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Agent Orange exposure and disease prevalence in Korean Vietnam veterans: The Korean veterans health study

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ABSTRACT

Between 1961 and 1971, military herbicides were used by the United States and allied forces for military purposes. Agent Orange, the most-used herbicide, was a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid, and contained an impurity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Many Korean Vietnam veterans were exposed to Agent Orange during the Vietnam War. The aim of this study was to evaluate the association between Agent Orange exposure and the prevalence of diseases of the endocrine, nervous, circulatory, respiratory, and digestive systems. The Agent Orange exposure was assessed by a geographic information system-based model. A total of 111,726 Korean Vietnam veterans were analyzed for prevalence using the Korea National Health Insurance claims data from January 2000 to September 2005. After adjusting for covariates, the high exposure group had modestly elevated odds ratios (ORs) for endocrine diseases combined and neurologic diseases combined. The adjusted ORs were significantly higher in the high exposure group than in the low exposure group for hypothyroidism (OR=1.13), autoimmune thyroiditis (OR=1.93), diabetes mellitus (OR=1.04), other endocrine gland disorders including pituitary gland disorders (OR=1.43), amyloidosis (OR=3.02), systemic atrophies affecting the nervous system including spinal muscular atrophy (OR=1.27), Alzheimer disease (OR=1.64), peripheral polyneuropathies (OR=1.09), angina pectoris (OR=1.04), stroke (OR=1.09), chronic obstructive pulmonary diseases (COPD) including chronic bronchitis (OR=1.05) and bronchiectasis (OR=1.16), asthma (OR=1.04), peptic ulcer (OR=1.03), and liver cirrhosis (OR=1.08). In conclusion, Agent Orange exposure increased the prevalence of endocrine disorders, especially in the thyroid and pituitary gland; various neurologic diseases; COPD; and liver cirrhosis. Overall, this study suggests that Agent Orange/2,4-D/TCDD exposure several decades earlier may increase morbidity from various diseases, some of which have rarely been explored in previous epidemiologic studies.

1. Introduction

Between 1961 and 1971, around 77 million liters of military herbicides were used by the United States and allied forces in Vietnam to defoliate forests, to clear the perimeters of military installations, and to destroy the enemy's crops (Stellman et al., 2003). The best-known and the most-used herbicide was Agent Orange, which was a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The phenoxy herbicides in Agent Orange, especially 2,4,5-T, were contaminated with varying levels of dioxin congeners including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Stellman et al., 2003).

Agent Orange was sprayed at base perimeters, roadways, and communication lines, mainly by C-123, military transport aircraft,

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AD, Alzheimer disease; aOR, adjusted odds ratio; AhR, aryl hydrocarbon receptor; ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EOI, Exposure Opportunity Index; GIS, geographic information system; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision; $Log_{10}E4$, log-transformed E4; NA, not available; NS, nerve system; PD, Parkinson disease; ROK, Republic of Korea; SCC, squamous cell carcinoma; TCDD, 2,3,7,8-tetrachloro-dibenzo-p-dioxin

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as well as helicopters, riverboats, and trucks (Michalek et al., 1990). Some ground troops who were not on spraying missions were stationed at or saw action in defoliated areas, and they were exposed to Agent Orange by soil contact, drinking water, or bathing (Institute of Medicine, 2011). From the initial deployment of 1964 to complete withdrawal on March 1973, around 320,000 Republic of Korea (ROK) military personnel were deployed in Vietnam (Yi et al., 2001) and many of those veterans were exposed to Agent Orange.

Initial studies on 2,4-D revealed neurotoxic effects of the exposure (Brahmi et al., 2003), and 2,4,5-T exposure was associated with neurotoxicity (Singer et al., 1982) as well as reproductive and developmental toxicity (Lemaire et al., 2006), while TCDD was found to be an endocrine disruptor and a carcinogen to humans, among other toxicities (Baan et al., 2009). The possibility that Agent Orange may cause non-malignant diseases has not received adequate attention; the association between related chemicals and diseases has been explored mainly by mortality studies (Barrett et al., 2001; Consonni et al., 2008; Cypel and Kang, 2010; Pesatori et al., 2003), in which individuals suffering less severe diseases sometimes are underestimated, especially in cases with more severe co-morbidities (Pesatori et al., 2003; Sin et al., 2006). Meanwhile, many non-cancerous morbidity studies have focused on a small number of diseases or broad categories of several diseases combined (Barrett et al., 2001; Goldner et al., 2010; Michalek et al., 2001; Michalek and Pavuk, 2008), and they have generally failed to explore various specific morbidities in populations potentially exposed to Agent Orange/TCDD-related chemicals, partly because of the small number of subjects included in their investigations.

This large-scale study in Korean Vietnam veterans examined the prevalence of various disorders of the endocrine, nervous, circulatory, respiratory, and digestive systems, and evaluated the hazardous effects of Agent Orange exposure on human health by exploring associations between Agent Orange exposure and specific morbidities, after adjusting for major health-related covariates. Agent Orange exposure was assessed by a geographic information system (GIS)-based model.

2. Material and methods

2.1. Study subjects

This study is a part of the Korean Veterans Health Study (KVHS), which was primarily established to evaluate the association between experience in Vietnam and Agent Orange exposure, and the morbidities and mortality from various diseases. In the KVHS study, the authors identified 187,897 veterans in 1999–2000 and then their current address and residence status were obtained as of June 2004 (Yi et al., 2013). Since the original KVHS cohort had information based only on military records during the Vietnam era, it lacked health-related variables and details about the unit in which the veterans had served. After excluding 23,689 individuals who were deceased or had emigrated, 164,208 living veterans were selected for a postal survey. The survey was sent out July 27, 2004, and 114,562 veterans replied (response rate of 69.8%). Finally, 111,726 veterans, whose Agent Orange exposure index was constructed, were included in the analysis. This study was approved by Institutional review board of Kwandong University.

2.2. Case ascertainment

The Korea National Health Insurance (KNHI) claims data from the Health Insurance Review and Assessment Service of Korea from January 1, 2000 to September 30, 2005 were collected. For medical care covered directly by the government through the Veterans Health Service, Veterans Health Service claims data of the same period were collected. The disease diagnosis was identified by the primary diagnosis and first coexisting condition based on the 10th revision of the International Classification of Diseases (ICD-10) codes that were reported in the claims data. We considered a veteran to be a prevalent case when he visited a medical institution for the diagnosed diseases at least once between January 1, 2000 and September 30, 2005 (period prevalence). The research investigated the prevalence of endocrine diseases (E00-E90), neurologic diseases (G00-G99), circulatory diseases (I00-I99), respiratory diseases (J00-J99), and digestive diseases (K00-K93).

2.3. Agent Orange exposure assessment

An Agent Orange exposure index was constructed for the study, adopting the GIS-based Exposure Opportunity Index (EOI) model E4 (Stellman et al., 2003; Yi et al., 2013). This index was based on the proximity of the veterans' military unit to an Agent Orange-sprayed area. A unit-level E4 score was calculated; then an individual E4 score was constructed from the unit served and period deployed. Thus, veterans with the same military unit and period would have the same exposure score. After adding 1 to each E4 score, the common log-transformed E4 score ($Log_{10}E4$) was used as the individual's index of exposure to Agent Orange (Yi et al., 2013). The average score $\pm$ standard deviation, minimum, and maximum of $Log_{10}E4$ were 2.6 ± 2.2, 0.0, and 6.3, respectively.

For the combat units, we used the average E4 score of the operational area when each unit participated in the operation, but when the unit was not part of the operation, we used the E4 score of the unit's post-location to determine the unit's E4 score. For the Construction Support Group, the average score of the tactical area of responsibility was used as the unit's E4 score, while the average score of the post locations was used as the unit's E4 score for the other 3 support units that did not have a tactical area of responsibility. For the veterans whose units served were not identified (0.5%, Table 1), the average score of all units was used as their E4 score.

The Veterans' deployed unit was obtained from the survey. The information on the combat unit in which a veteran served was obtained at the battalion or company level; meanwhile, for the support units, the veterans were asked in which unit they served among ROK Army Headquarters, the Construction Support Group, Naval Transport Group, and 100th Logistic Command. Information on each veteran's period of deployment was obtained from military records.

The veterans were categorized into 2 groups (low ($Log_{10}E4 < 4.0$) and high exposure ($Log_{10}E4 \geq 4$)) and 4 groups (no ($Log_{10}E4 < 0.1$), low ($0.1 \leq Log_{10}E4 < 4.0$), moderate ($4.0 \leq Log_{10}E4 < 5.0$), and high exposure ($Log_{10}E4 \geq 5.0$)). More details about the exposure index can be found elsewhere (Yi et al., 2013). In a total of 111,726 veterans, Agent Orange exposure at the battalion/brigade level was constructed. The distribution of no, low, moderate, and high exposure groups was 34,478 (30.9%), 34,827 (31.2%), 22,452 (20.1%), and 19,969 (17.9%) veterans, respectively.

2.4. Covariates

A veteran's age was calculated, as of January 1, 2000, using the birthdate in the resident registry, and the military rank was obtained from military records. Information on health-related variables, such as smoking, drinking, exercise, body mass index (BMI), domestic (non-military) use of herbicides, education, and household income, as well as the military unit at the battalion or company level in which veterans had served during the Vietnam War, was obtained from the survey. The BMI was calculated from self-reported weight (kg) divided by the squared value of the height (m).

2.5. Statistical analysis

A chi-squared test and ANOVA were performed to compare individual characteristics and prevalence by categories of Agent Orange exposure. Logistic regression analysis was performed to demonstrate the impacts of the exposure on disease prevalence while adjusting for age, military rank (enlisted soldier, noncommissioned officer, officer), smoking (current smoker, past smoker, never smoker), drinking frequency (times; 5 or more/week, 1–4/week, 1–3/month, 1–11/year, no drinking), physical activity (frequency, 10 min or more of moderate or vigorous physical activity; 4 or more times/week, 1–3/week, 1–2/month, no activity), experience of domestic herbicide use (never, ever), education (elementary school or no education, middle or high school, college or over), household income (Korean won, 1 USD=1170 Korean won as of August 1, 2004; < 1,000,000, 1,000,000–1,490,000, 1,500,000–2,490,000, ≥ 2,500,000) and BMI (< 20.5, 20.5–22.9, 23.0–24.9, 25.0–26.9, ≥ 27.0). The Agent Orange exposure was analyzed as a continuous variable ($Log_{10}E4$), and as categorical variables with 2 groups and 4 groups. Analysis for trend was done using an ordinal variable representing the 4 groups of Agent Orange exposure. The *p*-value was calculated with two-sided tests, and a statistical significance level of 0.05 was applied. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

The average age as of January 2000 in the low and high exposure groups was 53.9 ± 3.7 and 55.1 ± 3.1 years, respectively.

Table 1
Vietnam service characteristics and health-related variables by 2 categories of Agent Orange exposure among Vietnam veterans ($n=111,726$).

Characteristics	Classification	n	(%)	Agent Orange exposure level				p-value[a]
				Low ($n=69,305$)		High ($n=42,421$)		
				n	(%)	n	(%)	
Age as of January 1, 2000 (years)	< 50	5365	(4.8)	5167	(7.5)	198	(0.5)	< 0.001
	50–54	68,695	(61.5)	42,123	(60.8)	26,572	(62.6)	
	55–59	30,549	(27.3)	17,790	(25.7)	12,759	(30.1)	
	≥ 60	7117	(6.4)	4225	(6.1)	2892	(6.8)	
Deployed unit	Capital division (combat)	40,802	(36.5)	26,220	(37.8)	14,582	(34.4)	< 0.001
	9th Division (combat)	37,903	(33.9)	22,493	(32.5)	15,410	(36.3)	
	2nd Marine brigade (combat)	3866	(3.5)	2319	(3.3)	1547	(3.6)	
	ROK army headquarters	3021	(2.7)	2548	(3.7)	473	(1.1)	
	Construction support group	5808	(5.2)	3850	(5.6)	1958	(4.6)	
	Naval transport group	406	(0.4)	349	(0.5)	57	(0.1)	
	100th Logistic command	19,383	(17.3)	11,121	(16.0)	8262	(19.5)	
	Unknown	537	(0.5)	405	(0.6)	132	(0.3)	
Military rank	Enlisted	86,438	(77.4)	53,719	(77.5)	32,719	(77.1)	< 0.001
	Noncommissioned officer	15,893	(14.2)	9622	(13.9)	6271	(14.8)	
	Company officer	7696	(6.9)	4808	(6.9)	2888	(6.8)	
	Field officer or general	1699	(1.5)	1156	(1.7)	543	(1.3)	
Year first deployed to Vietnam	Up to 1966	19,834	(17.8)	14,424	(20.8)	5410	(12.8)	< 0.001
	1967–1968	30,407	(27.2)	8710	(12.6)	21,697	(51.1)	
	1969–1970	34,417	(30.8)	19,103	(27.6)	15,314	(36.1)	
	1971 and beyond	27,068	(24.2)	27,068	(39.1)	0	(0.0)	
Smoking	Current smoker	39,653	(35.5)	25,106	(36.2)	14,547	(34.3)	< 0.001
	Past smoker	51,057	(45.7)	31,563	(45.5)	19,494	(46.0)	
	Never smoker	21,016	(18.8)	12,636	(18.2)	8380	(19.8)	
Drinking frequency (times)	5 or more/week	11,842	(10.6)	7452	(10.8)	4390	(10.3)	< 0.001
	1–4/week	42,054	(37.6)	26,489	(38.2)	15,565	(36.7)	
	1–3/month	27,120	(24.3)	16,747	(24.2)	10,373	(24.5)	
	1–11/year	13,117	(11.7)	8060	(11.6)	5057	(11.9)	
	No drinking	17,593	(15.7)	10,557	(15.2)	7036	(16.6)	
Physical activity (times)	4 or more/week	18,899	(16.9)	11,569	(16.7)	7330	(17.3)	0.002
	1–3/week	43,629	(39.0)	27,225	(39.3)	16,404	(38.7)	
	1–2/month	11,693	(10.5)	7371	(10.6)	4322	(10.2)	
	No activity	37,505	(33.6)	23,140	(33.4)	14,365	(33.9)	
Domestic herbicide	No	80,753	(72.3)	50,167	(72.4)	30,586	(72.1)	0.302
Experience	Yes	30,973	(27.7)	19,138	(27.6)	11,835	(27.9)	
Education	Elementary school or no education	29,746	(26.6)	17,506	(25.3)	12,240	(28.9)	< 0.001
	Middle or high school	63,822	(57.1)	40,561	(58.5)	23,261	(54.8)	
	College or over	14,662	(13.1)	9299	(13.4)	5363	(12.6)	
Household income (unit: Korean Won)	< 1,000,000	33,466	(30.0)	20,021	(28.9)	13,445	(31.7)	< 0.001
	1,000,000–1,490,000	26,529	(23.7)	16,693	(24.1)	9836	(23.2)	
	1,500,000–2,490,000	27,452	(24.6)	17,393	(25.1)	10,059	(23.7)	
	≥ 2,500,000	18,987	(17.0)	12,343	(17.8)	6644	(15.7)	
Body mass Index (kg/m^2)	< 20.5	12,054	(10.8)	7342	(10.6)	4712	(11.1)	0.007
	20.5–22.9	30,636	(27.4)	19,048	(27.5)	11,588	(27.3)	
	23.0–24.9	33,515	(30.0)	20,844	(30.1)	12,671	(29.9)	
	25.0–26.9	21,105	(18.9)	13,273	(19.2)	7832	(18.5)	
	≥ 27.0	10,451	(9.4)	6554	(9.5)	3897	(9.2)	

ROK, Republic of Korea.

[a] Chi-squared test.

Relative to the low exposure group, members of the high exposure group tended to be over 60 years old and non-commissioned officers, to serve in the 100th Logistic Command, to be deployed during 1967–1968, and to be less likely to be current smokers (Table 1). Nearly all of the variables/characteristics showed small but significant differences among the exposure groups (Table 1).

The majority of Vietnam veterans were suffering from respiratory diseases (J00–J99)(86.3%), digestive diseases (K00–K93) (85.0%), and circulatory diseases (I00–I99)(59.2%). Less severe morbidities were more prevalent than more severe morbidities. For example, 14.6% of the veterans sought medical attention for angina pectoris, while 2.8% of the veterans visited medical facilities for myocardial infarction. The prevalence of most of the diseases increased as Agent Orange exposure increased from low exposure to high exposure (Table 2).

An increasing $Log_{10}E4$ was associated with high aORs for endocrine diseases combined (E00–E90), for all thyroid diseases including autoimmune thyroiditis, and for diabetes as well as for amyloidosis. In addition, the aORs for endocrine diseases combined, non-iodine-deficiency-related hypothyroidism, other nontoxic goiter, autoimmune thyroiditis, diabetes (including Type 1 and Type 2 diabetes), other endocrine gland disorders (including disorders of the pituitary gland such as hypopituitarism), and amyloidosis in high exposure group were found to be significantly higher than those in the low exposure group in the two group analysis (Table 3).

The aORs of neurologic diseases combined (G00–G99), systemic atrophies primarily affecting the nervous system (including spinal muscular atrophy), other degenerative neurologic diseases (including Alzheimer disease (AD)), epilepsy, nerve and plexus disorders, peripheral polyneuropathies, and paralytic syndromes were significantly

Table 2
Prevalence of disease by 2 categories of Agent Orange exposure.

Disease	ICD-10	Total	Agent Orange exposure level				*p*-value[a]
			Low (*n*=69,305)		High (*n*=42,421)		
			n	(%)	*n*	(%)	
Endocrine, nutritional, and metabolic diseases	E00–E90	50,188	30,657	(44.2)	19,531	(46.0)	< 0.001
Disorders of the thyroid gland	E00–E07	5408	3274	(4.7)	2134	(5.0)	0.021
Non-iodine-deficiency hypothyroidism	E03	1444	846	(1.2)	598	(1.4)	0.007
Other nontoxic goiter	E04	953	567	(0.8)	386	(0.9)	0.105
Thyrotoxicosis (Hyperthyroidism)	E05	2476	1525	(2.2)	951	(2.2)	0.648
Thyrotoxicosis with diffuse goiter	E05.0	418	259	(0.4)	159	(0.4)	0.977
Thyroiditis	E06	423	248	(0.4)	175	(0.4)	0.149
Autoimmune thyroiditis	E06.3	92	44	(0.1)	48	(0.1)	0.005
Diabetes mellitus (DM)	E10–E14	32,833	19,891	(28.7)	12,942	(30.5)	< 0.001
Insulin, dependent DM	E10	5080	2981	(4.3)	2099	(4.9)	< 0.001
Non-insulin-dependent DM	E11	27,606	16,725	(24.1)	10,881	(25.7)	< 0.001
Disorders of other endocrine glands	E20–E35	1003	573	(0.8)	430	(1.0)	0.001
Disorders of the pituitary gland	E22–E23, E24.0	264	141	(0.2)	123	(0.3)	0.004
Hyperfunction of the pituitary gland	E22	71	37	(0.1)	34	(0.1)	0.085
Hypofunction of the pituitary gland	E23	205	110	(0.2)	95	(0.2)	0.013
Hyperaldosteronism	E26	14	6	(0.0)	8	(0.0)	0.139
Primary hyperaldosteronism	E26.0	4	1	(0.0)	3	(0.0)	0.127
Metabolic disorders	E70–E90	27,118	16,683	(24.1)	10,435	(24.6)	0.046
Disorders of lipoprotein metabolism	E78	25,437	15,637	(22.6)	9800	(23.1)	0.037
Amyloidosis	E85	15	6	(0.0)	9	(0.0)	0.079
Diseases of the nervous system (NS)	G00–G99	39,999	24,198	(34.9)	15,801	(37.2)	< 0.001
Systemic atrophies primarily affecting the CNS	G10–G13	333	181	(0.3)	152	(0.4)	0.004
Spinal muscular atrophy	G12	290	158	(0.2)	132	(0.3)	0.008
Motor neuron disease (including ALS)	G12.2	102	57	(0.1)	45	(0.1)	0.200
Extrapyramidal disorders	G20–G26	1455	840	(1.2)	615	(1.4)	0.001
Parkinson disease	G20	474	261	(0.4)	213	(0.5)	0.002
Secondary parkinsonism	G21	177	94	(0.1)	83	(0.2)	0.014
Other degenerative diseases of the NS	G30–G32	669	368	(0.5)	301	(0.7)	< 0.001
Alzheimer disease	G30	106	49	(0.1)	57	(0.1)	0.001
Demyelinating diseases of the CNS	G35–G37	405	241	(0.3)	164	(0.4)	0.294
Multiple sclerosis	G35	334	194	(0.3)	140	(0.3)	0.137
Episodic and paroxysmal disorders	G40–G47	24,006	14,591	(21.1)	9415	(22.2)	< 0.001
Epilepsy	G40	3084	1803	(2.6)	1281	(3.0)	< 0.001
Nerve, nerve root, and plexus disorders	G50–G59	13,024	7787	(11.2)	5237	(12.3)	< 0.001
Polyneuropathies of the peripheral NS	G60–G64	11,434	6754	(9.7)	4680	(11.0)	< 0.001
Paralytic syndromes	G80–G83	2354	1363	(2.0)	991	(2.3)	< 0.001
Diseases of the circulatory system	I00–I99	66,131	40,518	(58.5)	25,613	(60.4)	< 0.001
Hypertensive diseases	I10–I13	50,298	30,701	(44.3)	19,597	(46.2)	< 0.001
Essential (primary) hypertension	I10	48,565	29,619	(42.7)	18,946	(44.7)	< 0.001
Ischemic heart diseases	I20–I25	20,270	12,226	(17.6)	8044	(19.0)	< 0.001
Angina pectoris	I20	16,302	9817	(14.2)	6485	(15.3)	< 0.001
Acute myocardial infarction	I21–I23	3139	1891	(2.7)	1248	(2.9)	0.036
Chronic ischemic heart disease	I25	7003	4213	(6.1)	2790	(6.6)	0.001
Conduction disorders	I44–I49	6108	3708	(5.4)	2400	(5.7)	0.028
Heart failure	I50	3616	2156	(3.1)	1460	(3.4)	0.002

Table 2 (*continued*)

Disease	ICD-10	Total	Agent Orange exposure level				*p*-value[a]
			Low (n=69,305)		High (n=42,421)		
			n	(%)	*n*	(%)	
Stroke	I60–I64	10,354	6024	(8.7)	4330	(10.2)	<0.001
Intracranial hemorrhage	I60–I62	1606	933	(1.3)	673	(1.6)	0.001
Cerebral infarction	I63	9210	5345	(7.7)	3865	(9.1)	<0.001
Atherosclerosis	I70	2665	1629	(2.4)	1036	(2.4)	0.330
Other peripheral vascular diseases	I73	5513	3315	(4.8)	2198	(5.2)	0.003
Diseases of the respiratory system	J00–J99	96,428	59,615	(86.0)	36,813	(86.8)	<0.001
Pneumonia not due to influenza	J12–J18	9412	5604	(8.1)	3808	(9.0)	<0.001
Chronic obstructive pulmonary diseases	J40–J44, J47	36,873	22,262	(32.1)	14,611	(34.4)	<0.001
Chronic bronchitis	J41–J42	19,572	11,704	(16.9)	7868	(18.5)	<0.001
Emphysema	J43	1297	797	(1.1)	500	(1.2)	0.664
Bronchiectasis	J47	2128	1219	(1.8)	909	(2.1)	<0.001
Asthma	J45–J46	17,910	10,739	(15.5)	7171	(16.9)	<0.001
Diseases of the digestive system	K00–K93	94,929	58,663	(84.6)	36,266	(85.5)	<0.001
Peptic ulcer	K25–K27	50,978	31,229	(45.1)	19,749	(46.6)	<0.001
Gastritis and duodenitis	K29	65,596	40,345	(58.2)	25,251	(59.5)	<0.001
Crohn disease	K50	1138	697	(1.0)	441	(1.0)	0.584
Ulcerative colitis	K51	913	555	(0.8)	358	(0.8)	0.437
Diseases of the liver	K70–K77	39,668	24,457	(35.3)	15,211	(35.9)	0.054
Alcoholic liver disease	K70	11,609	7206	(10.4)	4403	(10.4)	0.923
Toxic liver disease	K71	2187	1339	(1.9)	848	(2.0)	0.433
Chronic hepatitis, not elsewhere classified	K73	13,533	8353	(12.1)	5180	(12.2)	0.431
Liver cirrhosis	K74	3377	2031	(2.9)	1346	(3.2)	0.022
Disorders of the gallbladder and pancreas	K80–K87	4924	2960	(4.3)	1964	(4.6)	0.005

ALS, amyotrophic lateral sclerosis; CNS, central nervous system; DM, diabetes mellitus; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision; NS, nervous system.

[a] Chi-squared test.

elevated with an increased Log_{10}E4, and they were also higher in the high exposure group than in the low exposure group. Further, extrapyramidal disorders in the high exposure group, including Parkinson disease, had a marginally significantly higher OR than in the low exposure group (Table 3). Circulatory diseases combined (I00–I99) and respiratory diseases combined (J00–J99) did not show significant associations with Agent Orange exposure. Adjusted ORs for ischemic heart diseases such as angina pectoris, stroke including cerebral infarction, and chronic obstructive pulmonary diseases (COPD) including chronic bronchitis and bronchiectasis were elevated with an increase in the Log_{10}E4 of 1 unit, as well as in the high exposure group compared to low exposure group in the two group analysis. Asthma had a marginally significant excess OR, with an increase of 1 unit in the Log_{10}E4, and had a significantly higher OR in the high exposure group than in the low exposure group in the two group analysis. The OR of intracranial hemorrhage was significantly higher in the high exposure group than in the low exposure group (Table 3). aORs for digestive diseases combined (K00–K93) and liver diseases increased modestly with an increasing Log_{10}E4. The aORs for peptic ulcer and liver cirrhosis were elevated, with an increase of 1 unit in the Log_{10}E4, as well as in high exposure group compared to low exposure group (Table 3).

When a trend test across 4 groups of Agent Orange exposure was performed, the results were generally similar to those of analyses using Log_{10}E4 as a continuous variable. In the trend test across 4 groups of Agent Orange exposure, significant positive trends for endocrine diseases combined and neurologic diseases combined were found, while trends for overall circulatory, overall respiratory, and overall digestive disease did not show significant differences (Supplemental Table 3).

4. Discussion

A significant increase in the prevalence of disorders of the thyroid gland was observed with greater Agent Orange exposure in Korean Vietnam veterans. Several studies have shown modest evidence that TCDD can affect thyroid homeostasis (Calvert et al., 1999) and clinical diseases of the thyroid gland (Goldner et al., 2010; O'Toole et al., 2009; Zober et al., 1994). In the present study,

Table 3
Adjusted odds ratios (aOR)[a] of disease prevalence according to Agent Orange exposure ($Log_{10}E4$[b] and 2 groups) by logistic regression analysis.

Disease	ICD-10	A 1 unit increase in $Log_{10}E4$[b]			High exposure group compared to low exposure group		
		p-value	aOR	(95% CI)	*p*-value	aOR[c]	(95% CI)
Endocrine, nutritional, and metabolic diseases	E00–E90	0.006	1.01	(1.00, 1.01)	0.006	1.04	(1.01, 1.06)
Disorders of the thyroid gland	E00–E07	0.032	1.01	(1.00, 1.03)	0.053	1.06	(1.00, 1.12)
Non-iodine-deficiency hypothyroidism	E03	0.059	1.02	(1.00, 1.05)	0.029	1.13	(1.01, 1.25)
Other nontoxic goiter	E04	0.487	1.01	(0.98, 1.04)	0.049	1.14	(1.00, 1.31)
Thyrotoxicosis (Hyperthyroidism)	E05	0.191	1.01	(0.99, 1.03)	0.824	1.01	(0.93, 1.10)
Thyrotoxicosis with diffuse goiter	E05.0	0.972	1.00	(0.96, 1.05)	0.876	1.02	(0.83, 1.24)
Thyroiditis	E06	0.202	1.03	(0.98, 1.08)	0.123	1.17	(0.96, 1.43)
Autoimmune thyroiditis	E06.3	0.003	1.16	(1.05, 1.28)	0.002	1.93	(1.27, 2.94)
Diabetes mellitus (DM)	E10–E14	0.014	1.01	(1.00, 1.01)	0.006	1.04	(1.01, 1.07)
Insulin, dependent DM	E10	0.120	1.01	(1.00, 1.02)	0.001	1.10	(1.04, 1.17)
Non-insulin-dependent DM	E11	0.029	1.01	(1.00, 1.01)	0.015	1.04	(1.01, 1.07)
Disorders of other endocrine glands	E20–E35	0.095	1.03	(1.00, 1.06)	0.003	1.21	(1.07, 1.38)
Disorders of the pituitary gland	E22–E23,E24.0	0.128	1.04	(0.99, 1.11)	0.004	1.43	(1.12, 1.83)
Hyperfunction of the pituitary gland	E22	0.260	1.06	(0.95, 1.19)	0.133	1.44	(0.90, 2.30)
Hypofunction of the pituitary gland	E23	0.216	1.04	(0.98, 1.11)	0.011	1.44	(1.09, 1.90)
Hyperaldosteronism	E26	0.120	1.24	(0.95, 1.62)	0.227	1.94	(0.66, 5.66)
Primary hyperaldosteronism	E26.0	0.199	1.47	(0.82, 2.65)	0.183	4.74	(0.48, 46.9)
Metabolic disorders	E70–E90	0.077	1.01	(1.00, 1.01)	0.216	1.02	(0.99, 1.05)
Disorders of lipoprotein metabolism	E78	0.057	1.01	(1.00, 1.01)	0.156	1.02	(0.99, 1.05)
Amyloidosis	E85	0.037	1.32	(1.02, 1.71)	0.046	3.02	(1.02, 8.93)
Diseases of the nervous system (NS)	G00–G99	< 0.001	1.01	(1.01, 1.02)	0.001	1.04	(1.02, 1.07)
Systemic atrophies primarily affecting the CNS	G10–G13	0.039	1.06	(1.00, 1.11)	0.030	1.28	(1.02, 1.59)
Spinal muscular atrophy	G12	0.046	1.06	(1.00, 1.12)	0.047	1.27	(1.00, 1.61)
Motor neuron disease (including ALS)	G12.2	0.455	1.04	(0.94, 1.14)	0.296	1.24	(0.83, 1.85)
Extrapyramidal disorders	G20–G26	0.409	1.01	(0.99, 1.03)	0.080	1.10	(0.99, 1.22)
Parkinson disease	G20	0.281	1.02	(0.98, 1.07)	0.070	1.18	(0.99, 1.42)
Secondary parkinsonism	G21	0.796	1.01	(0.94, 1.08)	0.131	1.26	(0.93, 1.69)
Other degenerative diseases of the NS	G30–G32	0.024	1.04	(1.01, 1.08)	0.024	1.19	(1.02, 1.39)
Alzheimer disease	G30	0.015	1.12	(1.02, 1.23)	0.012	1.64	(1.12, 2.41)
Demyelinating diseases of the CNS	G35–G37	0.491	1.02	(0.97, 1.06)	0.764	1.03	(0.84, 1.26)
Multiple sclerosis	G35	0.264	1.03	(0.98, 1.08)	0.438	1.09	(0.88, 1.36)
Episodic and paroxysmal disorders	G40–G47	0.020	1.01	(1.00, 1.01)	0.259	1.02	(0.99, 1.05)
Epilepsy	G40	0.007	1.02	(1.01, 1.04)	0.012	1.10	(1.02, 1.18)
Nerve, nerve root, and plexus disorders	G50–G59	0.001	1.02	(1.01, 1.02)	0.003	1.06	(1.02, 1.10)
Polyneuropathies of the peripheral NS	G60–G64	< 0.001	1.02	(1.01, 1.03)	< 0.001	1.09	(1.04, 1.13)
Paralytic syndromes	G80–G83	0.050	1.02	(1.00, 1.04)	0.035	1.10	(1.01, 1.19)
Diseases of the circulatory system	I00–I99	0.929	1.00	(0.99, 1.01)	0.937	1.00	(0.98, 1.03)
Hypertensive diseases	I10–I13	0.704	1.00	(1.00, 1.01)	0.715	1.00	(0.97, 1.02)
Essential (primary) hypertension	I10	0.518	1.00	(1.00, 1.01)	0.908	1.00	(0.97, 1.02)
Ischemic heart diseases	I20–I25	0.012	1.01	(1.00, 1.02)	0.025	1.04	(1.00, 1.07)
Angina pectoris	I20	0.024	1.01	(1.00, 1.02)	0.028	1.04	(1.00, 1.08)
Acute myocardial infarction	I21–I23	0.699	1.00	(0.99, 1.02)	0.539	1.02	(0.95, 1.10)
Chronic ischemic heart disease	I25	0.166	1.01	(1.00, 1.02)	0.439	1.02	(0.97, 1.07)
Conduction disorders	I44–I49	0.766	1.00	(0.99, 1.01)	0.850	1.01	(0.95, 1.06)
Heart failure	I50	0.402	1.01	(0.99, 1.02)	0.769	1.01	(0.94, 1.08)
Stroke	I60–I64	< 0.001	1.02	(1.01, 1.03)	< 0.001	1.09	(1.04, 1.13)
Intracranial hemorrhage	I60–I62	0.108	1.02	(1.00, 1.04)	0.049	1.11	(1.00, 1.23)

Table 3 (*continued*)

Disease	ICD-10	A 1 unit increase in $Log_{10}E4$[b]			High exposure group compared to low exposure group		
		p-value	aOR	(95% CI)	*p*-value	aOR[c]	(95% CI)
Cerebral infarction	I63	0.001	1.02	(1.01, 1.03)	< 0.001	1.09	(1.04, 1.14)
Atherosclerosis	I70	0.584	1.01	(0.99, 1.02)	0.714	0.99	(0.91, 1.07)
Other peripheral vascular diseases	I73	0.372	1.01	(0.99, 1.02)	0.821	1.01	(0.95, 1.06)
Diseases of the respiratory system	J00–J99	0.123	1.01	(1.00, 1.01)	0.241	1.02	(0.99, 1.06)
Pneumonia not due to influenza	J12–J18	0.094	1.01	(1.00, 1.02)	0.063	1.04	(1.00, 1.09)
Chronic obstructive pulmonary diseases	J40–J44,J47	0.003	1.01	(1.00, 1.01)	0.003	1.04	(1.01, 1.07)
Chronic bronchitis	J41–J42	0.022	1.01	(1.00, 1.02)	0.004	1.05	(1.02, 1.08)
Emphysema	J43	0.431	0.99	(0.96, 1.02)	0.249	0.94	(0.83, 1.05)
Bronchiectasis	J47	0.002	1.03	(1.01, 1.05)	0.001	1.16	(1.06, 1.27)
Asthma	J45–J46	0.083	1.01	(1.00, 1.01)	0.015	1.04	(1.01, 1.08)
Diseases of the digestive system	K00–K93	0.044	1.01	(1.00, 1.02)	0.291	1.02	(0.98, 1.06)
Peptic ulcer	K25–K27	< 0.001	1.01	(1.00, 1.02)	0.011	1.03	(1.01, 1.06)
Gastritis and duodenitis	K29	0.066	1.01	(1.00, 1.01)	0.270	1.01	(0.99, 1.04)
Crohn disease	K50	0.498	0.99	(0.96, 1.02)	0.894	1.01	(0.89, 1.14)
Ulcerative colitis	K51	0.696	1.01	(0.98, 1.04)	0.608	1.04	(0.90, 1.19)
Diseases of the liver	K70–K77	0.004	1.01	(1.00, 1.01)	0.082	1.02	(1.00, 1.05)
Alcoholic liver disease	K70	0.243	1.01	(1.00, 1.01)	0.558	1.01	(0.97, 1.05)
Toxic liver disease	K71	0.683	1.00	(0.98, 1.02)	0.664	1.02	(0.93, 1.11)
Chronic hepatitis, not elsewhere classified	K73	0.350	1.00	(1.00, 1.01)	0.586	1.01	(0.97, 1.05)
Liver cirrhosis	K74	0.007	1.02	(1.01, 1.04)	0.034	1.08	(1.01, 1.16)
Disorders of the gallbladder and pancreas	K80–K87	0.091	1.01	(1.00, 1.03)	0.128	1.05	(0.99, 1.11)

aOR, adjusted odds ratio; ALS, amyotrophic lateral sclerosis; CI, confidence interval; CNS, central nervous system; DM, diabetes mellitus; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision; NS, nervous system.

[a] Adjusted for age as of January 1, 2000 (< 50, 50–54, 55–59, ≥ 60 years), military rank (enlisted, noncommissioned officer, officer), smoking (current smoker, past smoker, never smoker), drinking frequency (times; 5 or more/week, 1–4/week, 1–3/month, 1–11/year, no drinking), physical activity (frequency, times; 4 or more/week, 1–3/week, 1-2/month, No activity), domestic herbicide experience (never, ever), education (elementary school or no education, middle or high school, college or over), household income (Korean Won (KRW), 1 United States Dollar = 1170 KRW as of August 1, 2004; < 1,000,000, 1,000,000–1,490,000, 1,500,000–2,490,000, ≥ 2,500,000), Body mass index (kg/m^2; < 20.5, 20.5–22.9, 23.0–24.9, 25.0–26.9, ≥ 27.0).

[b] $Log_{10}E4$ is the common log-transformed E4 score which was constructed using a geographic information system-based model grounded in the proximity of the veterans' military unit to an Agent Orange-sprayed area.

[c] Compared to low exposure group (2-group analysis).

a significant elevation of the aORs of prevalence for non-iodine deficiency hypothyroidism and autoimmune thyroiditis in the high exposure group was confirmed relative to the low exposure group, and a marginally significant increase in the prevalence of hyperthyroidism across the 4 groups of Agent Orange exposure was revealed. The pituitary gland has been suggested to be a direct target of TCDD (Huang et al., 2002). The TCDD-induced genesis of pituitary gland tumors has been suggested (Vierimaa et al., 2006), and the tendency toward a higher risk of pituitary tumors, although not significant, in subjects with higher exposure was observed in previous research (Pesatori et al., 2008). In this study, the prevalence of pituitary diseases, including hyperpituitarism and hypopituitarism, was increased in the high exposure group compared to the low exposure group, although the increase in the prevalence of hyperpituitarism was not statistically significant. Overall, this study supports that Agent Orange/TCDD may affect the thyroid gland and pituitary gland (Huang et al., 2002).

Korean veterans had a modest but significantly elevated prevalence of diabetes with Agent Orange exposure, which was in accord with previous studies in US and Korean veterans (Cypel and Kang, 2010; Kang et al., 2006; Kim et al., 2003; Michalek and Pavuk, 2008). TCDD exposure, even at very low exposure levels, may be diabetogenic in humans. The diabetogenic effect of TCDD-related exposure, however, has been controversial, and was found to be relatively more apparent in low exposure groups than high exposure groups compared to a reference population, in occupational and environmental studies of populations more highly TCDD-exposed than Vietnam veterans (Calvert et al., 1999; Consonni et al., 2008; Steenland et al., 1999). These results may lead to the hypothesis that low doses of Agent Orange/TCDD affect diabetes mellitus and the relationship between diabetes and Agent Orange/TCDD is nonmonotonic (Vandenberg et al., 2012). In addition, a very modest increase in the prevalence of metabolic disorders including lipidemia was shown, and amyloidosis, which

has rarely been examined in previous research, was more prevalent with higher Agent Orange exposure in this study.

The prevalence of various neurologic disorders, except demyelinating diseases including multiple sclerosis (Quintana et al., 2008), were elevated in the high exposure group compared to the low exposure group. A recent meta-analysis showed that amyotrophic lateral sclerosis (ALS) was associated with the use of pesticides (Kamel et al., 2012). The mortality from ALS among workers potentially exposed to 2,4-D was increased relative to unexposed male workers (Burns et al., 2001). In this study, the prevalence of systemic atrophies affecting the central nervous system (including spinal muscular atrophy) was increased with Agent Orange exposure, although the increased prevalence of motor neuron diseases including ALS was not significant due to the small number of cases. The prevalence of peripheral neuropathies was increased with TCDD exposure in this study in accord with other studies in Seveso residents (Filippini et al., 1981), workers in Germany (Zober et al., 1994), Ranch Hand veterans (Michalek et al., 2001), and Korean veterans (Kim et al., 2003; Yi et al., 2013). A recent meta-analysis also showed that the risk of Parkinson disease was increased by exposure to pesticides/herbicides (Pezzoli and Cereda, 2013, van der Mark et al., 2012), and an association between pesticides and Alzheimer disease has been suggested (Baldi et al., 2003; Parrón et al., 2011). A majority of the neurologic disorders also showed a positive significant association across the 4 groups of Agent Orange exposure in a test-for-trend analysis. Overall, this study supports an earlier finding that TCDD exposure could damage the nervous system long after exposure (Urban et al., 2007).

Some evidence, however, that does not support the long-term neurotoxic effects of TCDD should be noted. The neurologic problems that initially developed in Seveso residents were not sustained 10 years after TCDD exposure, (Assennato et al., 1989) and peripheral neuropathy was not increased among US workers exposed to TCDD 15 years earlier (Sweeney et al., 1993). Despite the suggested association between pesticides/herbicides and neurodegenerative diseases such as ALS, Parkinson disease, and Alzheimer disease, the specific compounds causing the effect still need to be verified (Kamel et al., 2012; Pezzoli and Cereda, 2013; Zaganas et al., 2013), and the evidence for an association of pesticide exposure with an increased risk for some neurodegenerative diseases is still limited (Zaganas et al., 2013). The mortality from nervous system diseases among TCDD-exposed people in occupational and environmental cohort studies has rarely shown an increase. (Consonni et al., 2008; Flesch-Janys et al., 1998; Ruder and Yiin, 2011). The lack of an association between Agent Orange/TCDD and neurologic disorders in mortality studies may be explained by the small number of deaths and, partly, the possibility that more fatal comorbidities such as cancers obscure the risk of neurologic disorders in people susceptible to Agent Orange/TCDD-related chemical exposure.

The association between Agent Orange exposure and circulatory diseases was mixed in this study. Although the finding of very modestly increased prevalence from angina but non-increased prevalence from myocardial infarction was somewhat similar to that of the mortality study in Korean Vietnam veterans (Yi and Ohrr, 2011), myocardial infarction has been the main morbidity and mortality associated with herbicide/TCDD exposure, while angina has rarely been examined with herbicide/TCDD exposure in previous research mainly in US and European populations (Ketchum and Michalek, 2005; Vena et al., 1998). Furthermore, due to a modestly elevated prevalence of stroke but non-elevated prevalence of hypertension and atherosclerosis, two of the major risk factors for stroke, interpretation of the mechanism of action of Agent Orange/TCDD exposure is difficult.

The prevalence of chronic obstructive pulmonary diseases (COPD) (including chronic bronchitis and bronchiectasis) and asthma was modestly yet significantly increased with Agent Orange exposure, and a positive significant trend in the prevalence from COPD and asthma was observed across the 4 groups of Agent Orange exposure. Morbidity studies among Vietnam veterans have shown an increased prevalence of non-cancer respiratory diseases with potential TCDD exposure (Kang et al., 2006; O'Toole et al., 2009; Yi et al., 2013). A National Institute for Occupational Safety and Health study found an elevated prevalence of COPD (OR=1.55) based on 11 cases among workers exposed to TCDD, although the elevation of prevalence was not significant (Calvert et al., 1991). Among workers in Germany exposed to TCDD, the prevalence of COPD was increased in the severe chloracne group, but not in the moderate or no chloracne group compared to referents (Zober et al., 1994). The Agricultural Health Study has found an association between phenoxy herbicides and chronic bronchitis and allergic asthma (Hoppin et al., 2009). Mortality studies in populations exposed to TCDD among the Army Chemical Corps (Cypel and Kang, 2010), Seveso residents (Consonni et al., 2008), and US pentachlorophenol production workers (Ruder and Yiin, 2011) also showed an increased mortality from COPD. Although the mortality from non-malignant respiratory disorders combined, among workers exposed to TCDD, was not increased in several occupational cohort studies, mortality from COPD and asthma have rarely been explored specifically in those studies (Collins et al., 2009; McBride et al., 2009; Steenland et al., 1999). The direct chronic toxicity of TCDD to alveolar tissue was described decades ago (Kociba et al., 1979), and several AhR-mediated mechanisms such as immunomodulation, cell–cell adhesion interactions, and mucin production may account for the pathogenesis and exacerbation of COPD/asthma (Chiba et al., 2012).

The prevalence of liver cirrhosis and peptic ulcer was small yet significantly increased with increasing Agent Orange exposure. Some studies have shown that the morbidity from liver cirrhosis or peptic ulcer increased with possible TCDD exposure (Cypel and Kang, 2010; McBride et al., 2009; O'Toole et al., 2009), while other studies have not (Collins et al., 2009; Consonni et al., 2008; Vena et al., 1998; Yi et al., 2013). It would be worth noting that our prevalence study adjusted for some important variables, such as smoking and drinking. In animal models, 2,4-D, 2,4,5-T, and TCDD have been known to damage the liver, whereas an association between Agent Orange/TCDD-related chemicals and non-neoplastic gastrointestinal toxicity has rarely been evaluated (Institute of Medicine, 2011). At the same time, the prevalence of Crohn disease was not associated with Agent Orange exposure (Benson and Shepherd, 2011).

In this study, Agent Orange exposure was estimated from the GIS-based exposure opportunity model (Stellman et al., 2003). The current assessment of exposure to Agent Orange has some limitations in accuracy and precision for TCDD research (Institute of Medicine, 2008; Yi et al., 2013), especially compared to other studies in which TCDD exposure was validated with TCDD levels in human tissue. However, most research in Vietnam veterans has attempted to elucidate the exposure to Agent Orange by focusing on service in Vietnam or by assessment based on self-reported information (Decouflé et al., 1992; Yi et al., 2013). We believe that this GIS-based exposure index is not substantially influenced by information bias (Decouflé et al., 1992; Yi et al., 2013) and is more valid and reliable than assessments based on subjective self-report or Vietnam experience. It would also be worth noting that non-differential misclassification of the exposure index was possible in this study, which may have biased the relationships between exposure to Agent Orange and disease toward the null.

The current study has some other limitations. First, the prevalence of diseases was ascertained using the KNHI Claims Database. Since this data was compiled for the purpose of making

insurance claims, not performing research, diagnostic details could be questionable (Hong and Kang, 2013). The validity of the diagnosis, however, would not differ according to Agent Orange exposure. Thus, we do not believe that the results would be biased toward overestimation. Second, this study identified many significant diseases with aORs of 1.1 and lower in its analysis of 111,726 veterans. Although the small variations in prevalence may be a sign of uncontrolled or residual confounding (Yi et al., 2013), small but actual excess morbidity could be important at the population level (Bagnardi et al., 2013). Third, as a prevalence study, this study was more prone to prevalence-incidence bias compared to incidence studies (Sackett, 1979). However, if veterans with a high Agent Orange exposure and its subsequent consequences had died before 2004, the OR of a disease's prevalence according to Agent Orange exposure may be underestimated. Fourth, possible false positive associations due to analyzing many diseases cannot be completely excluded.

Despite some limitations, due to analyzing a large number of subjects ($n=111,726$), the authors were able to examine the effects of Agent Orange and probable TCDD exposure on various diseases, some of which have rarely been explored in previous research. By using the KNHI Claims Database as a source to identify the disease prevalence, this study was able to limit bias related to self-report-based prevalence (O'Toole et al., 2009). As a prevalence study, this study was also able to evaluate more cases from less-fatal and less-severe diseases than a mortality study could. Furthermore, adjusting for some important confounders such as smoking, drinking, BMI, and socio-economic status, which had not been done in many occupational and environmental studies (Calvert et al., 1992; Consonni et al., 2008), was another potential strength of this study.

5. Conclusions

The United States and allied forces sprayed military herbicides in Vietnam. Agent Orange, a mixture of 2,4-D and 2,4,5-T, was the most-used herbicide and was contaminated with high levels of TCDD. Numerous Vietnam veterans were exposed to TCDD-contaminated Agent Orange. This study confirmed that Agent Orange/TCDD could be positively associated with diabetes mellitus and various disorders of the thyroid gland and pituitary gland. This study also supported the long-term neurotoxic effects of Agent Orange/TCDD exposure and showed that neurologic disorders, such as spinal muscular atrophy, Alzheimer disease, and peripheral neuropathies, increased with Agent Orange exposure in Korean Vietnam veterans. The elevated prevalence of COPD (especially chronic bronchitis and bronchiectasis but not emphysema), asthma, and liver cirrhosis according to Agent Orange exposure is worth noting. The prevalence of ischemic heart diseases and stroke was positively associated with Agent Orange exposure. Overall, this study implies that Agent Orange/TCDD exposure several decades earlier may increase the morbidity from various diseases of the endocrine, nervous, circulatory, respiratory, and digestive systems. In this study, some results should be interpreted with discretion for various reasons such as very modest excess aORs for some diseases and possible false positive associations due to analyzing many diseases. Further research is needed to better understand the long-term effects of Agent Orange/TCDD exposure on human health.

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Competing financial interests

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

Institutional review board

This study was approved by Institutional review board of Kwandong University.

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Appendix A. Supplementary material

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