American Diabetes Association (ADA) as either fasting glucose level over 126 mg/dL or had ever taken diabetic medications to decrease blood sugar level (Resnick et al. 2000). Data on the cadmium concentration determined from blood samples in NHANES is also included in this study as a positive control for the pesticide exposure.

Statistical analysis

Sampling weights were used along with primary sampling units (PSUs) and strata. Stratification and clustering provided in the NHANES study were used into all statistical analyses to account for the complex and multistage sampling study design to represent the non-institutionalised US population, as well as to obtain accurate estimates (Zipf et al. 2013). Following the NHANES analytical guidelines (Johnson et al. 2013), the new sampling weight for the pooled NHANES survey data was calculated by dividing the 2-year weights for each period by 4 via Stata command [svyset] before analysis. In this study, the 8-year MEC weight [wtall] was used to analyse the demographic characteristics of all participants. Pesticide subsample weights of 2,4-D, 3,5,6- trichloropyridinol, Malathion and 3-PBA, respectively, were used to take account for analyses that were conducted from a smaller sub-sample in each wave.

We described demographic variables using weighted means, standard deviation, 95% confidence interval (CI), as well as weighted percentage. Log-transformation for pesticides and cadmium levels were applied in multivariate analyses. We utilised logistic regression to estimate the odds ratios (ORs) and 95% CIs of

the association between log-pesticide level and kidney function. OR estimation of log-cadmium with kidney function was included as a positive control, as cadmium is a nephrotoxic metal presenting in various pesticides that lead to direct exposure to workers and the community through contaminated soil and water. Covariates including age, sex, race/ethnicity, PIR (continuous variable), smoking and NHANES waves were adjusted in every multivariate regression model.

By excluding participants with previous hypertension and diabetes history, we also performed a sensitivity analysis to assess the robustness of findings and assess potential pathological pathway for underdetermined CKD (Pearce and Caplin 2019).

Original NHANES data available online was been converted to the Stata file format for management prior to data analysis. All statistical analyses were conducted using Stata version 15.1 (College Station, TX, USA). The Taylor Series Linearization method was applied to account for stratification and clustering. All data sources used in the analyses, along with fully reproducible code, are publicly available at https://github.com/MountStats/PestKidneyGrace

Results

Demographic characteristics of the study population

The demographic characteristics of the pooled population are shown in Table 1. A total of 41,847 participants were included in NHANES 2001–2004, 2007–2010.

Fifty one percent (51.1%) of the participants were females and the weighted mean age was 36.0 years old (SD: 0.26). The majority of participants (67.7%) were non-Hispanic White, following by non-Hispanic Black (12.0%), Mexican American (9.1%), and other races (6.3% of multi-racial people and 5.0% of other Hispanic). For the social economic status of this study population, 15.9% of the population lived under the threshold of poverty (PIR < 1).

A total of 5.1% of the participants (1,776 people) had CKD according to the definition described in Sect. 3.2. Just under half of participants were either current smokers (23.3%) or former smokers (24.6%). Symptoms of hypertension and diabetes were present in 29.9% and 18.5% of participants, respectively.

The demographic characteristics from sub-population analyses are also shown in Table 1.

Table 1
Demographic characteristics for participants in the National Health and Nutrition Examination Survey conducted in US between 2001–2004 and 2007–2010

Characteristics[†]	All participants (N = 41,847)[1]	2,4-D(n = 6232)[2]	3,5,6 (n = 4994)[3]	3-PBA (n = 4910)[4]	Malathion (n = 3557)[5]
Sex, % (95% CI)					
Male	48.9 (48.4–49.4)	48.7 (47.3–50.1)	48.6 (46.9–50.3)	48.4 (46.7–50.1)	48.6 (46.5–50.7)
Female	51.1 (50.6–51.7)	51.3 (50.0-52.8)	51.4 (49.7–53.1)	51.7 (49.9–53.3)	51.4 (49.4–53.5)
Age (years), mean (SD, 95% CI), n = 41,847	36.0 (0.26, 35.5–36.6)	45.7 (0.27, 45.1–46.2)	45.9 (0.33, 45.2–46.5)	46.0 (0.38, 45.3–46.6)	46.8 (0.36, 46.0-47.5)
Waist circumference (cm), mean (SD, 95% CI), n = 34,964	90.2 (0.21, 89.8–90.6)	97.3 (0.26, 96.7–97.8)	97.3 (0.31, 96.7–98.0)	97.2 (0.31, 96.6–97.8)	98.0 (0.34, 97.3–98.7)
Serum creatinine (mg/dL), mean (SD, 95% CI), n = 19,728	0.87 (0.01, 0.86–0.87)	0.87 (0.01, 0.86–0.88)	0.87 (0.01, 0.86–0.88)	0.87 (0.01, 0.86–0.89)	0.87 (0.01, 0.86–0.89)
Race, % (n, 95% CI)					
Mexican American	9.1 (9,836, 7.4–11.1)	8.3 (1,218, 6.7–10.2)	8.2 (956, 6.5–10.3)	8.3 (950, 6.6–10.4)	8.7 (646, 6.4–11.8)
Other Hispanic	5.0 (3,192, 3.8–6.6)	4.9 (495, 3.7–6.5)	5.1 (447, 3.6–7.1)	5.0 (435, 3.6–7.1)	4.9 (385, 3.4–7.1)
Non-Hispanic White	67.7 (17,274, 64.1–71.0)	69.8 (3,071, 66.2–73.1)	69.8 (2,439, 65.6–73.6)	70.1 (2,407, 66.0-73.8)	69.0 (1,703, 63.5–73.9)
Non-Hispanic Black	12.0 (9,512, 10.3–13.9)	10.7 (1,149, 9.1–12.7)	10.6 (917, 8.8–12.7)	10.4 (890, 8.7–12.5)	10.6 (643, 8.7–12.9)
Other Race/ multi-racial	6.3 (2,033, 5.4–7.4)	6.4 (299, 5.4–7.6)	6.3 (235, 5.2–7.7)	6.2 (228, 5.1–7.5)	6.8 (180, 5.4–8.6)
Family income-to-poverty ratio (PIR), % (n, 95% CI)					
Below poverty (PIR < 1)	15.9 (10,365, 14.8–17.0)	12.6 (1,122, 11.5–13.7)	12.8 (898, 11.7–14.0)	12.7 (876, 11.6–13.8)	13.3 (684, 11.9–14.8)

Characteristics[†]	All participants (N = 41,847)[1]	2,4-D(n = 6232)[2]	3,5,6 (n = 4994)[3]	3-PBA (n = 4910)[4]	Malathion (n = 3557)[5]
At or above poverty (PIR > = 1)	84.1 (31,482, 83.0-85.2)	87.4 (5,110, 86.3–88.5)	87.2 (4,096, 86.0-88.3)	87.3 (4,034, 86.2–88.5)	86.7 (2,873, 85.2–88.1)
Cigarettes smoking, % (n, 95% CI), n = 22,576[6]					
Current smoker	23.3 (4,967, 22.2–24.4)	23.4 (1,423, 21.9–24.8)	23.0 (1,128, 21.4–24.9)	23.0 (1,098, 21.3–24.8)	21.6 (777, 19.5–23.8)
Former smoker	24.6 (5,791, 23.5–25.6)	24.2 (1,578, 23.0-25.5)	24.1 (1,258, 22.6–25.6)	24.3 (1,248, 22.9–25.9)	23.7 (874. 22.2–25.4)
Non-smoker	52.2 (11,818, 50.6–53.7)	52.4 (3,226, 50.7–54.1)	52.9 (2,604, 50.7–55.0)	52.7 (2,560, 50.5–54.8)	54.7 (1,903, 52.0-57.4)
Alcohol consumption, % (n, 95% CI), n = 41,831[7]					
Current drinker	9.7 (2,993, 8.9–10.6)	12.3 (856, 11.2–13.4)	11.4 (661, 10.2–12.7)	11.5 (654, 10.2–12.8)	10.8 (457, 9.2–12.6)
Abstinence	90.3 (38,838, 89.4–91.2)	87.7 (5,373, 86.6–88.8)	88.6 (4,330, 87.3, 89.8)	88.5 (4,253, 87.2–89.8)	89.2 (3,097, 87.4–90.8)
Hypertension, % (n, 95% CI), n = 29,382[8]					
Yes	29.9 (9,026, 28.4–31.4)	34.9 (2,394, 33.1–36.7)	34.7 (1,941, 32.8–36.7)	34.7 (1,910, 32.8–36.8)	35.2 (1,428, 33.0-37.5)
No	70.2 (20,356, 68.7–71.6)	65.1 (3,443, 63.3–66.9)	65.3 (2,790, 63.4–67.2)	65.3 (2,740, 63.3–67.2)	64.8 (1,976, 62.5–67.0)
Diabetes, % (n, 95% CI), n = 14,946[9]					

Characteristics†	All participants (N = 41,847)[1]	2,4-D(n = 6232)[2]	3,5,6 (n = 4994)[3]	3-PBA (n = 4910)[4]	Malathion (n = 3557)[5]
Yes	18.5 (3,331, 17.6–19.5)	19.2 (855, 17.5–20.9)	19.9 (723, 18.0-21.8)	19.8 (711, 17.9–21.8)	22.9 (587, 20.4–25.6)
No	81.5 (11,615, 80.5–82.4)	80.9 (2,600, 79.1–82.5)	80.1 (2,103, 78.2–82.0)	80.2 (2,067, 78.2–82.1)	77.1 (1,473, 74.4–79.6)
Chronic Kidney disease, % (n, 95% CI), n = 26,619					
Yes	5.1 (1,776, 94.3–95.4)	4.8 (423, 4.2–5.4)	4.9 (346, 4.3–5.6)	5.0 (346, 4.5–5.7)	5.3 (267, 4.7–6.1)
No	94.9 (24,843, 4.6–5.7)	95.2 (5,809, 94.6–95.8)	95.1 (4,648, 94.4–95.7)	95.0 (4,564, 94.3–95.6)	94.7 (3,290, 93.9–95.4)

† N presented in the first column is for all participants only who had non-missing values.

[1]Every participant in NHANES 2001–2004, 2007–2010 is included. MEC weight applied.

[2]2,4-D abbreviates to 2,4-dichlorophenoxyacetic acid. Only participants aged 20 to 80 and with 2,4-D data available are included. Pesticide weight applied.

[3]3,5,6 abbreviates to 3,5,6-trichloropyridinol. Only participants aged 20 to 80 and with 3,5,6-rrichloropyridinol data available are included. Pesticide weight applied.

[4]3-PBA abbreviates to 3-phenoxybenzoic acid. Only participants aged 20 to 80 and with 3-PBA data available are included. Pesticide weight applied.

[5]Only participants aged 20 to 80 and with Malathion data available are included. Pesticide weight applied.

[6] 1) Current smoker: Smoke for at least 100 cigarettes during lifetime and report smoking every day or some days at the time participating in the survey. 2) Former smoker: Smoke for at least 100 cigarettes during lifetime and report not smoking at the time participating in the survey. 3) Non-smoker: Smoke for less than 100 cigarettes during lifetime. 4) Missing value: either refuse, don't know, or miss to answer the 2 questions.

[7] 1) Current drinker: self-reported of drinking at least 12 alcohol in lifetime. 2) Abstinence: self-reported of not drinking 12 alcohol in lifetime.

[8] Either systolic blood pressure (SBP) over 140 mmHg or diastolic blood pressure (DBP) over 90 mmHg or had ever taken anti-hypertensive medications.

[9] Either fasting glucose level over 126 mg/dL or had ever taken diabetic medications to decrease blood sugar level.

Risk of low kidney function from pesticide exposures

The odds ratio of low kidney function risk was presented after pesticide concentrations were log-transformed (Table 2). The odds of low kidney function were higher in the Malathion subgroup, as Malathion increased the risk of low kidney function among them in the adjusted model (aOR = 1.26, 95% CI = 1.01–1.56). Significantly increased risk of low kidney function was not found among 2,4-D, 3,5,6-trichloropyridinol (chlorpyrifos) and 3-PBA.

3.3 Sensitivity analysis

In the sensitivity analysis, we exclude participants with previous hypertension and diabetes history (Table 3). Results were mostly similar to the main analyses.

Table 2
Weighted logistic regression of the pesticide exposure and low kidney function for participants in the National Health and Nutrition Examination Survey conducted in US between 2001–2004 and 2007–2010

Pesticide	Crude OR	Adjusted OR*
log Cadmium (n = 19,468)	**1.40 (1.30–1.50)**	1.21 (1.05–1.38)
log 2,4-D (n = 6,232)	1.05 (0.89–1.23)	0.88 (0.72–1.09)
log 3,5,6-trichloropyridinol (n = 4,994)	1.07 (0.95–1.20)	0.96 (0.83–1.12)
log Malathion diacid (n = 3,557)	**1.30 (1.15–1.46)**	**1.26 (1.01–1.56)**
log 3-phenoxybenzoic acid (n = 4,910)	0.97 (0.88–1.06)	1.03 (0.94–1.13)
*Adjusted for age, sex, poverty income ratio, ethnicity, smoking, and NHANES wave.		

Table 3
Sensitivity analysis of pesticide and low kidney function after excluding participants with hypertension and diabetes in the National Health and Nutrition Examination Survey conducted in US between 2001–2004 and 2007–2010

Pesticide	Crude OR	Adjusted OR*
log Cadmium (n = 17,508)	**1.48 (1.36–1.61)**	**1.30 (1.10–1.52)**
log 2,4-D (n = 5,620)	1.12 (0.93–1.34)	0.97 (0.76–1.25)
log 3,5,6- trichloropyridinol (n = 4,480)	1.08 (0.93–1.25)	0.93 (0.79–1.10)
log Malathion diacid (n = 3,140)	**1.34 (1.16–1.54)**	**1.32 (1.01–1.73)**
log 3-phenoxybenzoic acid (n = 4,405)	0.96 (0.88–1.05)	1.02 (0.93–1.12)
*Adjusted for age, sex, poverty income ratio, ethnicity, smoking, and NHANES wave.		

Discussion

We wished to examine if exposure to pesticides was associated with kidney dysfunction, such as CKD, and acute kidney injury, while adjusting for a range of risk factors. By using an extant cohort with a range of exposure and outcome measures, we were also able to examine subgroups of kidney dysfunction that mimic CKDu (i.e. kidney dysfunction without diabetes and hypertension). In this study we observed an increased risk of low kidney function associated with Malathion exposure. The association between Malathion and low kidney function was also present when excluding participants that had diabetes or hypertension, suggesting an association between Malathion and CKDu is possible. We did not find 2,4-D, chlorpyrifos and 3-PBA exposures were associated with the risk of low kidney function in NHANES 2001–2004, 2007–2010 population. The increased risk of low kidney function was in the same effect size as our positive control, the known nephrotoxin cadmium.

Strengths and weaknesses of the study

We investigated the association of exposure to four pesticides from different classes and kidney function in a representative sample of the US non-institutionalised population using four NHANES waves. Measures of pesticide exposure (and cadmium) were derived from biosampling using a range of measurement techniques giving a known concentration of toxin exposure for individuals (https://www.cdc.gov/nchs/nhanes/index.htm). In order to make the study generalisable to the US population the study was designed using strategies including unequal probability sampling, non-response adjustment and post-stratification adjustment (Johnson et al. 2013).

The cross-sectional study design is the key limitation of NHANES and this study. A cross-sectional design is prone to reverse causation, preventing any conclusions on the direction of the association between pesticide exposures and kidney function. In addition, only single measurements of pesticides were determined, which does not represent chronic exposure. Similarly, kidney dysfunction is only measured at one time point, as opposed to a more classical CKD measure (two measures, three months or longer apart). The limitations of using the NHANES data highlight the need for longitudinal studies that will aid establishing the temporality and directionality of the relationship between exposure and outcome.

Pesticide exposures with kidney function loss and CKDu

Animal studies have identified herbicide and pesticides as the cause of tissue damage and renal dysfunction. An animal study found significant increase in plasma urea level and creatinine among rats administered to 2,4-D for 28 consecutive days (Tayeb et al. 2012), and the increased urea and creatinine level after acute chlorpyrifos exposures (Tanvir et al. 2016). In a study in rats, exposure to Malathion were found to increase in kidney weight, as well as serum creatinine and urea levels (Selmi et al. 2018), which are signals of kidney injury and kidney function loss.

Several studies in humans have suggested pesticides, including Malathion are linked to nephrotoxicity (Badr 2020). An El Salvadoran study did not find a relationship between “ever use” of 2,4-D, organophosphates and pyrethroids and reduced kidney function among sugarcane workers after harvest season, based on self-reported exposure (Garcia-Trabanino et al. 2015). Another study in Nicaragua also

did not find an association between “ever use” of 2,4-D or chlorpyrifos and low kidney function (Wesseling et al. 2016). The authors identified the lacking of biomarkers data and the lack of longitudinal design as key limitations to accurately quantifying the level of pesticide exposure (Wesseling et al. 2016). Another weakness was the use of a self-report questionnaire that may lead to information bias as the accuracy of workers recall may be different if they are surveyed during or after harvest season.

More recent studies using data from a prospective cohort study, did not find a positive association between cumulative lifetime use of 2,4-D, chlorpyrifos and Malathion exposure and ESRD among licensed pesticide applicators in the US (Lebov et al. 2016). This is important because the authors quantified the level of lifetime pesticide exposure by collecting the intensity and the duration of pesticide use using a self-administrated questionnaire (Lebov et al. 2016).

Malathion is the most widely used OP in the US (Bonner et al. 2007) and is used in agricultural setting as well as eradicating ectoparasites or household insects, as it is relatively less toxic than other OPs (Bogen and Singhal 2017). Malathion exposure has been found to affect kidney function in acute intoxication, as evidenced by a case of acute renal insufficiency with proteinuria (Albright et al. 1983), and a case of acute kidney injury and nephrotic syndrome after Malathion inhalation for 15 days (Yokota et al. 2017). However, epidemiological studies have not elucidated the relationship between Malathion exposure and kidney function loss/CKD (Lebov et al. 2016), potentially due to dose or memory recall of pesticides used.

Conclusions

This study provides evidence that exposure to the OP Malathion increases the risk of low kidney function in the general US population. There is a need to explore the interaction between pesticide exposure (acute and chronic) and other CKD risk factors such as diabetes, blood pressure, heat stress and environmental toxins. Further research is required to investigate if other pesticides are associated with kidney function loss in longitudinal studies, and in a range of exposure settings.

Declarations

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Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data, material and code: As mentioned in the paper, the code and the data are publically available at https://github.com/MountStats/PestKidneyGrace.

Authors’ contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by En-Tzu Wan, Darsy Darssan and Nicholas Osborne. The first draft of the manuscript was written by En-Tzu Wan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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