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Recruitment of population-based controls for ALS cases from the National ALS Registry

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Abstract

Objective: In 2010, the United States Agency for Toxic Substances and Disease Registry (ATSDR) created the National ALS Registry (Registry) to examine the epidemiology of ALS and potential risk factors. We are currently recruiting population-based controls for an epidemiologic case-control study to examine ALS environmental risk factors using this Registry. To date, we have recruited 181 non-diseased, population-based controls for comparison to Registry cases (n = 280). Here we report our recruitment methods for controls and the associated response rates and costs.

Methods: Eligible ALS cases had complete risk factor survey data, DNA analysis, and blood concentrations of persistent organic pollutants (POPs). Age, sex, and county-matched controls were identified from commercial/consumer databases using a targeted landline phone sample. Eligible controls were consented, surveyed, and mailed the POPs' blood analysis consent form. Once consented, phlebotomy was scheduled.

Results: We mailed 3760 recruitment letters for 181 potential case-matches across 42 states between 9/2018 and 3/2020. After making phone contact and determining eligibility, 146 controls agreed to participate (response rate = 11.4%, cooperation rate = 22.8%). To date, 127 controls

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Declaration of interest

The authors report no conflict of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the Agency for Toxic Substances and Disease Registry, the Centers for Disease Control and Prevention, and/or the United States Department of Health and Human Services (HHS).

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completed the survey and bloodwork. Though controls were matched to cases on age, sex, and county, unmatched characteristics (e.g. smoking) did not differ statistically. Interviewing and incentive costs are estimated at $211.85 per complete participation.

Conclusions: Recruiting matched population-based controls for comparison to cases from the Registry for a study involving completion of a detailed survey and blood specimen provision is relatively feasible and cost effective. This recruitment method could be useful for case-control studies of other rare disorders.

Keywords

Amyotrophic lateral sclerosis; registry; controls; biorepository; risk factor

Introduction

Recruitment of controls that are similar to cases on all aspects related to the outcome except for the exposure variable(s) of interest is imperative to the validity of findings derived from epidemiological case-control studies. We explore the efficiency and reliability of a recruitment method to identify and recruit matched controls for ALS cases enrolled in the National ALS Registry.

In 2010, the Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC) created the National ALS Registry (Registry) to examine the epidemiology and risk factors for ALS. The Registry involves a 2-pronged approach for identification of ALS cases. First, an algorithm searches large administrative databases to identify cases via signs, symptoms, and neurophysiologic tests. Second, participants self-enroll in the Registry using a web-portal (1). Persons with ALS (PALS) are encouraged to self-enroll by ALS physicians and ALS organizations. Upon enrollment PALS can complete brief web-based risk factor surveys and provide biospecimens for the National ALS Registry's Biorepository for the advancement of ALS research as well as participate in eligible clinical trials and epidemiological studies. To date, several studies involving case data from the National ALS Registry and/or biospecimens from the National ALS Biorepository have been published (2–4); however, methodology for identifying and recruiting controls for Registry cases for epidemiologic research is limited.

Here we describe the methodology for identifying and recruiting a matched sample of population-based controls for the National ALS Registry/Biorepository cases including associated costs, productivity, and strengths and limitations. In general, we provide practical information as it pertains to recruitment of controls for case-control studies, especially applicable for rare diseases and when biological specimens must be obtained.

Methods

Study design and population

A case-control study is being conducted to investigate environmental and occupational risk factors for ALS among ALS cases from the National ALS Registry and matched controls. Cases include persons with ALS (n = 280) with complete risk factor survey data and

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biospecimen materials who enrolled in the National ALS Biorepository. Controls (n = 181) are currently being recruited by the University of Pittsburgh into the study which involves two parts: 1) completion of a risk factor survey administered by personal interview by phone or self-administered via web and 2) provision of a blood specimen collected by a licensed phlebotomist for analysis of persistent organic pollutants (POPs) concentrations.

To identify a national sample of controls matched by age (±1 year of birth), sex, and county of residence to cases, commercial/consumer databases containing landline phone numbers, valid addresses, and demographic information were purchased through the vendor, Marketing Systems Group (MSG). This information is available from property records, product registrations, credit card statistics, and the U.S. Census. A landline sampling frame was chosen so that a sample of phone numbers drawn could be accurately tied to a geography, specifically the county of residence of the case at the time of their blood draw. For the first 80 cases, 15 potential controls were randomly selected from a targeted listed landline sample containing all who met selection criteria; for subsequent groups of cases, 20 potential controls were randomly selected to expedite the process of control identification. If the first set of records did not produce a willing and eligible control, additional sets were ordered until a match for a given case was identified. While 91% of cases needed only 15 or 20 records before a control was ascertained, a maximum of 55 records were purchased for any one case.

Recruitment, survey, and biospecimen collection and analysis

Information obtained from the ATSDR/CDC National ALS Registry/Biorepository for cases included risk factor survey data, collected via self-administered web-survey, and biospecimens data or materials. This involved results of ALS DNA analysis and POPs concentrations, and DNA material from carriers of the c9orf72 mutation. Eight of the 17 risk factor surveys available through the National ALS Registry are used in this study, including self-reported information on demographic characteristics, personal characteristics, occupational and residential history, as well as environmental and occupational exposures with the methods previously published (2). For the current study, a survey similar to those used by the National ALS Registry was created in Qualtrics and administered to controls by phone by trained interviewers using computer-assisted telephone interviewing (CATI), as described below. We also recently added an option for participants to complete a self-administered version of the survey instrument online.

The interviewers who administer the survey are each assigned a group of potential controls to call by the supervisor. The supervisor, who is responsible for maintaining up-to-date records of the recruitment progress, is notified by email each time a survey is completed. During weekly recruitment team meetings, the recruitment progress of controls is reviewed including the number of surveys and blood draws that have been completed and those that are still in process. Any barriers to recruitment are also discussed and addressed, including directing potential participants to the study website or to study personnel for more information or to establish legitimacy.

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The study for which the survey data was collected for the controls was approved by the Institutional Review Board of the University of Pittsburgh. ATSDR's role in this manuscript did not require IRB review.

Development of study recruitment materials, and identification and recruitment of controls

The study investigators developed recruitment materials for the study that included a pre-notification letter, brochure and website tailored to address the purpose of the research and specifically why controls were needed for a research study investigating ALS (i.e., to compare characteristics of people with and without the disease) (see **Appendix A for recruitment materials**). Recruitment materials also provided background information about ALS to explain that the cause is largely unknown, no cure exists, and death usually occurs within three years of symptom onset. As cases were identified from 42 U.S. states using the Registry, it was important that recruitment materials be tailored to a national audience to identify controls from similar geographic areas based on the specified matching criteria.

Potential controls are mailed a recruitment letter and study brochure describing the study that contains the website address as well as contact information for the principal investigator (PI) and study staff. Within one week of mailing the recruitment letter and if potential participants did not call to inquire about the study, interviewers called potential controls to determine interest in participating in the study and to assess eligibility. The maximum number of call attempts to a potential control is 10 attempts. If a potential control is interested and eligible to participate in the study, he/she is verbally consented by phone after which a 40-minute telephone survey is administered. Upon completing the survey (part 1 of the study), the control is mailed a $10 MasterCard debit card as remuneration for his/her time and effort along with a consent form for part 2 of the study which describes the blood draw to analyze POPs concentrations. The control is asked to review the consent form, contact study staff with any questions or concerns, and sign and return the signed consent form to the University of Pittsburgh using the included self-addressed, postage paid envelope. Once the signed consent is received from the control, the study research assistant schedules a one-time, non-fasting blood draw (10mL or 2 tablespoons) by a licensed phlebotomist to collect the specimen in-home or at work, or the control may visit a participating lab. Blood draws are completed by phlebotomists from ExamOne, a national phlebotomy company, and scheduling is carried out via the ExamOne web portal. A blood kit is also mailed to the control's address that contains the materials necessary for collecting and overnight mailing the blood specimen to the University of Pittsburgh for storage. As remuneration for the control's time and effort in completing the blood draw (step 2 of the study), $50 is loaded to the same MasterCard debit card that was previously mailed to the control after completing the interview.

Inclusion and exclusion criteria

In addition to the age and sex matching criteria, controls with self-reported diagnosis of any of the following neurological conditions: ALS, Parkinson's disease, Parkinsonism, or post-polio syndrome were excluded. Sampled units (i.e., phone numbers) were deemed ineligible for numerous reasons. First, if the mailed recruitment materials resulted in a *return to sender* notification or if the phone number was disconnected, identified as a fax machine, or had

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some technological barrier that prevented the caller from reaching a household member; the phone number was no longer attempted and deemed ineligible. Second, potential controls who were out of the country, deceased, or determined to be a non-English speaker, were deemed ineligible. Third, non-residence numbers (e.g. businesses) or households with no eligible person residing there were ineligible. Last, phone numbers were classified as ineligible if they were attempted at least once but remained unresolved due to successfully recruiting and completing a survey with another matched control (i.e., quota was filled).

Statistical analysis

Descriptive statistics were used to compare socio-demographic and personal characteristics of cases and controls. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and SPSS version 24.0 (IBM Corp, Armonk, NY).

Results

Since study recruitment commenced in September 2018, 3760 recruitment letters have been mailed to potential controls from 42 states, resulting in 181 potential case matches (as of March 31, 2020). Of these 181 cases, we are currently still active in the field recruiting controls for 30 cases. For another five cases, controls have been recruited who have completed a survey instrument but have refused the blood draw. Therefore, we will need to sample more phone numbers to recruit the additional five matched controls. Potential controls are classified by one of the following four groups: (1) eligible and participated, (2) eligible refused to participate, (3) eligibility unknown – unable/refused to participate, and (4) ineligible due to exclusion criteria (which included exclusion due to study criteria as well as sample unit ineligibility).

Eligible controls participating to date include 146 controls who completed the survey (part 1) of whom 127 have also completed the blood draw (part 2) and 19 are awaiting a blood draw. Of the 3760 sample units, 679 phone numbers were never contacted due to the successful recruitment of another control. Of the remaining 3081 phone numbers, 146 resulted in a completed survey, 493 resulted in contact but the potential control refused to participate, 637 were attempted without eligibility being determined or a final disposition being assigned, and 1800 were deemed ineligible of which only 9 were excluded due to study exclusion criteria.

Our cooperation rate to date is 22.8% and it is calculated by dividing the number of participants who completed the survey by the number who completed the survey plus those who refused the survey (146/146 + 493). Our overall response rate is 11.4% and is calculated by dividing completed interviews by completed interviews plus refusals plus unknown eligible (146/(146 + 493 + 637)) as defined by the American Association for Public Opinion Research (AAPOR)(5). Three of the 146 controls expressed an interest in completing the self-administered survey online and were sent personalized web links; however, only two of the three controls completed the survey online. Because the other control did not complete the interview survey within one week’s time, another control was recruited and completed the survey over the phone (Figure 1).

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To date, only 5 individuals have refused to provide a blood draw after completing the survey in part 1. Shown in Table 1 are characteristics of cases from the National ALS Registry (n = 127) and matched controls (n = 127) who completed both the interview and blood draw as of March 31, 2020.

Linkage of existing U.S. Environmental Protection Agency (EPA) criteria air pollutant data and EPA National Air Toxics Assessment (NATA) data by zip code to residential addresses of cases and controls recruited thus far and analysis of blood specimens are currently underway. Given the importance in this study of matching cases and controls on geography, we believe that the landline sample provides the best source for control recruitment, as many of the phone numbers can be linked to specific addresses and can be appended with household socio-demographic information.

Productivity and cost

Several costs are associated with identifying and recruiting controls that include interview and administrative hours, purchase of the commercial/consumer databases of landline numbers with addresses, preparation of mailings, and participant incentives (see Table 2). The costs associated with recruiting a single control for a given case ranged from $140.79 to $211.85 depending on whether or not a blood draw was collected. On average, 5.5 hours of combined interviewer and administrative time (i.e., scheduling, monitoring, sample management, quality control, and reporting) were needed for each completed survey of which 3.7 hours were dedicated solely to making call attempts and interviewing the willing control. Interview length varied greatly, ranging from 30 to 67 minutes.

Discussion

Through recruitment of population-based controls for cases from the National ALS Registry for an ongoing epidemiologic study investigating the association between environmental and occupational risk factors for ALS, we observed acceptable cooperation (22.8%) and response rates (11.4%). Nearly 1 in 4 people potential controls whom we talked to about the study agreed to participate despite the burden of both a personal interview and blood specimen collection. Our findings of successfully recruiting national controls for ALS, a rare disorder with a short life expectancy (2–5 years on average post diagnosis) (6) and no known cure, presents a useful methodology that may be helpful in identifying and recruiting controls for cases with available Registry data or for other rare diseases. Though Random Digit Dialing (RDD) has been a mainstay for recruitment of representative samples for case-control studies, a RDD sampling strategy in our study would likely be very inefficient requiring numerous attempts to locate and recruit a control that matches the case and is willing to participate. Our method utilizes the power of the landline sampling frame which has many demographic and geographic variables that can be appended to phone numbers. This method allows for pre-notification letters to be mailed in advance as an address is appended to the phone record and increases recruitment efficiency through demographic targeting in terms of sex, age, income, education, and race and ethnicity. As the cell phone frame becomes more robust in terms of geographic specificity and demographic information,

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the use of dual frame sampling methods becomes a more efficient method for recruiting controls.

Limitations

Inherent issues recruiting hospital or acquaintance controls related to confounding have limited past studies. Strengths of the current study include identification of population-based controls using a landline sample. As older adults are more likely to have a landline phone, a landline sample is advantageous for studying ALS, which has a mean/median onset age of 51-66 years (7). Additionally, landline samples provide high accuracy for geo-locating as well as appending addresses including zip codes and other demographic characteristics at high rates, and they are more cost effective. However, as the landline sampling frame continues to deteriorate and coverage error grows, new technologies on the cell phone sampling frame are emerging that will allow for similar demographic and geographic targeting. The coverage error associated with choosing to sample from the landline frame is estimated at approximately 30% for those age 65 and over living in wireless only households (8).

Cases (PALS) complete the web-based National ALS Registry risk factor surveys on their own or with assistance from caregivers or family members. Registry partners such as the ALS Association, Muscular Dystrophy Association, and the Les Turner ALS Foundation aid PALS with completing the surveys, when possible. The survey for controls is administered over the phone by personal interview by trained interviewers, with the option to complete a self-administered survey online. The differing methods of survey completion may lead to biases (e.g. interviewer and nonresponse) and lower response rates. Both methods (i.e., self-administered and telephone interviewing) are subject to recall bias, though with a trained interviewer, we believe recall bias may be reduced by way of interviewing skills including neutral probing and providing clarification.

Given that the recruitment efforts that we report here are for a study examining the environmental risk factor of ALS and thus require the completion of the risk assessment surveys, which were only administered to the web-portal sample (9) our sample is subject to self-selection bias associated with self-enrollment. Patients willing and able to self-enroll via a web-portal and complete the risk assessment questionnaires most likely would be more familiar with technology, younger, and more educated.

Future recruitment studies using the National ALS Registry may want to explore offering only a self-administered web-based version to reduce mode effects across cases and controls and evaluate the potential for cost savings by utilizing a push-to-web strategy. Moreover, the method of recruitment described here is specific to the US likely not entirely generalizable outside the US due to varying availability of sampling frames, public registries and directories, and the implications of varying telecommunication laws and regulations.

Conclusion

In summary, potential controls with landline telephones were contacted regarding participation in a two-part research study investigating risk factors for the development of

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ALS through completion of a detailed survey and provision of a blood specimen for analysis of POPs concentrations. The use of multiple sources of recruitment materials, personal contact by study staff, and establishing credibility for the research may have influenced control participation rates. The ability to recruit controls and collect, process, and analyze blood specimens using the same methodology as the National ALS Biorepository promotes conduct of case-control studies and future research aimed at identification of risk factors for ALS. This methodology may also be useful for the recruitment of controls for studies of other rare disorders.

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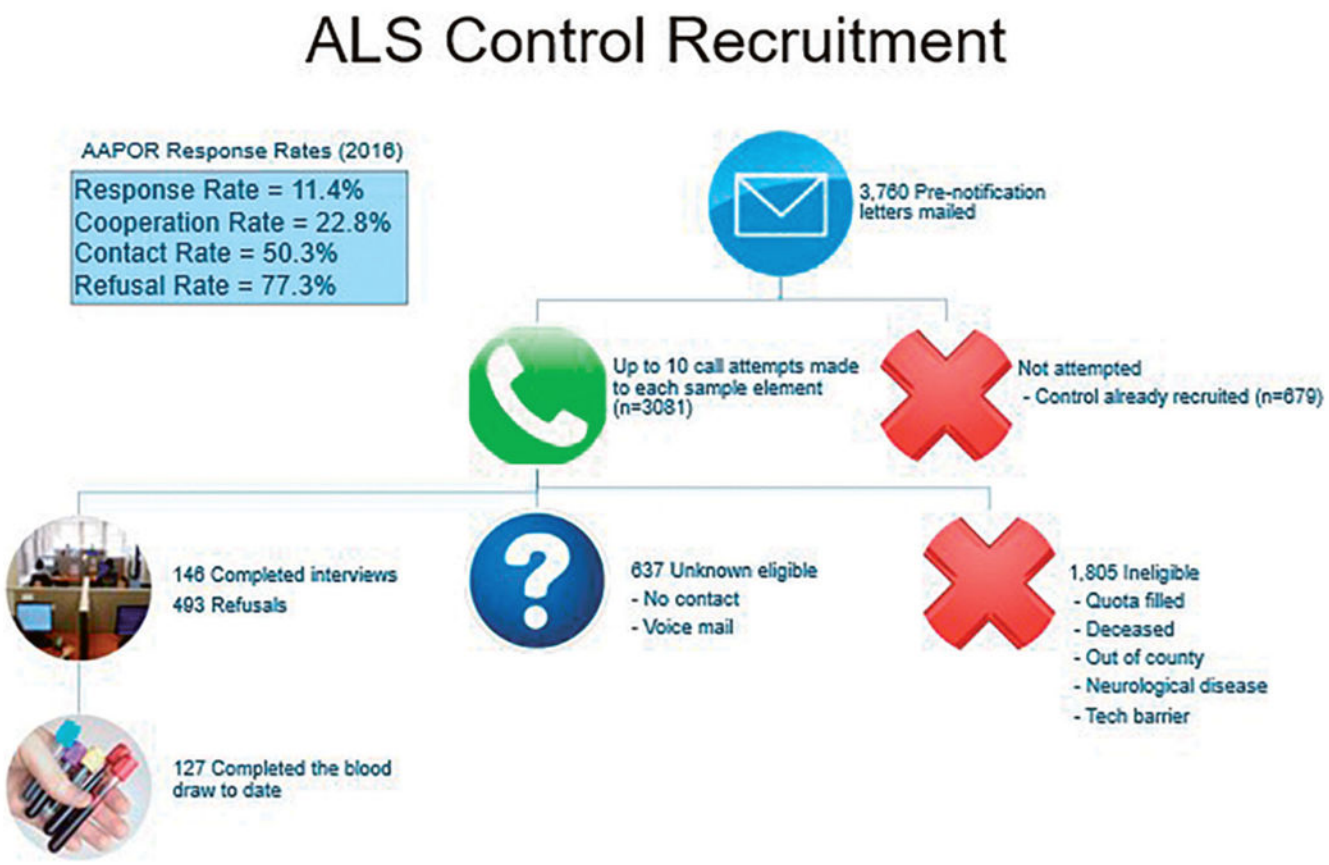

Figure 1.
ALS Control Recruitment.

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Table 1.

Characteristics of Cases from the National ALS Registry and Matched Controls with Completed Survey and Blood Draw as of 3/31/2020.

Characteristic	ALS Cases (*n* = 127) *n* (%)	Controls (*n* = 127) *n* (%)
Male	79 (62.2)	79 (62.2)
Year of birth		
≥1970	4 (3.1)	3 (2.4)
1960–69	25 (19.7)	25 (19.7)
1950–59	50 (39.4)	52 (40.9)
1940–49	41 (32.3)	39 (30.7)
<1940	7 (5.5)	8 (6.3)
White race (or part white)	126 (99.2)	127 (100)
Education		
Did not complete high school/GED	0 (0.0)	1 (0.8)
High school diploma/GED	10 (7.9)	13 (10.2)
Some college, technical/trade school diploma	27 (21.2)	25 (19.7)
College graduate or higher	87 (68.5)	86 (67.7)
Other	3 (2.4)	2 (1.6)
Member of armed forces	29 (22.8)	31 (24.4)
Smoking status		
Never smoker	74 (59.1)	78 (61.4)
Ever smoker[a]	52 (40.9)	49 (38.6)
Current smoker	5 (3.9)	5 (3.9)
Not current smoker	47 (37.0)	44 (34.6)

GED: General Education Development.

[a]Ever smoker was defined as smoking ≥1 cigarette per day for 6 or more months.

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Table 2.

ALS control recruitment productivity and costs.

Items	Hours or units	Rate	Costs
Calling Hrs. (attempts + interviewing)	536	$13.40	$7,182.40
Administration Hrs. /training/quality control	268	$30.00	$8,040.00
Sample units	3760	$0.28	$1,052.80
Pre-notification mailings	3760	$0.75	$2,820.00
Incentive (survey)	146	$10.00	$1,460.00
Incentive (blood draw)	127	$50.00	$6,350.00
Total (survey only)	146	$140.79	$20,555.20
Total (survey and blood draw)	127	$211.85	$26,905.20

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