Agent Orange Exposure and Birth Defects: Exploratory Data Analysis

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Abstract

For almost 40 years, the U.S. Department of Veterans Affairs has offered examinations to Vietnam-era veterans, during which it collects information on veterans' perceived exposure to herbicides such as Agent Orange, their health and the health of their children. To date, more than 668,000 veterans have undergone exams. Over that time, veterans groups and a federal advisory panel have called for more research on second-generation effects of exposure to Agent Orange, which contains dioxin, a highly toxic substance. The Agent Orange registry data has not previously been used in published research on this topic.

We analyzed the relationship between self-reported exposure to Agent Orange among Vietnam-era veterans and birth defects among their children, using data from this registry. We examined a cohort of 37,535 veterans who had children both before and during/after their service in the war. We found that veterans who self-reported Agent Orange exposure had greater odds of having children with birth defects born during or after the war, compared to veterans who were unsure of their exposure or who said they were not exposed.

Using a logistic regression, our analysis found that veterans who self-reported that they definitely handled or sprayed Agent Orange, or who said they were directly sprayed with Agent Orange, were more likely to have had a child born during/after the war with birth defects, controlling for other characteristics of the service member. The results were consistent across all model specifications. Using the same cohort, we also analyzed the relationship between exposure and spina bifida in veterans' children. While a larger percent of exposed veterans had a child with spina bifida, the relationship was not statistically significant in our primary model specification.

We view our analysis as an initial exploration of the data rather than a definitive evaluation of the association between exposure and birth defects. But our results point to a need for further research on the degree to which children of Vietnam-era veterans were affected by their parents' exposure to Agent Orange--and, if warranted, action to help those affected.

Background

During the Vietnam War, millions of gallons of herbicides were sprayed by the U.S. military to defoliate dense jungles and forests and to deny cover to enemy forces (Institute of Medicine (US) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides 1994). In the four decades since the war's end, veterans have steadfastly claimed a nexus between their exposure to herbicides and birth

defects in their children. Agent Orange was contaminated by the dioxin TCDD, considered by scientists to be one of the most toxic substances in the world.

Scientists and federal experts have called for additional research on whether Agent Orange is associated with ill effects in veterans' children, a call that has largely gone unheeded. Meanwhile, the field of epigenetics has advanced, showing how chemical exposures can change a cell's genetic expression while leaving the DNA sequence intact. This new research has provided at least a plausible biologic pathway in which a male's exposure to herbicides and other toxic chemicals could impact his offspring (Skinner 2014; Manikkam et al. 2012; National Academies of Sciences, Engineering, and Medicine 2016).

A variety of studies have attempted to tackle the question of whether dioxin exposure is associated with an increased risk of birth defects, but the studies did not benefit from these recent advances in scientific understanding. In 1984, for example, the Centers for Disease Control and Prevention published a study examining babies born with and without birth defects in the metropolitan Atlanta area. It found "no evidence to support the position that Vietnam veterans have had a greater risk than other men for fathering babies with all types of serious structural birth defects combined" (J. D. Erickson et al. 1984; J. David Erickson et al. 1984). In 1988, the CDC published another study examining reproductive outcomes among Vietnam veterans. The 1988 CDC study found that "The rates of total, major, minor, and suspected defects were similar among children of Vietnam and non-Vietnam veterans" (Calle et al. 1988).

The United States Air Force Research Laboratory has also studied birth defects in children of Vietnam veterans (Lathrop et al. 1984; Michalek, Albanese, and Wolfe 1998; Wolfe et al. 1992; Wolfe et al. 1995; Albanese 1988). The Air Force studies compared the children of veterans in the Air Force unit responsible for spraying Agent Orange in Vietnam with the children of Air Force veterans who served in Southeast Asia but who didn't handle the herbicides. The Air Force studies found an increase in the proportion of birth defects in the Air Force unit responsible for spraying compared to other Air Force veterans, but the researchers discounted the elevated risk because the results did not show a dose-response relationship between dioxin levels in blood and birth defects. Some dose classifications depended on calculating a veteran's dioxin level in the past, a calculation which assumed a fixed elimination rate. More recent research suggests that may have been an incorrect assumption (Emond et al. 2005; Knafl and Schwartz 2003).

Studies conducted in Vietnam have also reported evidence of an association, but some researchers have faulted the rigor with which those studies were performed (Anh D. Ngo et al. 2006; Anh Duc Ngo, Taylor, and Roberts 2010; Schecter and Constable 2006).

Under its current policy, the VA does not provide benefits to the children of Vietnam veterans for birth defects, with two exceptions: children of exposed veterans (male or female) with spina bifida, in which the spinal cord fails to close properly; and children of exposed female veterans with 18 other birth defects. A VA spokesman told ProPublica that from January 2001 to November 2016, 1,325 children met those criteria and received benefits.

Data and Methods

Data source

Our study relied on data in the Agent Orange registry, which was launched by the VA in 1978 and remains active. All veterans who served in Vietnam between 1962 and 1975 are eligible for a registry exam, which consists of a battery of in-person tests and questions. Additionally, veterans are eligible if they served in certain time periods and/or locations in Korea or Thailand, or if they may have been exposed to herbicides during a military operation or as a result of testing, transporting, or spraying herbicides for military purposes (U.S. Department of Veterans Affairs 2016). The number of veterans eligible for an exam could not be determined, but it has been reported that about 9.2 million Americans served in the military during the Vietnam era (1964-75) and about 2.6 million military personnel served in Vietnam itself and were potentially exposed to Agent Orange from January 1965 to April 1970 (Gelman 2013; U.S. Department of Veterans Affairs, Office of Public and Intergovernmental Affairs 2009).

All told, more than 668,000 veterans have undergone registry examinations since 1978. Participation in the exams remains high; more than 20,000 veterans per year have completed an exam in every year since 2001. Research using this registry is limited. A VA spokesman told ProPublica that the VA was only able to locate seven published studies and presentations based on the registry data and most date back to the 1990s. The VA has indicated that it views the registry to be a self-selected, and perhaps non-representative, sample.

The VA advertises the availability of the exam on its website and in its veteran publications, and veterans groups similarly publicize it. The exam is voluntary and conducted in person. The results do not entitle a veteran to benefits, but veterans who undergo the exam are placed on a mailing list and receive updates from the VA about Agent Orange.

We first sought access to the registry data under the Freedom of Information Act, but were denied veteran-level data on privacy grounds. After our research protocol was approved by a third-party Institutional Review Board (Schulman IRB) in April 2016, the VA agreed to share the data. We received data from the Agent Orange registry in September 2016, covering all exams conducted from 1978 through September 2016. No personally identifiable information--such as veterans' names, addresses, Social Security numbers or full dates of birth--was requested or provided. Instead, the VA created an anonymous identifier for each veteran and for each exam. (Some veterans had multiple exams over the years. Their anonymous identifier was consistent across exams.) The research protocol submitted as part of our IRB application, which is available upon request, pre-specified our main analysis questions.

Most of the exam questionnaire is devoted to demographic and health information about the veteran, but questions about children include the number of children born before and during/after the war; the number of children born with spina bifida in each time period, the number of children born with other birth defects in each time period, and the age of the mother at the time of conception of the first child born with spina bifida or other birth defects. Beyond the distinction between spina bifida and other birth defects, the questionnaire did not collect data on the type or severity of birth defects. The full questionnaire can be found in Appendix A. A list of the fields provided to ProPublica follows in Appendix B.

We cleaned the data to address data quality issues and missing data. We excluded veterans who only had exams prior to 2001 due to data quality concerns (see Appendix C for details). We also excluded veterans with logically inconsistent answers, and veterans with missing data on certain questions: exposure to Agent Orange, number of children born before and during/after the war with spina bifida or other birth defects, year of birth, branch of service, year in which last period of service ended, overall health self-assessment, date of exam, and total number of children born before and during/after the war. That left 323,587 veterans with useable data. Most veterans only completed one exam from 2001 to 2016. For veterans with multiple exams, our analysis used only their most recent exam because we believe it captured the fullest available data on a veteran's children. Veterans who reported declining numbers of children (or declining numbers of children with birth defects) across multiple exams were excluded. Details can be found in Appendix C.

Methods

Of the 323,587 veterans in the cleaned data, our main analysis focused on 37,535 veterans who had children born both before and during/after the war. The 37,535 veterans in our sample had a total of 56,627 children born before the war and 73,076 children born during/after the war.

We chose to limit our primary analysis to veterans who had children born both before and during/after the war. This allowed us to use the number of a veteran's children born before the war with spina bifida or birth defects as a covariate in our model. Controlling for birth defects in a veteran's children born before the war captures socioeconomic status, exposure to environmental toxins in childhood and genetic traits that are also inherited by the veteran's children who are born during/after the war.

Table 1: Sample selection

Our main analysis included 37,535 veterans who completed a registry exam in 2001 or later, who had no logical inconsistencies or missing values in their data, and who had children born both before and during/after the war. Sensitivity analyses included veterans with data issues, and veterans without children born before the war.

	Number of veterans	Number of children	
		born before the war	born during/ after the war
Completed a registry exam, 1978 through September 2016	668,941	†	†
Completed a registry exam, 2001 through September 2016	414,075	136,373	709,573
Had no logical inconsistencies or missing data	323,587	107,615	564,176
Had one or more child born during/after the war	247,753	56,627	564,176
Had one or more child born before the war and one or more child born during/after the war	37,535	56,627	73,076
Had one or more child born before the war and one or more child born during/after the war (regardless of logical inconsistencies, but with no missing data)	44,610	68,081	88,212

† Data quality concerns prevented this calculation.

Our analysis cohort represented about 11.6 percent of the veterans with useable registry data. Only about 18 percent of the veterans had children born before the war, unsurprising given that many Vietnam

veterans were in their teens or early twenties at the time of their service. About 6.5 percent of veterans had children born before the war, but no children born during/after. (See Appendix Table D1.) It was not surprising, therefore, that our analysis sample was about two years older, on average, than the registry as a whole. (We only had year of birth for each veteran, not a specific date of birth.) While our main analysis cohort includes only veterans who had children before and after the war, sensitivity analyses (Appendix E) show results for all veterans who had children after the war.

Table 2 shows characteristics of the veterans in our analysis. Measures are shown for all 247,753 veterans who had children during/after the war, and also for our main analysis cohort of 37,535 veterans who also had children before the war. The main analysis cohort is further broken out by exposure to Agent Orange.

Though the registry questionnaire included five questions that dealt with Agent Orange exposure, we focused on two: direct handling or spraying of the herbicide and being directly sprayed with it. If a veteran said "definitely yes" to either of those questions, we counted him as exposed for purposes of our study. All others were counted as unexposed. (Appendix Table D2 shows responses to all five Agent Orange exposure questions. Analyses in Appendix E use other measures of Agent Orange exposure.)

In all groups, nearly all of the veterans are men. Most served in Vietnam, and a majority served in the Army. The main analysis cohort of 37,535 veterans with children born both before and during/after the war is similar to the larger pool of veterans with children born during/after the war on most characteristics captured in the questionnaire. Within the main analysis sample, comparisons are shown between exposed and unexposed veterans. Differences between exposure groups were tested for using two-sided z-tests (for continuous measures) or chi square tests (for categorical measures). The exposed and unexposed veterans were found to be statistically different from each other on many measures, though only some of these differences are of substantive interest. The exposed group served in different branches of the military, which is unsurprising given that certain branches, especially the Air Force, were more involved in spraying Agent Orange. Notably, the exposed and unexposed groups were equally likely to have children with birth defects born before the war. Compared to the unexposed group, the exposed group reported being in worse overall health at the time of their exam.

Table 2: Sample characteristics, by exposure group

Our main analysis uses a cohort of 37,535 veterans who had children both before and during/after the war. These veterans are a subset of the 247,753 veterans who had children during/after the war. On many characteristics captured in the questionnaire, the main analysis cohort is similar to the larger pool of veterans with children born during/after the war. Within the analysis cohort, exposed veterans (those who handled, sprayed, or were sprayed with Agent Orange) are statistically different from unexposed veterans on many measures, though on most measures the difference is of little substantive interest. Notably, the exposed and unexposed groups were equally likely to have children with birth defects born before the war. Compared to the unexposed group, the exposed group reported being in worse overall health at the time of their exam.

	veterans with children born during/after the war	veterans with children born both before and during/after the war			
		all	exposed	unexposed	
	(n=247,753)	(n=37,535)	(n=3,573)	(n=33,962)	p
Had any children with defects, born before the war† (%)					
any birth defects	0.4	2.6	2.8	2.6	0.64
spina bifida	0.1	0.7	0.5	0.7	0.32
other birth defects	0.3	2.0	2.3	2.0	0.20
Year of birth (average)	1946.3	1944.2	1943.9	1944.2	<0.001 ***
Sex (%)					0.045 **
Male	99.8	99.9	99.7	99.9	
Female	0.2	0.1	0.3	0.1	
Year last period of service ended (average)	1971.0	1972.2	1972.3	1972.2	0.23
Location of Service (%)					<0.001 ***
Vietnam	95.5	94.8	93.5	95.0	
Korea (1968 to 1969)	1.5	1.3	1.2	1.3	
Both	0.9	1.7	2.7	1.6	
Neither (other locations)	2.0	2.1	2.5	2.1	
no answer	0.1	0.1	0.1	0.1	
Branch of Service (%)					<0.001 ***
Army	61.1	60.7	58.8	60.9	
Air Force	11.2	16.1	22.2	15.4	
Navy	12.8	10.9	8.0	11.2	
Marines	13.7	10.7	9.2	10.9	
Multiple	1.0	1.4	1.7	1.4	
Coast Guard	0.2	0.1	0.1	0.1	
Other	0.0	0.1	0.0	0.1	
Number of children (average)					
born before the war	0.2	1.5	1.6	1.5	0.002 ***
born during/after the war	2.3	1.9	1.9	1.9	0.42
Year of last registry exam (average)	2008.6	2008.0	2007.6	2008.0	<0.001 ***
Number of Exams, 2001-2016 (%)					<0.001 ***
1	91.0	91.4	87.5	91.8	
2	8.0	7.6	10.9	7.3	
3+	1.0	1.0	1.6	0.9	
Health Self-Assessment at time of exam (%)					<0.001 ***
Very Good	3.4	2.9	2.2	3.0	
Good	25.5	22.1	15.0	22.8	
Fair	44.5	45.0	43.1	45.2	
Poor	21.6	24.1	30.1	23.5	
Very Poor	5.0	6.0	9.6	5.6	
Marital Status (%)					0.53
Married	76.2	77.0	76.9	77.0	
Divorced	17.7	16.4	16.9	16.3	
Separated	1.4	1.8	1.8	1.8	
Widowed	2.6	3.0	2.8	3.0	
Single, Never Married	1.9	1.8	1.5	1.8	
no answer	0.1	0.1	0.2	0.1	

Notes: Among the 37,535 veterans who had children born both before and during/after the war, differences between exposure groups were examined with two sided z-tests (for continuous measures) or chi square tests (for categorical measures.) Stars indicate statistical significance at the following levels: *** 1 percent; ** 5 percent; * 10 percent.
† Veterans who did not have any children born before the war were counted as having no children with defects born before the war. (Most of the 247,753 Vietnam veterans who had children after the war did not have children before the war.)

We looked at two categories of birth defects: spina bifida and other non-spina bifida birth defects. Our main analysis focused on the prevalence of any birth defects in veterans' children. We also analyzed the prevalence of spina bifida and other birth defects separately. We were able to calculate the percent of veterans who had a child with each, or either, condition. We were also able to calculate the percent of children born with spina bifida, and the percent of children who had other birth defects. Because of the design of the questionnaire, we were unable to calculate the percent of children with either spina bifida or another birth defect.

Within our cohort of veterans who had children both before and during/after the war, we used multivariate logistic regression to model the odds of a veteran having a child with birth defects.

Controls used in the model include characteristics of the veteran and details of his/her service, including year of birth, branch of service, year the veteran's most recent period of service ended, year of the exam, self-assessment of health, number of children born before and after the war, and the number of children born before and after the war with spina bifida and other birth defects[1]. Adjusted odds ratios and 95% profile likelihood confidence intervals were reported. P-values ≤ 0.05 were considered statistically significant. Two-sided z-tests were used to test the null hypothesis that having a child born during/after the war with a birth defect is independent of a veteran's self-reported Agent Orange exposure. The null hypothesis is rejected if the 95% confidence interval for the adjusted odds ratio does not include 1. (An adjusted odds ratio of 1 indicates equal odds of having a child with birth defects in exposed and unexposed veterans). All analyses were conducted using R statistical software.

Additional regressions with different sample definitions and exposure measures were conducted as sensitivity analyses.

Results

Overall, the distribution of responses to questions about Agent Orange exposure, spina bifida, and birth defects appeared reasonable. Less than 6 percent of veterans' children born during or after the war had a non-spina bifida birth defect. This is similar to the post-war proportion of children with birth defects found in the Air Force study of Vietnam veterans (Wolfe et al. 1992). The CDC has estimated that major birth defects affect about 3 percent of births in the United States (Center for Disease Control and Prevention 2008). Less than 1 percent of veterans' children born after the war had spina bifida. Fewer than 10 percent of veterans in our analysis indicated that they had definitely handled the chemicals or had been directly sprayed with them. The rest either said they were unsure of their exposure or were definitely not exposed. A detailed table of responses to the Agent Orange exposure questions can be found in Appendix D.

Table 3A shows the number of veterans who had a child born before the war with any birth defects, and the number of veterans who had a child born during/after the war with any birth defects, broken out by the veteran's exposure to Agent Orange. Table 3B shows the number of children with non-spina bifida

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[1] We modeled three different dependent variables: having a child with any birth defects, having a child with spina bifida, and having a child with other (non-spina bifida) birth defects. A separate model was used for each dependent variable. All three models were specified in the same way, except for the inclusion of two control variables: the number of children born after the war with spina bifida and the number of children born with other birth defects. The controls are left out when they were directly used to construct the dependent variable.

birth defects, broken out by time of birth and by parent's exposure status. Additional tables in Appendix D show the number of veterans who had children with spina bifida and non-spina bifida birth defects, and the number of children who had spina bifida.

Children born before the war to both exposed and unexposed veterans had fewer birth defects than those born during/after the war. Less than two percent of children born before the war had a non-spina bifida birth defect. The proportion was similar, but not identical, for children of veterans who were later exposed to Agent Orange and children of veterans who were not exposed or were not sure. Compared to children born before the war, children born during/after the war had a much higher risk of having a non-spina bifida birth defect, regardless of their parent's exposure to Agent Orange. Over five percent of children born during/after the war had a non-spina bifida birth defect. The proportion of children with spina bifida also increased post-war for both exposure groups.

Table 3A: Risk of having a child with any birth defect (veteran-level)

We examined 37,535 veterans who had children born both before and during/after the war. Slightly more than 13% of veterans who reported they were exposed to Agent Orange had a child with any birth defect born during/after the war, compared to almost 10% of veterans who reported they were not exposed. Controlling for other characteristics of the veteran, the odds of having a child with any birth defect born after the war is 34% higher for exposed veterans than for unexposed veterans.

		had a child with any birth defect							
		born before the war				born during/after the war			
	total	yes	no	risk	odds	yes	no	risk	odds
exposed	3,573	99	3,474	2.8%	0.03	468	3,105	13.1%	0.15
unexposed	33,962	891	33,071	2.6%	0.03	3,343	30,619	9.8%	0.11
total	37,535	990	36,545	2.6%	0.03	3,811	33,724	10.2%	0.11

unadjusted odds ratio: 1.38
adjusted odds ratio: 1.34 (1.20,1.49)

Note: Adjusted odds ratio was calculated using multivariate logistic regression. 95% confidence interval shown in parentheses.

Table 3B: Risk of having a non-spina bifida birth defect (child-level)

We examined the children of 37,535 veterans who had children born both before and during/after the war. Regardless of parents' exposure to Agent Orange, 1.4% of children born before the war had a non-spina bifida birth defect, compared to 5.6% of children born during/after the war.

		had a non-spina bifida birth defect								
		born before the war				born during/after the war				
	total	yes	no	risk	odds	total	yes	no	risk	odds
exposed	5,556	92	5,464	1.7%	0.02	6,897	546	6,351	7.9%	0.09
unexposed	51,071	726	50,345	1.4%	0.01	66,179	3,574	62,605	5.4%	0.06
total	56,627	818	55,809	1.4%	0.01	73,076	4,120	68,956	5.6%	0.06

Veterans who handled or sprayed Agent Orange, or who were directly sprayed with Agent Orange were more likely to report having a child with birth defects during/after their service, controlling for other

characteristics of the service member. The odds of an exposed veteran having a child with birth defects born during/after the war was 34% higher than the odds for unexposed veterans.[2]

To understand the difference between exposed and unexposed veterans in terms of risk, not odds, we used the coefficients from our model to calculate the risk for a service member who was typical of those in our analysis[3]. For an 'average' service member who said he definitely handled, sprayed, or was directly sprayed with Agent Orange, the risk of having a child born during/after the war with birth defects was about 12.4 percent, compared to about 9.5 percent for an 'average' service member who was not exposed.

As seen in Table 4, year of birth and poor self-reported health were positively correlated with having a child with birth defects during/after the war. The number of children with birth defects born before the war was also positively correlated with having a child with birth defects born after the war.

Results from our sensitivity analyses were similar, and can be seen in Appendix Table E1.

We did not find a statistically significant link between Agent Orange exposure and having a child with spina bifida born during/after service in Vietnam. As with the analysis of all birth defects, we controlled for other characteristics of the service member. Results from our sensitivity analyses were mixed. (See Appendix Table E3.) The lower incidence of spina bifida, as compared to other birth defects, may contribute to these mixed results.

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[2] Logistic regression results in Table 4, model 1 shows a coefficient of 1.34 for having handled, sprayed, or been sprayed with Agent Orange. (This is also the adjusted odds ratio in Table 3A.) This estimated coefficient is the odds ratio of having a child between exposed and unexposed veterans, holding constant other characteristics of the veteran.

[3] The 'average' service member, for whom we calculated risk, was born in 1944, served in the Army, ended his service in 1972, reported his health as 'fair,' completed his last registry exam in 2007, had 1.5 children born before the war and 1.9 children born after the war.

Table 4: Main results, multivariate logistic regression

Having handled, sprayed or been sprayed with Agent Orange was positively correlated with having a child born after the war with any birth defects. Agent Orange exposure is also positively correlated with having a child born after the war with a non-spina bifida birth defect. The correlation between Agent Orange exposure and having a child born after the war with spina bifida is not statisitcally significant.

	any birth defects				non-spina bifida birth defects				spina bifida			
	OR	95% CI	p		OR	95% CI	p		OR	95% CI	p	
Handled, sprayed or was sprayed with AO	1.34	(1.20,1.49)	<0.001	***	1.36	(1.22,1.51)	<0.001	***	1.25	(0.91,1.67)	0.15	
Year of birth	1.01	(1.01,1.02)	<0.001	***	1.02	(1.01,1.03)	<0.001	***	0.99	(0.97,1.02)	0.56	
Branch of Service												
Army (reference category)	--	--	--		--	--	--		--	--	--	
Air Force	0.98	(0.89,1.08)	0.71		1.00	(0.90,1.11)	0.99		0.84	(0.62,1.11)	0.22	
Navy	0.95	(0.84,1.06)	0.36		1.02	(0.90,1.14)	0.78		0.47	(0.30,0.70)	<0.001	***
Marines	1.04	(0.93,1.16)	0.51		1.06	(0.95,1.19)	0.31		0.87	(0.62,1.19)	0.41	
Multiple	1.77	(0.71,3.78)	0.18		1.99	(0.80,4.27)	0.10		0.00	(0.00,0.19)	0.96	
Coast Guard	1.19	(0.33,3.28)	0.76		0.70	(0.11,2.38)	0.63		5.15	(0.87,18.76)	0.032	**
Other	1.44	(1.09,1.86)	0.007	***	1.53	(1.16,1.99)	0.002	***	0.85	(0.33,1.79)	0.70	
Year last period of service ended	0.99	(0.99,1.00)	0.045	**	0.99	(0.99,1.00)	0.066	*	0.99	(0.98,1.01)	0.44	
Health Self-Assessment at time of exam												
Very Good (reference category)	--	--	--		--	--	--		--	--	--	
Good	1.29	(1.01,1.68)	0.048	**	1.34	(1.03,1.76)	0.035	**	1.10	(0.56,2.49)	0.80	
Fair	1.50	(1.18,1.93)	0.001	***	1.52	(1.18,1.99)	0.002	***	1.43	(0.75,3.17)	0.33	
Poor	1.68	(1.32,2.18)	<0.001	***	1.73	(1.34,2.27)	<0.001	***	1.52	(0.79,3.40)	0.26	
Very Poor	1.94	(1.48,2.56)	<0.001	***	2.02	(1.53,2.71)	<0.001	***	1.26	(0.59,3.02)	0.57	
Year of last registry exam	0.99	(0.99,1.00)	0.16		0.99	(0.98,1.00)	0.017	**	1.03	(1.01,1.06)	0.005	***
Number of children born before the war												
total	1.03	(0.99,1.07)	0.11		1.03	(0.99,1.07)	0.11		0.98	(0.87,1.10)	0.77	
with spina bifida	2.02	(1.61,2.53)	<0.001	***	1.11	(0.81,1.46)	0.49		5.42	(3.98,7.31)	<0.001	***
with other birth defects	2.67	(2.29,3.10)	<0.001	***	2.64	(2.26,3.08)	<0.001	***	2.00	(1.36,2.79)	<0.001	***
Number of children born after the war												
total	1.15	(1.12,1.17)	<0.001	***	1.15	(1.12,1.17)	<0.001	***	1.12	(1.05,1.20)	<0.001	***
with spina bifida	--	--	--		1.57	(1.30,1.88)	<0.001	***	--	--	--	
with other birth defects	--	--	--		--	--	--		1.55	(1.31,1.80)	<0.001	***

Notes: OR = Odds Ratio; 95% CI = 95% Confidence Interval; p = pvalue; AO = Agent Orange. Stars indicate statistical significance at the following levels: *** 1 percent; ** 5 percent; * 10 percent.

Discussion

These results strongly suggest that self-reported Agent Orange exposure (i.e. handling, spraying or being directly sprayed with it) was associated with adverse outcomes in the children of Vietnam veterans. The results were consistent across all model specifications. These findings are notable especially in light of emerging epigenetic research showing a possible biologic pathway through which a father's environmental exposures could impact his offspring. Although the multigenerational effects of Agent Orange have been a recurring topic of discussion among veterans and their children, they have received comparably less research attention than the chemical's effects on veterans. Our findings suggest that additional research is needed.

Our analysis has several limitations, most notably that exposure and birth defect information was self-reported and not externally verified, either against military or medical records. In responding to the registry questionnaire, there is no direct incentive for veterans to provide incorrect information. The Agent Orange registry exams are not used to determine a veteran's eligibility for benefits, and veteran's children generally are not eligible for benefits through the VA if they have birth defects other than spina bifida.

Whether a veteran has a child with birth defects was not confirmed with exams or against medical records of the children. In addition, the Agent Orange registry questionnaire does not define birth defect, leaving it to veterans and their examining clinicians to define it. The Air Force study on the health effects of Agent Orange exposure verified self-reported birth defects against medical records and found that some of the self-reported data was incorrect. Some birth defects reported by parents were not confirmed in medical records, and some cases of birth defects identified in medical records were not reported by parents (Wolfe et al. 1992). A body of research has found that self-reported health information can be a good proxy for clinical record data, especially for diseases with unambiguous criteria (Bush et al. 1989; Martin et al. 2000; Harlow and Linet 1989; Merkin et al. 2007; Klungel et al. 1999). The VA has used self-reporting as a means of gathering information on veterans' health in a number of cases (Cypel et al. 2016).

Our measure of Agent Orange exposure was similarly limited. Self-reported exposure could not be verified against military records, because no such records exist (Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (Ninth Biennial Update), Board on the Health of Select Populations, and Institute of Medicine 2014). Previous research has found an association between self-reports of having sprayed Agent Orange and biological measures of dioxin levels in the body (Kang et al. 2001). Some veterans responded that they were unsure of their exposure. We classified these veterans as unexposed, which likely resulted in an underestimation of the relationship between exposure and birth defects. In addition, the accuracy of a veteran's memory of their exposure to Agent Orange may have been influenced by whether or not they had a child with birth defects. Compared to the parent of healthy children, the parent of a child with birth defects may have spent more time reviewing his memories of possible exposure, making his recall more accurate or possibly creating false memories. This recall bias could cause an overestimation of the relationship between exposure and birth defects.

Our sensitivity analysis provides some suggestion of a dose-response relationship. Appendix table E1, model 2 shows results for all five Agent Orange exposure questions included in the questionnaire. The

more intensive forms of exposure (having directly handled or sprayed Agent Orange, or having been directly sprayed with it) are more highly correlated with having a child born after the war with a birth defect, compared to other measures of exposure (for example, having been in a recently sprayed area).

Another limitation of our study was that those receiving registry exams were self-selected. The sample of veterans in the cleaned post-2001 registry data, who have no data quality issues or missing data, may be different from the population of all veterans who served in the Vietnam-era in several ways, including their health status, their Agent Orange exposure, and the health of their children. However, it is less likely that the relationship between Agent Orange exposure and a child's health operates differently for the veterans in our analysis than for those who did not complete an exam. Confining our analysis to registry exams in 2001 or later may confound our analysis with a survival bias, leaving out veterans whose deaths might be from conditions related to Agent Orange exposure. This is likely to make our analysis an underestimate of the actual prevalence of birth defects among the children of veterans.

One interesting finding is that regardless of the degree of parental Agent Orange exposure, children born during/after the war were much more likely to have a birth defect. It is unclear why this is the case, but it may be due to a variety of factors: increased parental age, physical effects to the parent of his service, social/economic effects of service on the post-service lives of veterans and their children, and use of tobacco or alcohol, which were common in the Vietnam era. It is also possible that the veterans we classified as unexposed had some level of exposure to Agent Orange. The post-war increase in birth defects warrants further analysis, both for Vietnam veterans and veterans of more recent operations. The VA is currently in the midst of a Vietnam experience study. Other multi-generational effects of service are also becoming clear, for example, recent economic analyses found decreased earnings among men whose fathers were likely to have been drafted (Goodman and Isen 2015).

Our study was intended as a preliminary analysis of the underutilized data in the Agent Orange Registry. The analysis was not intended to be the final word on causation. Self-reported Agent Orange exposure may be correlated with other aspects of military service that may put a service member at greater risk. We do not know, for instance, the total years of service for each veteran or whether he/she had other exposures before or after the war.

Our analysis showed mixed evidence of an increase in spina bifida in exposed veterans' children born during or after the war. Spina bifida is the one illness for which the VA currently provides benefits for children of men and women who served in Vietnam. In the past, The Institute of Medicine, a federal advisory committee, found "limited/suggestive" evidence of a link between Agent Orange exposure and spina bifida in the offspring of Vietnam veteran. Earlier this year, noting that recent studies have not found evidence of a link between Agent Orange exposure and spina bifida, The Institute of Medicine recommended classifying the evidence of a link as "inadequate/insufficient" (National Academies of Sciences, Engineering, and Medicine 2016). The mixed findings of our spina bifida analyses suggest further research is necessary.

We view our analysis as an initial exploration of the data rather than a definitive evaluation of the association between exposure and birth defects. But our results point to a need for further research on the degree to which children of Vietnam-era veterans were affected by their parents' exposure to Agent Orange. Going forward, we would suggest that the VA or other researchers conduct a larger evaluation, which could improve upon our work, perhaps by verifying self-reported information against medical

records. Another suggestion is to contact veterans in the cohort to solicit additional information. Any future studies should have peer-reviewed protocols and be overseen by a science advisory board, to avoid problems that have plagued government-run Agent Orange research.

Acknowledgements

Appendix A: Agent Orange Registry Questionnaire

VA | Department of Veterans Affairs | AGENT ORANGE REGISTRY CODE SHEET

| TT | #5 | Facility Number (Use PTF No. only) (2 - 4) | | | | Suffix (5 - 7) | | | |

This information is collected in accordance with the clearance requirements of section 3507 of the Paperwork Reduction Act of 1995. The public reporting burden for this collection of information is estimated to average 20 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. This collection of information is to collect data for research on exposure to Agent Orange. Response to this survey is voluntary and failure to participate will have no adverse effect on benefits to which you might otherwise be entitled. The information the veteran supplies may be disclosed outside the VA to Federal, State and local government agencies and National Health Organizations to assist in the development of programs for research purposes and other uses as stated in the Notice of Systems of VA Records" published in the Federal Register in accordance with the Privacy Act of 1974.

INSTRUCTIONS: Registry Physicians and Coordinators:
Please print. Use only one letter or number per block. If possible use black ballpoint or felt-tip pen.

PART 1 - OBTAIN THIS INFORMATION FROM PATIENT'S CHART ONLY.

2. LAST NAME (8-33)

3. FIRST NAME (34-48)

4. MIDDLE NAME (49-58)

5. TYPE (59)

6. SOCIAL SECURITY NUMBER (60 - 69) (Begin entering SSN in Block 61. If SSN is pseudo number, enter "P" in Block 60.)
(60)

7. SERVICE SERIAL NO (70 - 79) (Begin at left, leave unused blocks blank. Enter "U" if service number is unknown.)

8. DATE OF BIRTH (80 - 87)
Month   Date   Year

9. ADDRESS (Street Name and Apartment Number, if applicable)

CITY OR TOWN (114-139)

| COUNTY | | STATE | ZIP CODE (140-144) | PLUS 4 *(Optional)*(145-148) | COUNTY (149-151) | STATE (152-153) |

10. Race/Ethnicity (Enter one code in Block 154)   (154)
   1 = American Indian or Alaskan Native;   2 = Asian or Pacific Islander;   3 = Black, Not Hispanic Origin;
   4 = White, Not Hispanic Origin;   5 = Hispanic;   6 = Unknown

11. Marital Status (Enter one code in Block 155)   (155)
   1 = Married;   2 = Divorced;   3 = Separated;   4 = Widowed;   5 = Single, Never Married

12. Sex (Enter one code in Block 156)   (156)   13. Current Status (enter code in Block 157.)   (157)
   M = Male   F = Female
   1 = Inpatient;   2 = Outpatient;   3 = Incarcerated;
   4 = Active Duty, Inpatient;   5 = Active Duty, Outpatient

14. Branch of Service (If more than 1, enter latest Branch of Service in Block 158.)   (158)
   1 = Army;   2 = Air Force;   3 = Navy;   4 = Marines;   5 = Coast Guard;   6 = Other

15. Does veteran have military service in Vietnam, Korea or other locations where Agent Orange or other herbicides were tested, transported or sprayed for military purposes? (Enter one of the following codes in Block 159):   (159)

   If served in other locations, but **neither Vietnam nor Korea,** use "Code 4" and describe under Item 33.
   If served in **either Vietnam or Korea**, list appropriate dates in Blocks 160-183.

   1 = Vietnam
   2 = Korea (1968 or 1969)
   3 = Both
   4 = Neither (Other locations)

| 15A. Last Period of Service | FROM Month (160-161) | FROM Year (162-165) | TO Month (166-167) | TO Year (168-171) | 15B. Next to Last Period of Service | FROM Month (172-173) | FROM Year (174-177) | TO Month (178-179) | TO Year (180-183) |

16. Did you serve in any of the following:
   Enter Y = Yes,   N = No, or "U" = Unknown in Blocks 184-189.
   If "Other," (Block 189) describe in Item 33, "Remarks."

| (184) I Corps | (185) II Corps | (186) III Corps | (187) IV Corps | (188) Sea Duty | (189) Other |

17. List military units in which veteran served. Specify complete unabbreviated title (Company, Battalion)

_____   _____   _____

_____   _____   _____

AGENT ORANGE REGISTRY CODE SHEET (CONTINUED)

NAME *(Last, First, Middle Initial)*	SOCIAL SECURITY NUMBER

18. ENTER THE DATES OF THE LAST TWO PERIODS OF SERVICE, IF OTHER THAN VIETNAM OR KOREA.

18A. Last Period of Service	FROM		TO		18B. Next to Last Period of Service	FROM		TO	
	Month (190-191)	Year (192-195)	Month (196-197)	Year (198-201)		Month (202-203)	Year (204-207)	Month (208-209)	Year (210-213)

19. VETERAN'S EXPOSURE TO AGENT ORANGE: (Enter the appropriate number in Blocks (214-219) using the following codes:

   1= Definitely Yes;   2= Not Sure;   3= Definitely No

19A. I was involved in handling or spraying Agent Orange.	(214)
19B. I was not directly sprayed but was in a recently sprayed area.	(215)
19C. I was exposed to herbicides other than Agent Orange.	(216)
19D. I was directly sprayed with Agent Orange.	(217)
19E. I ate food or drink that could have been sprayed with Agent Orange.	(218)
20. Veteran's assessment of own health. (Enter one of the following codes in Block 219.) 1= Very Good; 2= Good; 3= Fair; 4= Poor; 5= Very Poor	(219)

PART II - REGISTRY PHYSICIAN, COORDINATOR AND CODING STAFF SHOULD COMPLETE THIS SECTION.

21. Date of Registry Examination: (Enter Month, Day and Year in Blocks 220-227)	Mo. (220-221)	Day (222-223)	Year (224-227)

22.   Veteran's Complaint(s). VA Coders, enter ICD-9 in Blocks 228-242. (If more than 3 complaints/symptoms, list under Item 22D.)
(Left justify all codes - If there are no complaints/symptoms, enter 78000 in Blocks 228-232.)

	(228)	(229)	(230)	(231)	(232)
22A.					

	(233)	(234)	(235)	(236)	(237)
22B.					

	(238)	(239)	(240)	(241)	(242)
22C.					

22D. Additional Complaints:

ENTER APPROPRIATE CODES IN BLOCKS IN COLUMN AT RIGHT

23. Does veteran attribute chief complaint to Agent Orange exposure? Y = Yes; N = No; or U =Unknown		(243)
24. Enter total number of veteran's complaints in Blocks 244-245. *(Describe any complaint over 3 in Item 22D)* (e.g.; If veteran has 2 complaints, enter slash zero in Block 244 and 2 in Block 245. If none, enter slash zeros in Blocks 244 and 245 and go to Item 25.)	(244)	(245)

25.   Evidence of Birth Defects among Vietnam veteran's children. Enter numbers in listed blocks.

25A. How many children does veteran have? (Enter number in Blocks 246-247.) (e.g.; If veteran has 2 children, enter slash zero in Block 246 and 2 in Block 247. If none, enter slash zeros in Blocks 246 and 247 and go to Item 26.)	(246)	(247)

NOTE: Items 25B through 25K are to be completed by Vietnam veterans only. If veteran served outside Vietnam, skip to item 26.

25B. How many children were born before veteran's military service in the Republic of Vietnam? (Enter number in Blocks 248-249. (If none, enter slash zeros in Blocks 248 and 249 and go to Item 25G)	(248)	(249)

NAME *(Last, First, Middle Initial)*	SOCIAL SECURITY NUMBER

		(250)	(251)
25C.	How many of the children born before the veteran's military service in the Republic of Vietnam showed evidence of spina bifida? (Enter number of children in Blocks 250 and 251. If none, enter slash zeros and go to Item 25E.)		
25D.	Mother's age at conception of first child conceived before the veteran's military service in the Republic of Vietnam showing evidence of spina bifida. (Enter age in Blocks 252 and 253.)	(252)	(253)
25E.	How many of the children born before the veteran's military service in the Republic of Vietnam showed evidence of other birth defects? (Enter number in Blocks 254 and 255. If none, enter slash zeros and go to Item 25G.)	(254)	(255)
25F.	Mother's age at conception of first child conceived before the veteran's military service in the Republic of Vietnam showing evidence of other birth defects. (Enter age in Blocks 256 and 257.)	(256)	(257)
25G.	How many children were born during or after the veteran's military service in the Republic of Vietnam? (Enter number in Blocks 258 and 259. If none, go to Item 26.)	(258)	(259)
25H.	How many of the children born during or after the veteran's military service in the Republic of Vietnam showed evidence of spina bifida? (Enter number in Blocks 260 and 261. If none enter slash zeros and go to Item 25J.	(260)	(261)
25I.	Mother's age at conception of first child conceived during or after the veteran's military service in the Republic of Vietnam showing evidence of spina bifida. (Enter age in Blocks 262 and 263.)	(262)	(263)
25J.	How many of the children born during or after the veteran's military service in the Republic of Vietnam showed evidence of other birth defects? (Enter number in Blocks 264 and 265. If none, enter slash zeros and go to Item 26.)	(264)	(265)
25K.	Mother's age at conception of first child conceived during or after the veteran's military service in the Republic of Vietnam showing evidence of other birth defects. (Enter age in Blocks 266 and 267.)	(266)	(267)

26. Diagnostic Workup/Consultations. (Use one of the following codes in Blocks 268-275):

    1 = No workup done.
    2 = Workup/consultation done. Diagnosis undetermined (veteran with symptoms but diagnosis cannot be determined).
    3 = Workup/consultation done. Diagnosis established.
    4 = Workup/consultation done. No diagnosis (veteran without symptoms and no evidence of illness).
    5 = Workup/consultation in process. Results pending.
    6 = Workup/consultation scheduled - veteran was a "no show"

26A. Dermatology	(Enter code in Block 268.)	(268)
26B. Pulmonary	(Enter code in Block 269.)	(269)
26C. Reproductive Health	(Enter code in Block 270.)	(270)
26D. Hematology/Oncology.	(Enter code in Block 271.)	(271)
26E. Urology.	(Enter code in Block 272.)	(272)
26F. Neurology	(Enter code in Block 273.)	(273)
26G. ENT	(Enter code in Block 274.)	(274)
26H. Other	(Enter Y = Yes or N = No in Block 275.)	(275)
26I. Hepatitis C (With veteran's consent)	(In Block 276, enter: P = Positive or N = Negative or X = No testing done.)	(276)

VA FORM **10-9009**
MAY 2001 (RS)

Existing stock of VA Form 10-9009, JUL 2000, will not be used.

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AGENT ORANGE REGISTRY CODE SHEET (CONTINUED)

NAME *(Last, First, Middle initial)*	SOCIAL SECURITY NUMBER

27. Specify any additional workups not listed in Item 26 on the following lines

28. Diagnoses. Examiner will list up to three definite medical diagnoses on lines 28A-C. Coders will enter corresponding ICD9 codes in Blocks 277-291. If there are more than three diagnoses, list these under Item 33 - "Remarks." Do not duplicate complaints/symptoms already listed under Item 22. If neoplasia is listed under Item 29, do not duplicate under Item 28 A-C.

	(277)	(278)	(279)	(280)	(281)
A					
B	(282)	(283)	(284)	(285)	(286)
C	(287)	(288)	(289)	(290)	(291)

29. Evidence of neoplasia. Enter Code Y = Yes or N = No in Block 292.

If "Yes,"describe below and enter ICD9 code in Blocks 293-297. If "No," leave blank. Use Items A through C above if there is evidence of more than one case of neoplasia.

(292)	(293)	(294)	(295)	(296)	(297)

30. If no disease/diagnosis is found enter a Code "1" in Block 298.

(298)

31. Enter year of onset for each diagnosis listed in Blocks 277-291 and 293-297. Leave blank if unknown.

First Diagnosis				Second Diagnosis				Third Diagnosis				Fourth Dx (Neoplasia)			
(299)	(300)	(301)	(302)	(303)	(304)	(305)	(306)	(307)	(308)	(309)	(310)	(311)	(312)	(313)	(314)

32. Disposition (Enter one of the following codes in each Block: Y = Yes or N = No.) All Blocks must be completed. If veteran has no diagnosis and you have answered "YES" in Blocks 317 - 319, explain why under remarks (Item 33.)

A. Exam Completed?	(315)	B. Hospitalized at VAMC for further tests?	(316)	C. Hospitalized at VAMC for treatment?	(317)	D. Referred for VA Outpatient Treatment	(318)
E. Referred to private physician; non-VA clinic or Non-VA hospital?	(319)	F. Biopsy?	(320)	G. Specimens to be Sent to AFIP?	(321)		

33. Remarks (Please indicate whether you have made any remarks by entering a Y for Yes or N for No in Block 322.)

(322)

34. PRINT FULL NAME OF EXAMINER/REGISTRY PHYSICIAN	35. FULL TITLE OF EXAMINER
36. SIGNATURE OF EXAMINER	37. SIGNATURE OF REGISTRY PHYSICIAN

Appendix B: Questionnaire fields

ProPublica obtained the following fields from the registry data. Cell numbers corresponding to the questionnaire are in parentheses:

- Year of birth (86-87)
- State (152-153)
- Race/ethnicity (154)
- Marital status (155)
- Sex (156)
- Branch of service (158)
- Location of military service (159)
- Month and year of start and end of last period of service (168-171)
- Agent Orange Exposure (214-218)
- Self-assessment of health (219)
- Year of registry exam (224-227)
- Veteran's Complaints (228-242)
- Does the veteran attribute their chief complaint to Agent Orange exposure? (243)
- Number of children
  - total (246-7)
  - born before service in Vietnam (248-9)
  - born during/after service in Vietnam (258-9)
- Children with spina bifida
  - number of children with spina bifida born before service in Vietnam (250-1)
  - mother's age at conception of first child conceived before the veteran's service in Vietnam with spina bifida (252-3)
  - number of children with spina bifida born during/after service in (260-261)
  - mother's age at conception of first child conceived during/after the veteran's service in Vietnam with spina bifida (262-3)
- Children with birth defects (other than spina bifida)
  - number of children with birth defects born before service in Vietnam (254-5)
  - mother's age at conception of first child conceived before the veteran's service in Vietnam with birth defects (256-7)
  - number of children with birth defects born during/after service in (264-5)
  - mother's age at conception of first child conceived during/after the veteran's service in Vietnam with birth defects (266-7)
- Diagnostic workup complaints (268-276)
- Diagnoses (277-291)

Appendix C: Data quality concerns

We identified some data quality issues in the registry data. From an initial population of 668,941 veterans, our analysis excluded people with the following data quality issues:

- 254,866 people did not have an exam in 2001 or later. The data prior to 2001 may be incomplete or may have been miscoded. Before 2000, less than 1 percent of exams conducted in each year reported veterans as having any children. In 2000, the percent was also implausibly low. It is possible that changes to the questionnaire over the years have made the data more precise among veterans who received their exams more recently. The results from 2001 going forward appeared reliable on their face. Our analysis used only exams in 2001 or later.

- 90,488 additional people had data quality issues and/or had missing data. A person may have had both data quality issues and missing data.

    - 60,134 people had data quality issues. (A person may be included in more than one of the following.)

        - 51,131 people said "definitely yes" to two contradictory questions about Agent Orange exposure: that they were directly sprayed with Agent Orange and also that they were definitely not directly sprayed (with Agent Orange) but were in a recently sprayed area.

        - 3,803 people had multiple exams, and their reported number of kids (total or number with birth defects) changed in impossible ways across exams. This includes people whose number of kids born before the war changed in any way across exams, and/or who had the number of kids born after the war go down across exams.

        - 3,386 people reported a number of kids that did not make sense. (E.g. total number of kids was not equal to the sum of kids born before and during/after the war; total number born during/after the war was less than the number born during/after the war with a birth defect; number of kids was improbably large, such as more than 15 kids born during/after the war, or more than 5 kids with spina bifida born during/after the war.)

        - 2,999 people likely did not serve during the years in which Agent Orange was used in the Vietnam War, based on their reported year of birth. People born in 1910 or earlier were excluded because they would have been in their 50's in 1962, when herbicide use in Vietnam started. People born in 1954 or later were excluded because they would have been under 18 years old in 1971, when use of herbicides in Vietnam stopped. (Most veterans in the registry were born in the same decade. Over 80% of veterans who completed a registry exam in 2001 or later were born from 1943 to 1951.)

- 361 people reported a last period of service that ended before 1961 (before the start of the Vietnam war) or who reported that their last period of service will end far in the future (after 2050).

  - 35,557 people had missing data. (A person may be included in more than one of the following.)

    - 35,478 people had missing data on questions used as covariates in our models: year of birth, branch of service, year in which last period of service ended, overall health self-assessment, date of exam,total number of children born before and during/after the war, number of children born before the war with spina bifida, and number of children born before the war with other birth defects.

    - 7,709 people did not answer questions about the number of children they had with spina bifida or other birth defects born during/after the war.

    - 4,782 people did not answer questions about their exposure to Agent Orange.

While these respondents are left out of our main analysis, many are included in the sensitivity analyses. Respondents who did not answer questions about their exposure or children's health, and/or who are missing data on covariates used in our models are not included in the sensitivity analyses. (See Appendix Tables E1-3, model number 5).

Appendix D: Additional data characteristics

Parenthood before and after the war

Only about 18 percent of the veterans had children born before the war, unsurprising given that many Vietnam veterans were in their teens or early twenties at the time of their service. About 6.5 percent of veterans had children born before the war, but no children born during/after.

Appendix Table D1: Parenthood before and after the war

had any children born before the war	had any children born during/after the war	Count	Percent
No	No	54,646	16.9
No	Yes	210,218	65.0
Yes	No	21,188	6.5
Yes	Yes	37,535	11.6
	total:	323,587	

Agent Orange exposure

The questionnaire included five different measures of Agent Orange exposure. The responses to each exposure measure are shown below, among veterans who had children before and after the war. Questions 1 and 4 (having handled, sprayed or been directly sprayed with Agent Orange) are the most intensive measures of exposure on the questionnaire. Our main analyses construct a single measure of Agent Orange exposure: veterans who handled, sprayed or were directly sprayed with Agent Orange. These veterans answered 'Definitely Yes' to questions 1 and/or 4. Veterans who answered 'Definitely No' or 'Not Sure' to both questions 1 and 4 are included in the unexposed group. Of veterans who had children before and after the war, 9.5 percent responded that they definitely were involved in handling or spraying, or were definitely sprayed by Agent Orange.

Appendix Table D2: Agent Orange Exposure

	Definitely No	Not Sure	Definitely Yes
(1) I was involved in handling or spraying Agent Orange.	72.5	20.5	7.1
(2) I was not directly sprayed but was in a recently sprayed area.	6.3	39.4	54.4
(3) I was exposed to herbicides other than Agent Orange.	10.6	76.1	13.3
(4) I was directly sprayed with Agent Orange.	45.7	51.0	3.2
(5) I ate food or drink that could have been sprayed with Agent Orange.	6.5	54.1	39.4
			(n=37,535)

Birth defect frequency

Appendix Table D3: Risk of having a child with spina bifida (veteran-level)

We examined 37,535 veterans who had children born both before and during/after the war. 1.4% of veterans who reported they were exposed to Agent Orange had a child with spina bifida born during/after the war, compared to 1.1% of veterans who reported they were not exposed. Controlling for other characteristics of the veteran, the odds of having a child with any birth defect born after the war is 25% higher for exposed veterans than for unexposed veterans, though the result is not statistically significant.

| | | had a child with spina bifida | | | | | | | |
| | | born before the war | | | | born during/after the war | | | |
	total	yes	no	risk	odds	yes	no	risk	odds
exposed	3,573	19	3,554	0.5%	0.01	50	3,523	1.4%	0.01
unexposed	33,962	235	33,727	0.7%	0.01	371	33,591	1.1%	0.01
total	37,535	254	37,281	0.7%	0.01	421	37,114	1.1%	0.01

unadjusted odds ratio: 1.29
adjusted odds ratio: 1.25 (0.91,1.67)

Notes: Adjusted odds ratio was calculated using multivariate logistic regression. 95% confidence interval shown in parentheses.

Appendix Table D4: Risk of having a child with a non-spina bifida birth defect (veteran-level)

We examined 37,535 veterans who had children born both before and during/after the war. Slightly more than 12% of veterans who reported they were exposed to Agent Orange had a child with a non-spina bifida birth defect born during/after the war, compared to 9% of veterans who reported they were not exposed. Controlling for other characteristics of the veteran, the odds of having a child with a non-spina bifida birth defect born after the war is 36% higher for exposed veterans than for unexposed veterans.

| | | had a child with a non-spina bifida birth defect | | | | | | | |
| | | born before the war | | | | born during/after the war | | | |
	total	yes	no	risk	odds	yes	no	risk	odds
exposed	3,573	83	3,490	2.3%	0.02	434	3,139	12.1%	0.14
unexposed	33,962	676	33,286	2.0%	0.02	3,043	30,919	9.0%	0.10
total	37,535	759	36,776	2.0%	0.02	3,477	34,058	9.3%	0.10

unadjusted odds ratio: 1.40
adjusted odds ratio: 1.36 (1.22,1.51)

Notes: Adjusted odds ratio was calculated using multivariate logistic regression. 95% confidence interval shown in parentheses.

Appendix Table D5: Risk of having spina bifida (child-level)

We examined the children of 37,535 veterans who had children born both before and during/after the war. Regardless of parents' exposure to Agent Orange, 0.5% of children born before the war had spina bifida, compared to 0.7% of children born during/after the war.

	had spina bifida								
	born before the war					born during/after the war			
	total	yes	no	risk	odds	total	yes	no	risk	odds
exposed	5,556	21	5,535	0.4%	0.00	6,897	56	6,841	0.8%	0.01
unexposed	51,071	279	50,792	0.5%	0.01	66,179	451	65,728	0.7%	0.01
total	56,627	300	56,327	0.5%	0.01	73,076	507	72,569	0.7%	0.01

Appendix E: Sensitivity Analyses

For each outcome measure (any birth defects; spina bifida; other birth defects), we ran a few variations of the model:

Models use one of the following measures of Agent Orange exposure:

1. A single exposure measure, indicating that a veteran definitely handled, sprayed, or was sprayed with Agent Orange (models 1, 4 and 5).

2. Measures of several types of Agent Orange exposure, with responses of 'Definitely Yes' and 'Not Sure' each compared to responses of 'Definitely No' (model 2).

3. Measures of several types of Agent Orange exposure, with responses of 'Definitely Yes' compared to responses of either 'Not Sure' or 'Definitely No' (model 3).

Models use one of the following sample definitions:

1. Veteran-level, only for veterans who have children born both before and after the war (models 1, 2, 3, and 5).

2. Veteran-level, for all veterans who have children born after the war (model 4).

All models exclude respondents with logically inconsistent data except for model 5, which includes these respondents. All models exclude respondents with missing data.

All five models in Appendix Table E1 tell a consistent story: there is a correlation between Agent Orange exposure and birth defects in veteran's children. Similarly, all models of non-spina bifida birth defects in Table E2 show a correlation between Agent Orange exposure and non-spina bifida birth defects.

Our main analysis found no correlation between Agent Orange exposure and having a child with spina bifida (Appendix Table E3, model 1). However, two of four alternate model specifications in Appendix Table E3 show evidence of a link between Agent Orange exposure and spina bifida in the children of veterans.

Appendix Table E1: Any birth defects sensitivity analyses, multivariate logistic regression

Having handled, sprayed, or been sprayed with Agent Orange was possitively correlated with having a child born after the war with any birth defect. This was true in our main model specification (1) as well as under several different model specifications (2-5).

	(1)		(2)		(3)		(4)		(5)	
Include cases with no kids born before the war?	No		No		No		Yes		No	
Include responses with data issues?	No		No		No		No		Yes	
Observations	37,535		37,535		37,535		247,753		44,610	
	OR	p	OR	p	OR	p	OR	p	OR	p
Handled, sprayed or was sprayed with AO	1.34	<0.001 ***					1.313	<0.001 ***	1.472	<0.001 ***
Handled or Sprayed AO										
Yes			1.23	0.001 ***	1.25	<0.001 ***				
Not Sure			0.94	0.20						
Was in a recetly sprayed area										
Yes			1.14	0.11	1.21	<0.001 ***				
Not Sure			0.94	0.42						
Exposed to herbicides other than AO										
Yes			1.02	0.80	0.98	0.74				
Not Sure			1.04	0.53						
Was directly sprayed with AO										
Yes			1.44	<0.001 ***	1.41	<0.001 ***				
Not Sure			1.07	0.077 *						
Ate food or drink that could have been sprayed with AO										
Yes			1.18	0.040 **	1.20	<0.001 ***				
Not Sure			0.98	0.83						
Year of birth	1.01	<0.001 ***	1.02	<0.001 ***	1.02	<0.001 ***	1.02	<0.001 ***	1.02	<0.001 ***
Branch of Service										
Army (reference category)	--	--	--	--	--	--	--	--	--	--
Air Force	0.98	0.71	1.01	0.78	1.01	0.79	0.96	0.080 *	0.97	0.46
Navy	0.95	0.36	0.99	0.85	0.99	0.86	1.03	0.19	0.96	0.46
Marines	1.04	0.51	1.04	0.54	1.04	0.50	1.07	<0.001 ***	1.03	0.51
Multiple	1.77	0.18	1.81	0.16	1.83	0.15	0.85	0.35	1.65	0.18
Coast Guard	1.19	0.76	1.24	0.70	1.27	0.68	0.87	0.69	1.30	0.59
Other	1.44	0.007 ***	1.47	0.005 ***	1.46	0.005 ***	1.41	<0.001 ***	1.35	0.015 **
Year last period of service ended	0.99	0.045 **	0.99	0.036 **	0.99	0.036 **	1.00	0.015 **	0.99	0.004 ***
Health Self-Assessment at time of exam										
Very Good (reference cagetory)	--	--	--	--	--	--	--	--	--	--
Good	1.29	0.048 **	1.27	0.063 *	1.28	0.061 *	1.13	0.006 ***	1.18	0.16
Fair	1.50	0.001 ***	1.44	0.004 ***	1.45	0.003 ***	1.26	<0.001 ***	1.40	0.003 ***
Poor	1.68	<0.001 ***	1.58	<0.001 ***	1.59	<0.001 ***	1.42	<0.001 ***	1.60	<0.001 ***
Very Poor	1.94	<0.001 ***	1.78	<0.001 ***	1.79	<0.001 ***	1.60	<0.001 ***	1.85	<0.001 ***
Year of last registry exam	0.99	0.16	0.99	0.084 *	0.99	0.065 *	0.99	<0.001 ***	1.00	0.19
Number of children born before the war										
total	1.03	0.11	1.03	0.12	1.03	0.13	1.05	<0.001 ***	1.04	0.011 **
with spina bifida	2.02	<0.001 ***	2.03	<0.001 ***	2.03	<0.001 ***	2.04	<0.001 ***	1.24	0.019 **
with other birth defects	2.67	<0.001 ***	2.68	<0.001 ***	2.68	<0.001 ***	2.70	<0.001 ***	2.52	<0.001 ***
Number of children born after the war										
total	1.15	<0.001 ***	1.14	<0.001 ***	1.14	<0.001 ***	1.21	<0.001 ***	1.12	<0.001 ***

Notes: OR = Odds Ratio; 95% CI = 95% Confidence Interval; p = pvalue; AO= Agent Orange. Stars indicate statistical significance at the following levels: *** 1 percent; ** 5 percent; * 10 percent.

Appendix Table E2: Birth defects other than spina bifida sensitivity analyses, multiple logistic regression

Having handled, sprayed, or been sprayed with Agent Orange was possitively correlated with having a child born after the war with a non-spina bifida birth defect. This was true in our main model specification (1) as well as under several different model specifications (2-5).

	(1)		(2)		(3)		(4)		(5)	
Include cases with no kids born before the war?	No		No		No		Yes		No	
Include responses with data issues?	No		No		No		No		Yes	
Observations	37,535		37,535		37,535		247,753		44,610	
	OR	p	OR	p	OR	p	OR	p	OR	p
Handled, sprayed or was sprayed with AO	1.36	<0.001 ***					1.30	<0.001 ***	1.49	<0.001 ***
Handled or Sprayed AO										
Yes			1.26	<0.001 ***	1.28	<0.001 ***				
Not Sure			0.93	0.15						
Was in a recetly sprayed area										
Yes			1.18	0.048 **	1.22	<0.001 ***				
Not Sure			0.97	0.73						
Exposed to herbicides other than AO										
Yes			1.01	0.90	0.98	0.68				
Not Sure			1.03	0.60						
Was directly sprayed with AO										
Yes			1.44	<0.001 ***	1.39	<0.001 ***				
Not Sure			1.07	0.082 *						
Ate food or drink that could have been sprayed with AO										
Yes			1.15	0.10	1.19	<0.001 ***				
Not Sure			0.96	0.61						
Year of birth	1.02	<0.001 ***	1.02	<0.001 ***	1.02	<0.001 ***	1.02	<0.001 ***	1.02	<0.001 ***
Branch of Service										
Army (reference category)	--	--	--	--	--	--	--	--	--	--
Air Force	1.00	0.99	1.03	0.54	1.03	0.56	0.96	0.065 *	0.97	0.57
Navy	1.02	0.78	1.06	0.32	1.06	0.31	1.03	0.12	1.00	0.94
Marines	1.06	0.31	1.06	0.33	1.06	0.30	1.07	<0.001 ***	1.06	0.27
Multiple	1.99	0.10	2.04	0.092 *	2.07	0.085 *	0.92	0.66	1.84	0.099 *
Coast Guard	0.70	0.63	0.72	0.66	0.73	0.67	0.76	0.48	0.85	0.79
Other	1.53	0.002 ***	1.57	0.001 ***	1.56	0.001 ***	1.39	<0.001 ***	1.41	0.007 ***
Year last period of service ended	0.99	0.066 *	0.99	0.054 *	0.99	0.054 *	1.00	0.01 **	0.99	0.021 **
Health Self-Assessment at time of exam										
Very Good (reference cagetory)	--	--	--	--	--	--	--	--	--	--
Good	1.34	0.035 **	1.32	0.045 **	1.32	0.044 **	1.13	0.005 ***	1.20	0.15
Fair	1.52	0.002 ***	1.47	0.004 ***	1.47	0.004 ***	1.27	<0.001 ***	1.42	0.004 ***
Poor	1.73	<0.001 ***	1.63	<0.001 ***	1.63	<0.001 ***	1.43	<0.001 ***	1.64	<0.001 ***
Very Poor	2.02	<0.001 ***	1.86	<0.001 ***	1.86	<0.001 ***	1.59	<0.001 ***	1.90	<0.001 ***
Year of last registry exam	0.99	0.017 **	0.99	0.007 ***	0.99	0.005 ***	0.98	<0.001 ***	0.99	0.014 **
Number of children born before the war										
total	1.03	0.11	1.03	0.12	1.03	0.13	1.04	<0.001 ***	1.03	0.038 **
with spina bifida	1.11	0.49	1.11	0.48	1.11	0.49	1.07	0.64	0.80	0.001 ***
with other birth defects	2.64	<0.001 ***	2.66	<0.001 ***	2.66	<0.001 ***	2.67	<0.001 ***	2.55	<0.001 ***
Number of children born after the war										
total	1.15	<0.001 ***	1.14	<0.001 ***	1.14	<0.001 ***	1.21	<0.001 ***	1.12	<0.001 ***
with spina bifida	1.57	<0.001 ***	1.57	<0.001 ***	1.57	<0.001 ***	1.79	<0.001 ***	1.31	<0.001 ***

Notes: OR = Odds Ratio; 95% CI = 95% Confidence Interval; p = pvalue; AO= Agent Orange. Stars indicate statistical significance at the following levels: *** 1 percent; ** 5 percent; * 10 percent.

Appendix Table E3: Spina bifida sensitivity analyses, multivariate logistic regression

In our main model specification (1) and under several other model specifictions (2 and 3) having handled, sprayed, or been sprayed with Agent Orange was not correlated with having a child born after the war with spina bifida. However, under model specifications (4 and 5), a corrolation was observed.

	(1)		(2)		(3)		(4)		(5)	
Include cases with no kids born before the war?	No		No		No		Yes		No	
Include responses with data issues?	No		No		No		No		Yes	
Observations	37,535		37,535		37,535		247,753		44,610	
	OR	p	OR	p	OR	p	OR	p	OR	p
Handled, sprayed or was sprayed with AO	1.25	0.15					1.45	<0.001 ***	1.26	0.020 **
Handled or Sprayed AO										
Yes			1.20	0.31	1.22	0.27				
Not Sure			1.03	0.81						
Was in a recetly sprayed area										
Yes			0.86	0.47	1.12	0.30				
Not Sure			0.72	0.14						
Exposed to herbicides other than AO										
Yes			1.18	0.43	1.15	0.32				
Not Sure			1.04	0.82						
Was directly sprayed with AO										
Yes			1.27	0.37	1.31	0.30				
Not Sure			1.10	0.39						
Ate food or drink that could have been sprayed with AO										
Yes			1.17	0.51	1.16	0.17				
Not Sure			1.01	0.97						
Year of birth	0.99	0.56	0.99	0.52	0.99	0.55	1.02	0.003 ***	1.02	0.1
Branch of Service										
Army (reference category)	--	--	--	--	--	--	--	--	--	--
Air Force	0.84	0.22	0.85	0.26	0.85	0.28	0.99	0.93	0.88	0.34
Navy	0.47	<0.001 ***	0.48	<0.001 ***	0.49	<0.001 ***	0.95	0.47	0.65	0.01 **
Marines	0.87	0.41	0.87	0.40	0.87	0.41	1.04	0.50	0.80	0.14
Multiple	0.00	0.96	0.00	0.96	0.00	0.96	0.00	0.92	0.00	0.95
Coast Guard	5.15	0.032 **	5.07	0.034 **	5.32	0.028 **	2.09	0.29	6.90	0.002 ***
Other	0.85	0.70	0.85	0.70	0.85	0.71	1.37	0.092 *	0.91	0.81
Year last period of service ended	0.99	0.44	0.99	0.42	0.99	0.43	1.00	0.94	0.98	0.035 **
Health Self-Assessment at time of exam										
Very Good (reference cagetory)	--	--	--	--	--	--	--	--	--	--
Good	1.10	0.80	1.09	0.83	1.09	0.82	0.98	0.90	1.14	0.70
Fair	1.43	0.33	1.38	0.38	1.39	0.36	1.11	0.42	1.33	0.38
Poor	1.52	0.26	1.41	0.35	1.43	0.33	1.24	0.11	1.37	0.34
Very Poor	1.26	0.57	1.15	0.74	1.17	0.70	1.55	0.003 ***	1.40	0.35
Year of last registry exam	1.03	0.005 ***	1.03	0.006 ***	1.03	0.006 ***	1.00	0.55	1.04	<0.001 ***
Number of children born before the war										
total	0.98	0.77	0.98	0.74	0.98	0.74	1.12	<0.001 ***	1.05	0.12
with spina bifida	5.42	<0.001 ***	5.39	<0.001 ***	5.39	<0.001 ***	5.60	<0.001 ***	1.47	0.002 ***
with other birth defects	2.00	<0.001 ***	1.99	<0.001 ***	1.98	<0.001 ***	1.94	<0.001 ***	1.64	<0.001 ***
Number of children born after the war										
total	1.12	<0.001 ***	1.12	<0.001 ***	1.12	<0.001 ***	1.18	<0.001 ***	1.05	0.088 *
with other birth defects	1.55	<0.001 ***	1.52	<0.001 ***	1.53	<0.001 ***	1.72	<0.001 ***	1.22	<0.001 ***

Notes: OR = Odds Ratio; 95% CI = 95% Confidence Interval; p = pvalue; AO= Agent Orange. Stars indicate statistical significance at the following levels: *** 1 percent; ** 5 percent; * 10 percent.

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Updates to this document

December 16, 2016: A footnote was added to Table 2 to provide additional information about the percent of veterans who had any children with defects, born before the war.