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Agricultural exposures and stroke mortality in the Agricultural Health Study

Jessica L. Rinsky, MPH[1], **Jane A. Hoppin, ScD**[2,*], **Aaron Blair, PhD**[3], **Ka He, MD, ScD**[4], **Laura E. Beane Freeman, PhD**[5], and **Honglei Chen, MD, PhD**[6]

Jessica L. Rinsky: jrinsky@email.unc.edu; Aaron Blair: blaira@mail.nih.gov; Ka He: kahe@indiana.edu; Laura E. Beane Freeman: freemala@mail.nih.gov; Honglei Chen: chenh2@niehs.nih.gov

[1]Department of Epidemiology, University of North Carolina Gillings School of Global Public Health. Chapel Hill, NC

[2]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services. Research Triangle Park, NC

[3]Occupational and Environmental Epidemiology Branch, National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Bethesda, MD

[4]Departments of Nutrition and Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC and Department of Epidemiology and Biostatistics, School of Public Health, Indiana University Bloomington. Bloomington, IN

[5]Occupational and Environmental Epidemiology Branch, National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Bethesda, MD

[6]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services. Research Triangle Park, NC

Abstract

Exposures associated with common agricultural activities may increase risk of stroke. The authors evaluated associations between self-reported agricultural activities including pesticide use and handling of crops and stroke mortality among 51,603 male pesticide applicators enrolled in the Agricultural Health Study (AHS). Vital status was obtained through 2008. Stroke mortality was defined by underlying or contributing cause of death (ICD-9 430–438, ICD-10 I60-I69). Information regarding lifetime pesticide use, working with crops or animals, engagement in other agricultural activities, and potential confounders was self-reported at enrollment. Cox proportional hazards models, with age as the time scale, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) adjusted for state of residence, smoking status, and alcohol consumption. Median follow-up time was 13 years, during which 308 stroke deaths occurred. No measure of overall or specific pesticide use was positively associated with mortality due to stroke. Stroke mortality was inversely associated with handling hay, grain, or silage at least once each year as reported at enrollment (HR: 0.75; 95% CI: 0.58, 0.98). There was no evidence of an association between pesticide use and stroke mortality. The inverse association between handling of hays and grains and stroke mortality may be due to (1) those engaging in such activities being healthier than those who did not or (2) exposure to some biological agent present in hays and grains. Further

*Corresponding author: Epidemiology Branch, NIEHS, NIH, DHHS, MD A3-05, P.O. Box 12233, Research Triangle Park, NC 27709-2233, USA, Phone: (919) 541-7622, Fax: (919) 541-2511, hoppin1@niehs.nih.gov.

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investigation of incident stroke, rather than stroke mortality, as well as stroke subtypes are needed to determine the full role of agricultural exposures and stroke.

INTRODUCTION

Stroke is the third leading cause of death in the United States and the second leading cause globally(Grysiewicz et al. 2008). Stroke is responsible for a large proportion of long-term disability and health-care costs. Although there are well-established lifestyle and clinical risk factors for stroke, much of the risk remains unexplained (Ohira et al. 2006; Grysiewicz et al. 2008; Reynolds et al. 2003). Experimental and observational studies indicate that environmental exposures to air pollution, inhaled dust, and exogenous chemicals may contribute to the risk of cardiovascular disease, including stroke (Ha et al. 2007; Yorifuji et al. 2011; Lee et al. 2012; Mastin 2005; Yang et al. 2004). In addition, epidemiologic data provide some evidence to support associations between environmental exposures and well-established stroke risk factors including diabetes, metabolic syndrome, weight gain, and other cardiovascular conditions (Bar-Meir et al. 2007; Montgomery et al. 2008; Roth et al. 1993; Saadeh et al. 1997). Possible biological pathways through which these environmental exposures may operate include oxidative stress and endothelial and vascular damage leading to pro-inflammatory events or through disturbances in coagulation (Bombick et al. 1984; Ha et al. 2007; Hennig et al. 2002; Lovati et al. 1984; Toborek et al. 1995; Ghio et al. 2012; Park et al. 2010).

Farmers and other agricultural workers come into contact with a variety of environmental exposures including pesticides and inhaled dusts from crops and animals as part of their work(Coble et al. 2002; Thomas et al. 2010; Hines et al. 2011; Poole et al. 2010; Burch et al. 2010). Few studies have examined the association between these farming-related exposures and stroke or related mortality. As farmers are known to have lower rates of morbidity and mortality due to cerebrovascular disease and other associated conditions as compared to the general public(Blair et al. 2005; Mills et al. 2009; Waggoner et al. 2011), the Agricultural Health Study (AHS) provides a unique opportunity to examine associations between a range of agricultural exposures and stroke mortality in a large cohort of pesticide applicators, consisting mainly of farmers. The present study aimed to determine if exposure to pesticides or other farming activities is associated with stroke mortality among participants of the AHS.

METHODS

Study Population

The AHS is a large, prospective cohort study of licensed pesticide applicators and their spouses residing in North Carolina and Iowa (N = 89,655). The study design has been described in detail elsewhere (Alavanja et al. 1996). Briefly, private pesticide applicators (mainly farmers, N=53,394) and their spouses (N = 32,345) and commercial pesticide applicators (N = 4,916) enrolled in the cohort between 1993 and 1997. Applicators enrolled in the study by completing a self-administered questionnaire which collected information about pesticide use, farming activities, demographics, and health, when they applied for, or renewed their pesticide license. Approximately 44% of applicators returned, by mail, a take-home questionnaire, which included additional information regarding work-related activities (copies of both questionnaires are available at the AHS web site http://www.aghealth.org/questionnaires.html).

The present study was restricted to male private and commercial pesticide applicators (Figure 1). Further, 4,144 applicators (7%) (82 stroke deaths) with missing information on either smoking or alcohol consumption were excluded leaving 51,603 applicators for the present analysis.

Stroke Mortality

The cohort is linked regularly to state and national death registries to determine vital status of all participants. Through this linkage, underlying and contributing causes of death were obtained from enrollment through December 31, 2008, the most recent year available. Mortality from stroke was identified as either the underlying or a contributing cause of death on the death certificate, according to the *International Classification of Diseases*, Ninth Revision (ICD-9), codes (430–438), or Tenth Revision (ICD-10), codes I60-I69 (World Health Organization 2009). ICD-9 codes were converted to equivalent ICD-10 codes. Although information was available for type of stroke (ischemic, hemorrhagic, and unspecified subtypes) for some decedents, results from analyses examining all stroke mortality only are presented due to a high proportion of unspecified cases (65%) a problem that has been previously noted throughout the United States (Cheng et al. 2012).

Exposure Assessment

As part of the enrollment questionnaire, participants reported overall lifetime days of pesticide use, including total years and days/year of pesticide use. Participants reported ever use of 50 commonly used pesticides and lifetime frequency and duration of use for 22 of those pesticides. Information regarding use of chemical-resistant gloves while handling pesticides was also reported. Use of chemical-resistant gloves has been demonstrated in the AHS cohort to be the item of personal protective equipment associated with the greatest reduction in pesticide exposure among those examined (Hines et al. 2011; Thomas et al. 2010; Waggoner et al. 2011) and consequently this was considered as a marker of reduced exposure and protective behavior.

Participants reported characteristics of the farm where they live or work including the size of the farm and the number and type of livestock and poultry raised. Information regarding the frequency of performance of agricultural activities was also collected. Participants reported handling hays, grains, or silage, or performing work in swine or poultry confinement areas at least once each year at enrollment.

As part of the take-home questionnaire, participants reported detailed use information on the remaining 28 pesticides for which this information was not provided on the enrollment questionnaire, as well as a history of doctor-diagnosed pesticide poisoning, or having experienced a high-pesticide exposure event, defined as an “incident or experience while using *any* type of pesticide which caused you *unusually high* personal exposure.” Individuals responding to the take-home questionnaire provided more detailed information regarding frequency of farm activities including use of diesel and gasoline tractors, trucks, and combines.

Statistical Analyses

The distribution of demographic and health characteristics was examined within the study population. A Poisson regression model was used to generate incidence rate ratios (IRR) adjusted for age in categories and 95% confidence intervals (CI) illustrating the association between each demographic and behavioral characteristic and stroke mortality. Separate directed acyclic graphs (DAGs) were created to represent the association between each category of exposure (pesticide use, handling of crops, presence of animals, farm characteristics) and stroke mortality.

All multivariable analyses were conducted using Cox proportional hazards models with age as the time scale in order to produce hazard ratios (HR) and 95% CIs. For each category of exposure, covariates identified as potential confounders based on DAGs were further examined to determine the association between the covariate and exposure and the covariate and outcome.

Body mass index (<25, 25–29.9, ≥30 kg/m^2), ever receiving a doctor diagnosis of diabetes (yes/no), use of chemical-resistant gloves (yes/no), and state of residence (Iowa, North Carolina) were considered as potential effect measure modifiers and race/ethnicity (non-Hispanic white vs. other) and education (high school or less vs. beyond high school) as potential confounders of each association. A backward elimination model building approach was used to determine the final model. No evidence of modification based on stratum-specific estimates and likelihood ratio tests (α=0.10) was observed and consequently the previously mentioned potential modifiers were assessed for confounding. A change-in-estimate (<0.10) approach was used to identify confounders. Final models were adjusted for state of residence (Iowa, North Carolina), smoking status (never, past, current), and alcohol consumption (none, 1–4, 5–30, >30 drinks/month). In order to maintain statistical stability, analyses were only performed for exposures with at least 5 cases in each level of exposure. Consequently, no analyses were performed examining use of individual pesticides with fewer than 5 exposed or unexposed cases.

Our analysis included all stroke-related deaths occurring within the study population during the study period. Some of those included could have experienced a non-fatal stroke prior to enrollment. Therefore, the impact of this choice was assessed by limiting the analysis to only those participants with stroke identified as the underlying cause of death (N=187). In addition, as older participants may be in poorer health at baseline and poor health status may have a stronger effect on stroke death than agricultural exposures, analyses restricted to the study population younger than 65 years old at enrollment were conducted. Results from these additional analyses were similar to those with no restrictions and therefore are not presented here.

Prior to excluding pesticide applicators with missing information on smoking or alcohol consumption, the distribution of missing data was examined (**see** Table, Supplemental Digital Content 1). Missing data for smoking and alcohol consumption were determined to be not missing completely at random. To determine the impact of this exclusion on results, a set of assumptions regarding the distribution of missing information were tested. All analyses were conducted under the following assumptions: 1) all those missing information were considered current smokers/heavy drinkers; 2) all those missing information were considered never smokers/never drinkers; 3) all cases missing information were current smokers/heavy drinkers and all non-cases were never smokers/never drinkers; and, 4) all cases missing information were never smokers/never drinkers and all non-cases were current smokers/heavy drinkers. These analyses produced similar results to the complete-case analysis and consequently it was determined that exclusion of these individuals did not significantly bias results and therefore, only results from the complete-case analysis are presented here.

All statistical analyses were completed in SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina) using the AHS data releases P1REL0906.00 and REL0905.00. The AHS was reviewed and approved by institutional review boards at the National Institutes of Health and its contractors. This analysis was also reviewed and approved by the institutional review board at the University of North Carolina at Chapel Hill.

RESULTS

A total of 308 stroke-related deaths occurred among male pesticide applicators between enrollment and the end of 2008 (median 13 years of follow-up). Twenty six percent of deaths due to stroke were recorded as hemorrhagic and 9% ischemic, while the rest were of an "unspecified" or other type. Most known risk factors for stroke were associated with stroke mortality (Table 1). Participants who were older, current smokers, lived in North Carolina, or reported a history of heart disease, diabetes or hypertension had an increased rate of death due to stroke. A slightly J-shaped association between alcohol consumption and stroke mortality was observed.

No consistent positive associations between overall pesticide use and stroke mortality were identified (Table 2). While there was no evidence of an association of overall use of pesticides with stroke mortality, individuals who used chemical-resistant gloves had a slightly reduced rate of stroke death (HR: 0.83; 95% CI: 0.65, 1.05) and those reporting having had a diagnosed pesticide-poisoning event had a slightly increased rate of stroke death (HR: 1.73; 95% CI: 0.77, 3.92) but neither association was statistically significant. When we examined ever use of 50 individual pesticides, there was no evidence of an association between individual chemicals and increased stroke mortality, either for ever use (**see** Table, Supplemental Digital Content 2) or lifetime days of use (data not shown). Reported use of the herbicide, metribuzin, was associated with a reduced rate of stroke mortality. Grouping of pesticides by functional group or chemical class showed no evidence of an association with stroke mortality.

Estimates of associations between other farming factors and stroke mortality varied around the null with some significant associations observed (Table 3). Individuals who handled grain, hay, or silage had a reduced rate of stroke death (HR: 0.75; 95% CI: 0.58, 0.98). This reduction in stroke mortality was observed when all three activities were combined and when assessed independently. Individuals reporting work on farms that were 5 or more acres had a slightly reduced rate of stroke. As number of livestock increased, the association with stroke mortality approached unity. When type of livestock present on the farm was considered, a slightly reduced hazard of stroke was present for those reporting cattle (dairy or beef) as a major income producing crop. No positive or negative associations were found between stroke mortality and the use of diesel or gasoline trucks or tractors, combines, or work in animal confinement facilities (data not shown).

DISCUSSION

Stroke is a leading cause of morbidity and mortality in the United States and abroad (Grysiewicz et al. 2008). Few studies have characterized associations between agricultural exposures and the risk of stroke mortality. Data from the AHS was used to examine the hypothesis that pesticide applicators (mainly farmers) who perform work-related activities that may bring them into contact with exogenous chemicals or particulate matter may have an increased rate of stroke mortality compared with those who do not engage in these activities. There is some evidence that pesticides and particulate matter, including organic dusts and diesel exhaust, may be associated with stroke and consequently stroke mortality, through inflammatory processes producing tissue damage leading to various disease states, coagulation disturbances, and through effects on the cardiac system (Anderson et al. 2011; Bhatnagar 2006; Hennig et al. 2002; Hong et al. 2002; Lovati et al. 1984; Roth et al. 1993; Saadeh et al. 1997; Seaton et al. 1999; Toborek et al. 1995; Ha et al. 2007; Montgomery et al. 2008; Toren et al. 2007; Park et al. 2010). However, in the present analysis no evidence was observed to support the hypothesis that the occupational activities examined here are associated with an elevated rate of stroke mortality among pesticide applicators participating in this large U.S. cohort study.

No association was observed between total lifetime days or years of pesticide use or use of any of 50 individual pesticides and stroke mortality. Although some crude rate ratios for use of individual pesticides appeared to indicate an increased rate of stroke mortality for individuals reporting use of specific pesticides, this association was no longer observed once age was considered. Use of one herbicide, metribuzin, was associated with a significantly lower rate of stroke mortality. Although, a reduced rate of stroke mortality was observed for individuals reporting ever using metribuzin, no clear biological mechanism is available to explain this and no other herbicides exhibited a similar association.

The results reported here differ from two previous studies that noted increased stroke-related mortality among individuals occupationally exposed to pesticides.(Cantor et al. 1999; Charles et al. 2010) Both studies relied on job title to define exposure to pesticides and did not assess information regarding use of or exposure to individual pesticides. Among Japanese-American men enrolled in the Honolulu Heart Study, a 70% increased rate of stroke mortality was observed among those determined to have the highest level of exposure to pesticides compared to those with no exposure (Charles et al. 2010). Similarly, a study of aerial pesticide applicators reported an almost two-fold elevation in stroke-related mortality as compared to flight instructors in the United States (Cantor et al. 1999). When overall lifetime pesticide use was examined, no association with stroke mortality was observed. The differences in the findings in the present study and the two previous studies may be due to differences in the demographic make-up of the study populations, calendar year of exposure, and the occupations examined. Further, the routes and definitions of exposures differed between the present and previous studies. The previous study relied on primary job title to determine likelihood of exposure to pesticides, a method that has been demonstrated to lead to misclassification of exposure (MacFarlane et al. 2009), while in the present study information regarding pesticide use was ascertained from participants.

In addition to the previous stroke mortality studies, Lee and colleagues (2012) reported a positive association between elevated plasma concentrations of three organochlorine (OC) pesticides and incident stroke among an elderly population in Sweden (Lee et al. 2012). OCs were measured in plasma up to 5 years prior to stroke diagnosis among individuals aged 70 and older. Those in the ≥95th percentile of a summary measure of OC pesticides had 9 times the odds of stroke compared to those in the lowest quartile (OR= 9.5 95% CI: 2.3, 38.9). Although these results were statistically significant they were based on a small number of cases (6 exposed; 5 unexposed) in a highly selected group (healthy individuals 70 and over). No evidence of an elevated rate of stroke mortality associated with specific OC pesticides or OCs as a group was noted in the present sample of younger individuals in the AHS followed for a longer period. Future studies with longer follow-up time and good characterization of timing of incident stroke will be useful to further explore this hypothesis.

In contrast to Lee et al. (2012), it was not possible in the present study to examine biomarkers of pesticide exposure and consequently relied on self-reported information to define exposure, and therefore some misclassification may be present. However, several steps have been taken to assess the potential for misclassification in the larger cohort. Internal validation studies showed 70–90% repeatability of self-reported pesticide use one-year after completion of the enrollment questionnaire (Blair et al. 2002). In another study, self-reported use of pesticides was found to compare reasonably well with pesticide registration information (Hoppin et al. 2002). A high reliability of report of covariates including smoking, alcohol consumption and reported disease history, and agricultural factors was also demonstrated (Blair et al. 2002). Despite the general high quality characterization of agricultural exposures for this study, it is important to note that some exposure misclassification undoubtedly occurs and that in a prospective cohort study it is likely to bias relative risks toward the null (Blair et al. 2011). Further, the AHS study is unique in that it is one of the largest prospective studies to include detailed information regarding agricultural exposures and covariates.

The present analysis examined stroke mortality defined by causes of death as recorded on the death certificate. This approach has demonstrated high specificity but a range of sensitivities in capturing stroke-related deaths with a clear improvement in recent years, indicating there may be some misclassification of stroke-related death (Corwin et al. 1982; Iso et al. 1990). In order to improve ascertainment of cases of stroke death, both underlying and contributing causes of death listed on the death certificate were considered. Although no associations between many of the agricultural activities examined and stroke-related mortality was observed, it was not possible to explore the timing, severity, or subtype of stroke and therefore exposures associated with non-fatal stroke or a specific stroke subtype are not examined here.

In addition to pesticide use, agricultural activities that would provide opportunity for exposure to particulate matter and, specifically, organic material from animals and crops were examined. No evidence to support a positive association between any of these activities and stroke mortality was found. A reduced rate of stroke mortality among farmers who reported handling hay, grain, and silage at least once each year was observed. In considering this finding it is important to note, individuals could only be classified as having handled hays, grains, and silage at least once each year as of enrollment or not. No further information regarding frequency or intensity of these activities was available, and therefore only this crude measure of exposure was assessed.

The inverse associations observed here may be explained, in that, participants reporting handling hay, grain or silage at least once each year at enrollment were in general different than those who did not reported such activities. For example, those who reported engaging in such activities were more active or healthier, and remained that way over time, and therefore demonstrated decreased risk of mortality related to stroke than those who did not report such activities. To this end, those who reported engaging in these activities were younger and a smaller proportion reported diabetes, heart disease, and hypertension diagnoses at enrollment than those who did not report engaging in these activities.

It is also possible that activities involving handling hay, grain, and silage provide chronic low-dose exposure to biological agents such as endotoxin (Spaan et al. 2006). Although little research in humans exists, some experimental research indicates that chronic exposure to low-levels of endotoxin may protect against, or reduce severity of, a range of injury thought to be associated with inflammatory processes including stroke and many of its risk factors (Biswas et al. 2009; Draisma et al. 2009; Drake et al. 2011; Eising et al. 1996; Fan et al. 2004; Iadecola et al. 2011; Liebers et al. 2006; Marsh et al. 2009; McColl et al. 2009; McColl et al. 2008; Rosenzweig et al. 2007; Doyle et al. 2012). However, the potential mechanism and impact of endotoxin exposure on stroke remains unclear.

A reduced rate of stroke mortality was also observed among farmers reporting cattle (beef or dairy) as a major income producing crop. Handling of hays, grains, and silage is very common among individuals producing cattle. It was found that only 4% of individuals reporting cattle as a major income producing crop did not handle hay, grain, or silage, with only 5 cases of stroke death included in this group. Therefore, it is difficult to separate the independent effects of exposure to cattle and handling of hays, grains, and silage.

Consistent with other published studies, the age-adjusted stroke mortality rate standardized to the 2000 U.S. population among male participants in the AHS cohort (19.1 stroke deaths/ 100,000 person-years) was lower than that observed for non-Hispanic, white males older than 15 in the general public (61 stroke deaths/100,000 person-years) and in Iowa (65 stroke deaths/100,000 person-years) and North Carolina (71 stroke deaths/100,000 person-years) during a similar period (1999–2010).(Centers for Disease Control and Prevention 2012). A previous study of this cohort reported a standardized mortality ratio (SMR) for cerebrovascular and arterial diseases of 0.51 (95% CI: 0.46, 0.57) and similar SMR for associated conditions including diabetes and hypertension (Waggoner et al. 2011). Because farmers have been observed to have lower rates of conventional risk factors for stroke (e.g., tobacco use, alcohol use) and increased physical activity levels, than the general public (Blair et al. 1992; Stellman et al. 1988; Sterling et al. 1978), the AHS is a unique population in which to examine associations between agricultural exposures and stroke mortality. Participants in the AHS reside in states where the underlying rates of stroke mortality are quite different allowing for the examination of these associations in different areas of the country (Lanska et al. 1995; Lanska 1993; United States Geological Survey 2002). As expected, participants from North Carolina displayed a higher rate of stroke mortality than participants from Iowa (Lanska et al. 1995; NHLBI). Despite the differences between the two states, the associations between stroke mortality and known risk factors or exposures were similar, potentially due to real similarities or a lack of power to detect differences between the states.

The present analysis is one of the first explorations of associations between agricultural activities and stroke mortality. The findings of no significant association between a number of well-characterized pesticide use parameters and stroke mortality over a median 13-years of follow-up and the potential for a reduced rate of stroke mortality among those reporting handling of hay, grain, and silage warrant further investigation to determine if the results represent a true effect or are a product of some bias. Analyses conducted in large populations with improved exposure assessment and the ability to examine incident stroke and stroke outcomes by subtype will improve the present knowledge regarding the role of environmental and occupational exposures in the burden of stroke, an important cause of morbidity and mortality globally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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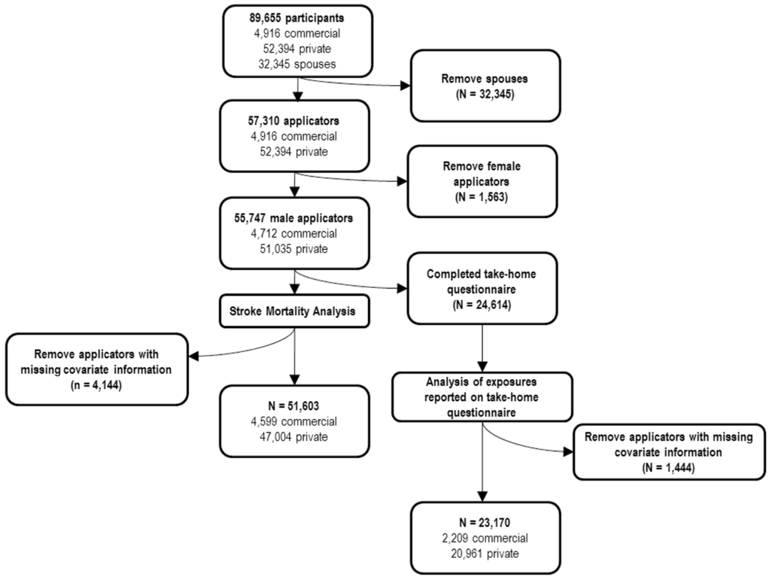

Fig. 1.

Illustration of participants included in the present analysis of the association between agricultural activities and stroke mortality in the Agricultural Health Study Cohort, 1993–2008.

Table 1

General characteristics of 51,603 male pesticide applicators by stroke mortality outcome, Agricultural Health Study, 1993–2008.[a]

	Cases[b]		Noncases[c]		Person Time	Incidence Rate Ratio[d]	95% Confidence Interval	
	(N = 308)	%	(N = 51,295)	%				
Site								
NC	194	63	16591	32	218426	1		
Iowa	114	37	34704	68	457408	0.43	0.34	0.55
Smoking status								
Never	116	38	27230	53	362046	1		
Past	135	44	15530	30	201973	1.21	0.94	1.55
Current	57	19	8535	17	111815	2.37	1.72	3.27
Age (years)								
<50	27	9	31983	62	431181	1		
50–59	50	16	10356	20	135751	5.88	3.69	9.39
60–69	120	39	6818	13	85287	22.48	14.81	34.12
70+	111	36	2138	4	23645	75.00	49.23	114.17
Race/Ethnicity								
White, non-Hispanic	295	96	49607	97	653862	1		
Other	12	4	1606	3	20934	1.07	0.60	1.91
Education								
High school of less	207	69	28493	57	372228	1		
Beyond high school	91	31	21663	43	288718	1.07	0.83	1.37
BMI (kg/m^2)								
<25	80	36	9573	26	127407	1		
25–29.9	102	46	19105	51	253118	0.64	0.50	0.82
>=30	38	17	8745	23	115694	0.63	0.44	0.89
Drinks per month at enrollment								
None	184	60	16450	32	214040	1		
1–4	63	20	13917	27	184014	0.72	0.54	0.96
5–30	36	12	13727	27	182045	0.57	0.39	0.80
>30	25	8	7201	14	95735	0.80	0.52	1.22

	Cases[b]		Noncases[c]		Person Time	Incidence Rate Ratio[d]	95% Confidence Interval	
	(N = 308)	%	(N = 51,295)	%				
Heart disease								
No	236	81	47750	95	632603	1		
Yes	55	19	2590	5	30975	1.41	1.04	1.90
Diabetes								
No	242	84	48897	97	645814	1		
Yes	46	16	1419	3	17438	3.11	2.26	4.27
Hypertension[e]								
No	91	59	19029	84	254169	1		
Yes	62	41	3665	16	46840	1.74	1.25	2.42

[a]Data not available for all participants due to missing values in some categories.

[b]Cases are defined as deaths with an underlying or contributing cause attributed to stroke on state death certificates by using *International Classification of Diseases*, Tenth Revision, codes I60-I69.

[c]Non-cases are participants who did not experience a stroke-related death during study follow-up.

[d]Adjusted for age in categories.

[e]The hypertension question asked on the take-home questionnaire was answered by 23,170 participants (161 stroke deaths).

Table 2

Associations between pesticide use activities and stroke mortality among 51,603 male private and commercial pesticide applicators, Agricultural Health Study, 1993–2008.[a]

Pesticide Use	Cases[b] (N = 308)	%	Non-cases[c] (N = 51,295)	%	Person Time	Hazard Ratio[d]	95% Confidence Interval	
Lifetime exposure, days								
0–50	49	18	8788	19	116646	1		
51–100	46	17	3648	8	47366	1.56	1.04	2.33
101–250	82	30	16957	36	223916	1.13	0.79	1.62
>250	98	36	18078	38	237819	1.09	0.78	1.55
Years mixed/applied pesticides								
≤ 5 years	27	10	8120	17	109332	1		
6–10 years	40	14	7598	15	101490	1.41	0.87	2.30
11–20 years	52	19	15935	32	212009	0.93	0.58	1.48
21–30 years	69	25	11427	23	148579	1.14	0.72	1.78
>30 years	93	33	6055	12	76339	1.31	0.84	2.02
Days/year mixed								
<5 days	80	28	8777	18	115011	1		
5–9 days	70	25	10881	22	142286	0.97	0.71	1.35
10–19 days	74	26	14041	29	184932	0.98	0.71	1.34
≥ 20 days	58	21	15078	31	200930	0.90	0.64	1.26
Use of chemical- resistant gloves								
No	156	51	14839	29	193863	1		
Yes	152	49	36456	71	481971	0.83	0.65	1.05
	Cases[b] (N = 191)		Non-cases[c] (N = 23,009)					
High-pesticide-exposure event [e,g]								
No	140	91	18941	85	251256	1		
Yes	14	9	3448	15	45923	0.91	0.52	1.58
Diagnosed pesticide-poisoning event [f,g]								

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Pesticide Use	Cases[b] (N = 308)	%	Non-cases[c] (N = 51,295)	%	Person Time	Hazard Ratio[d]	95% Confidence Interval	
No	151	96	22205	98	294572	1		
Yes	6	4	455	2	6038	1.73	0.77	3.92

[a]Data not available for all participants due to missing values in some categories.

[b]Cases are defined as deaths with an underlying or contributing cause attributed to stroke on state death certificates by using *International Classification of Diseases*, Ninth Revision (430–438), or Tenth Revision (I60-I69) codes.

[c]Non-cases are participants who did not experience a stroke-related death during study follow-up.

[d]Results were obtained from Cox proportional hazards regression adjusted for state, smoking status, and alcohol consumption.

[e]Participants were asked the question, "Have you ever had an incident or experience while using *any* type of *PESTICIDE* which caused you *unusually high* personal exposure?"

[f]Participants were asked if a doctor had ever diagnosed them with pesticide poisoning.

[g]Questions asked on the take-home questionnaire were answered by 23,170 participants (161 stroke deaths).

Table 3

Associations between agricultural activities, characteristics and stroke mortality among 51,603 male pesticide applicators, Agricultural Health Study, 1993–2008.[a]

Agricultural activity	Cases[b] (N = 308)	%	Non-cases[c] (N = 51,295)	%	Person Time	Hazard Ratio[d]	95% Confidence Interval	
Handle stored grain	124	40	35350	69	466566	0.72	0.56	0.94
Handle stored hay	109	35	28382	55	374820	0.77	0.61	0.98
Handle silage	26	8	10597	21	139209	0.70	0.47	1.06
Handle grain or hay or silage	131	43	36044	70	475744	0.75	0.58	0.98
Acres farmed the year before enrollment								
<5 acres	64	23	3967	9	52267	1		
5–49	45	16	4247	9	55428	0.59	0.40	0.86
50–199	72	26	8226	18	106935	0.83	0.58	1.17
200–499	59	21	12913	28	169839	0.68	0.46	1.01
≥ 500	37	13	17108	37	226657	0.54	0.34	0.84
Poultry on farm[e]	20	8	4298	8	57124	0.91	0.58	1.44
No. of livestock on farm								
None/Did not work on farm	138	53	15468	34	202428	1		
<50	43	16	6165	13	80772	0.74	0.52	1.04
50–99	20	8	3784	8	49504	0.69	0.43	1.11
100–499	30	11	8859	19	116742	0.82	0.54	1.23
≥500	31	12	11587	25	153914	1.03	0.67	1.57
Type of livestock on farm[f]								
Cattle	83	27	20566	40	270789	0.73	0.56	0.94
Swine	52	17	16285	32	216588	1.07	0.78	1.46
Other	12	4	2500	5	33130	1.17	0.65	2.08

[a] Data not available for all participants due to missing values in some categories.

[b] Cases are defined as deaths with an underlying or contributing cause attributed to stroke on state death certificates by using *International Classification of Diseases*, Ninth Revision (430–438), or Tenth Revision (I60-I69) codes.

[c] Non-cases are participants who did not experience a stroke-related death during study follow-up.

[d]Results were obtained from Cox proportional hazards regression adjusted for state, smoking status and alcohol consumption.

[e]The number of poultry present on farm was examined but collapsed into a dichotomous variable (poultry present/absent) based on a small number of cases in each category.

[f]Does not include poultry.