
COMPREHENSIVE PSYCHIATRY

(Official Journal of the American Psychopathological Association)

VOL. 44, NO. 2

MARCH/APRIL 2003

Psychopathology Among Persons Responding to Participation as Normal Controls in Behavioral Research Studies

David B. Huang, Hoonmo Koo, Don Dougherty, and Yusuf Hassan

This study examined the characteristics of persons responding to an advertisement to participate as normal controls in behavioral research studies. Applicants (N = 3,289) inquired by telephone for more information. Of the applicants responding by telephone, 18% met the criteria for a DSM-III-R diagnosis, including psychoactive substance abuse (9%), mood disorder (4%), personality disorder (3%), schizophrenia (1%), anxiety disorder (1%), and neurological disorder (16%). Thirty-two percent (n = 1,045) of individuals passing the telephone interview were evaluated in person. After in-person evaluation, 16% met the criteria for a DSM-III-R diagnosis, including psychoac-

tive substance abuse (9%), mood disorder (3%), personality disorder (3%), schizophrenia (0.1%), anxiety disorder (1%), and neurological disorder (11%). Only 13% (n = 431) of individuals responding by telephone were included as normal controls in ongoing studies. Overall, 79% (n = 2,244) and 57% (n = 590) were excluded by telephone and in-person evaluation, respectively. These results suggest that a high percentage of individuals seeking to participate as normal controls in behavioral research studies have some psychopathology.

Copyright 2003, Elsevier Science (USA). All rights reserved.

NORMAL CONTROLS participating in behavioral research studies provide fundamental normal values for physiological, psychological, and pharmacological processes for which they can be compared to an index groups of patients.^{1,2} However, defining "normal controls" has been especially difficult and controversial in behavioral research studies.³ The definition is often by exclusion, whereby individuals are considered "normal" if they are not mentally ill. Many physicians believe that even with the current DSM criteria, mental disorder diagnoses are still descriptive and subjective, and liable to being influenced by the physician's values, ideas, and background, as well as those of current society.⁴ This may explain the high prevalence of psychopathology found in volunteers reported as normal controls. Two studies involving college students participating in drug studies found that 48% and 50% of normal control subjects had psychiatric diagnoses.^{5,6} The National Institute of Mental Health found that 52% of normal control volunteers participating in behavioral studies had a psychiatric diagnosis.⁷

The difficulties involved with selection criteria of normal controls include persons who cannot be matched according to factors of the study, persons

not representative of society, and/or unwillingness of subjects to comply with the requirements of the protocol.⁸ Key objectives to subject recruitment include finding participants from whom one can generalize findings to society, having a representative group of subjects, and conducting careful screening for normal controls.^{9,10} Having a representative group is often taken for granted as subject population biases may lead to flawed conclusions. Thus, knowledge of normal control demographic characteristics provides important information for interpretation and replication of findings. Therefore, it is essential to recruit normal controls with characteristics reflective of society. The intent of

From the Department of Internal Medicine, Baylor College of Medicine, Houston, TX; and the Department of Psychiatry and Behavioral Sciences, The University of Texas-Houston Medical School, Houston, TX.

Supported by a grant from the National Institute on Alcohol Abuse and Alcoholism (AA-10095).

Address reprint requests to David B. Huang, M.D., M.P.H., Department of Internal Medicine, One Baylor Plaza, BCM 286, Room N1319, Houston, TX 77030.

Copyright 2003, Elsevier Science (USA). All rights reserved.

0010-440X/03/4402-0003\$30.00/0

doi:10.1053/comp.2003.50016

this study was to evaluate the characteristics of persons responding to an advertisement to participate as normal controls in behavioral research studies. We hypothesized that a high percentage of psychopathology would exist among individuals being assessed as normal controls.

METHODS

Subjects

Individuals (N = 3,289) responded to advertisements in a classified employment section of local and city newspapers from 1993 to 1994. A total of 12 advertisements were placed under the general employment section of several different newspapers over a period of 1 year. Employment involved participating as normal controls in behavioral research studies at the University of Texas-Houston Health Sciences Center. The ads were worded as "Healthy individuals aged 18-45 are needed for participation at the University of Texas at Houston Health Science Center for paid behavioral research." Participation in this study was voluntary and required written informed consent of subjects prior to enrollment. This study was approved by the Committee for the Protection of Human Subjects of the University of Texas-Houston Health Science Center.

Procedure

Individuals interested in participating as normal controls in behavioral studies inquired by telephone. Prior to the interview, information regarding the purpose, procedures, and protocol of the research was read to callers. Three trained interviewers using a standard form (available upon request) gathered information about sociodemographics, and the neurological and drug background of each applicant. Drugs were categorized according to the drug classification scheme in the Structured Clinical Interview for DSM-III-R: Non-patient Version.¹¹ Applicants were informed that all about their medical and drug history would be kept confidential. General information was given about the work position.

Exclusion Criteria

The exclusion criteria were designed to allow for normal controls to participate in studies involving pharmacology and behavior. The list is based on previously published studies and includes a history or presence of axis I disorder (by DSM-III-R criteria); neurological disease (e.g., seizures, cerebrovascular diseases, head trauma, spinal cord dysfunction, neuromuscular disease, chronic headaches) and/or use of medications that may affect pharmacological challenges and/or behavior; age below 18 or above 45 years; abnormal physical examination (including neurological exam); and abnormal laboratory data (including cell blood count, chemistry panel, thyroid function tests, rapid plasma reagin, urine toxicological analysis, positive pregnancy test, or abnormal ECG).¹

In-Person Screening

Persons not meeting the exclusion criteria by telephone interview were invited for an in-person screening. The Structured Clinical Interview for DSM-III-R: Non-patient Version was used at the in-person screening to detect psychopathology.¹¹ This

semistructured clinical interview allowed a more detailed clinical history to be obtained. More detailed information regarding research study purpose, procedure, protocol, and work position was given to all individuals during the in-person screening. All persons not meeting exclusion criteria were then given a medical screening by a licensed physician.

Medical Screening

A board-certified internist conducted a formal history and physical examination during the in-person screening on all qualified individuals. Subjects with a normal history and physical examination then received a panel of laboratory tests and an ECG. Individuals not meeting any exclusion criteria were then invited to participate in ongoing behavioral research studies.

RESULTS

Inquiries (N = 3,289) were made for the behavioral research subject positions. Of the inquiries, 1,689 were Caucasian, 942 African American, 467 Hispanic, 91 Asian, and 100 other; there were 1,875 men and 1,414 women; and the mean age was 28 ± 8 years. The number of exclusions by telephone, in-person screening, and medical screening are listed in Table 1. Of the applicants responding by telephone, 18% met the criteria for a DSM-III-R diagnosis, including psychoactive substance abuse (9%), mood disorder (4%), personality disorder (3%), schizophrenia (1%), anxiety disorder (1%), and neurological disorder (16%). Twenty three percent (n = 762) of these individuals were uninterested or reported they were unavailable for participation after the purpose, procedure, and protocol of the research study was stated over the telephone. Eleven percent (n = 368) did not fit our current need for balancing controls to patients on sociodemographic characteristics, and they were assigned "low priority." These individuals were placed on file to await further evaluation.

Thirty-two percent (n = 1,045) were subsequently evaluated in person. After the in-person evaluation, 16% met the criteria for a DSM-III-R diagnosis, including psychoactive substance abuse (9%), mood disorder (3%), personality disorder (3%), schizophrenia (0.1%), anxiety disorder (1%), and neurological disorder (11%). Twelve percent (n = 130) of the individuals scheduled for an in-person evaluation did not show up for their appointment and 17% (n = 173) were uninterested after receiving a more detailed explanation of the purpose, procedure, and protocol. The psychopathological characteristics of qualified nonparticipating normal controls are listed in Table 2. No

Table 1. Number of Exclusions by Telephone, In-Person, and Medical Screening

	Telephone	In-Person	After Evaluation
Total no. of subjects screened	3,289	1,045	455
Uninterested/unavailable	762	173	6
No-show for evaluation/study	—	130	9
DSM-III-R diagnosis	581	176	5
Psychoactive substance use	289	95	2
Mood disorder	123	31	0
Personality disorder	89	35	3
Schizophrenia	33	2	0
Anxiety disorder	44	12	0
Eating disorder	3	1	0
Neurological history	533	111	4
Low priority	368	—	—
Accepted for evaluation	1,045	455	431

differences in psychopathological or neurological disorders were found between the nonparticipating and participating normal controls. After in-person evaluation, 14% ($n = 455$) of individuals from the initial screening were included as normal controls in ongoing studies.

Of 2,834 excluded individuals, 79% were excluded by telephone ($n = 2,244$) and 21% by in-person screening ($n = 590$); of 1,045 applicants passing the telephone interview, 57% were excluded by in-person evaluation. A large number of volunteers ($n = 533$) did not qualify due to their neurological history: 16% determined by telephone screening and 11% by in-person screening. The remaining 14% ($n = 455$) underwent medical evaluation by a physician and 431 were accepted as normal controls in ongoing studies.

DISCUSSION

A high prevalence of psychopathology, neurological disorders, and past/current drug usage was found in individuals inquiring about participating

as normal controls in behavioral research. As a result, only a small fraction (14%) of the total persons was enrolled. These results confirm other smaller studies, where only 9% and 23% of total individuals assessed were invited for participation as normal controls in research.^{1,12} The initial screening by telephone excluded a significant proportion (79%) of individuals with psychiatric and neurological disorders, and the in-depth diagnostic psychiatric interview excluded an additional (57%) individuals who had passed the telephone interview.

Previous studies using the structured psychiatric assessment, the Structured Clinical Interview for DSM-III-R: Non-patient Version, recruited 252 of 1,284 volunteers by telephone interview and 76 of 312 interviewees by psychiatric interview.¹ In another study, 7% (8 of 109) were excluded by telephone interview and 47% (23 of 49) by psychiatric evaluation.¹² These results reinforce the idea that a systematic clinical assessment of normal controls should be an essential component of screening

Table 2. Psychopathological and Neurological Disorders of Nonparticipating and Qualified Individuals Participating as Normal Controls

	Nonparticipating	Participating
Total no. qualified	173	455
DSM-III-R diagnosis	7	5
Psychoactive substance use	1	2
Mood disorder	2	0
Personality disorder	1	3
Schizophrenia	0	0
Anxiety disorder	2	0
Eating disorder	1	0
Neurological history	2	4

psychiatric illnesses in volunteers, and the combination of telephone and in-person screening may provide a more efficient means of screening for normal controls.

The difficulty of subject recruitment is well established. One of the problems in attaining a potential research subject may lie in the scheduled hours for recruited subjects to work. Thus, subject recruitment may want to target organizations and/or "average" working persons by scheduling studies after normal work hours or even on weekends. More subjects may also be enrolled by offering more substantial remunerative payments.¹ Another area that may require more investigation is cost-effective strategies of advertising for subject solicitation.

Psychiatric history is usually not included in studies that are not directly involved in behavioral research. However, behavior analysis depends on systematic replication rather than randomization of subject selection and assignment in order to obtain generality of its results. Traditionally, subject description has been limited to routine demographic information such as age, gender, education level, and diagnostic categories. However, one of the most important pieces of information necessary for experimental replication is selection criteria of subjects, which is often not included in published reports.⁹ This is true despite the fact that knowledge of subject selection can affect both interpretation of results and conclusions as well as replication of studies.⁸ With the results of this study and previous studies displaying an increased incidence of mental illness in volunteer control subjects,^{1,2,4,12,13} psychiatric evaluation should be con-

sidered as an essential component of the selection process of all volunteer subjects for both biological and psychiatric studies. Many of the individuals responding to research participation solicitation may not be indicative of the general population.^{1,12} Previous studies have found a higher incidence of psychopathology in volunteers than would be expected in the general population, with up to 52% of "normal healthy" volunteers having a psychiatric illness.¹⁴⁻¹⁶ Other studies have demonstrated a broad range of detected psychopathology from 16.5% to 65% in "normal" volunteers.^{3,5,6,17-21} The use of different diagnostic procedures from the ones used in our study must be taken into account. In addition, the high prevalence of psychopathology among these individuals inquiring about participation in behavioral research studies may be explained by the increased motivation of thrill-seeking, release from inhibitions, and self-discovery of volunteering compared to individuals who are motivated by financial gain or scientific curiosity.⁴

This study supports the importance of more scrutiny placed in the recruitment of normal controls. Given their heterogeneity, screening normal controls may require as much rigor and standardization as screening and assessment of patients.¹ In addition, inclusion and exclusion criteria need more standardization. Implementing screening of control patients with telephone and in-person screening may provide for a more effective way to include normal subjects in behavioral research. It is clear from the present study and past research that further studies are warranted to investigate the process by which controls are selected.^{1,2}

REFERENCES

1. Shtasel DL, Gur R, Mozley D, Richards J, Taleff M, Heimberg C, et al. Volunteers for biomedical research. *Arch Gen Psychiatry* 1991;48:1022-1025.
2. Gibbons RD, Davis JM, Hedeker DR. A comment on the selection of 'healthy control' for psychiatric experiments. *Arch Gen Psychiatry* 1990;47:785-786.
3. Grinker RR Sr, Grinker RR Jr, Timbertlake J. "Mentally healthy" young males. *Arch Gen Psychiatry* 1962;6:405-453.
4. Halbreich U, Bakhai Y, Bacon K, Goldstein S, Asnis G, Endicott J, et al. The normalcy of self-proclaimed "normal volunteers." *Am J Psychiatry* 1989;146:1052-1055.
5. Esecover H, Malitz S, Wilkens B. Clinical profiles of paid normal subjects volunteering for hallucinogen drug studies. In: Newman R, Ladimer I (eds). *Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects*. Boston, MA: Boston University Law-Medicine Research Institute, 1963:450-460.
6. Lasagna L, von Felsinger JM. The volunteer subject in research. In: Newman R, Ladimer I (eds). *Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects*. Boston, MA: Boston University Law-Medicine Research, 1963:440-445.
7. Pollin W, Perlin S. Psychiatric evaluation of 'normal control' volunteers. *Am J Psychiatry* 1958;115:129-133.
8. Zweben A, Donovan DM, Randall CL, Barrett D, Dermen K, Kabela E, et al. Issues in the development of subject recruitment strategies and eligibility criteria in multisite trials of matching. *J Stud Alcohol* 1994;12(Suppl):62-69.
9. Homer AL, Peterson L, Wonderlich SA. Subject selection in applied behavior analysis. *Behav Analyst* 1983;6:39-45.
10. Sears DO. College sophomores in the laboratory: influences of a narrow data base on social psychologies vies of human nature. *J Pers Soc Psychol* 1986;51:515-530.
11. Spitzer RL, Williams JW, Gibbon M. Structured Inter-

view for DSM-III-R: Non-patient Version (SCIRD-NP). New York, NY: New York State Psychiatric Institute.

12. Thaker G, Moran M, Lahti A, Adami H, Tamminga C. Psychiatric morbidity in research volunteers [letter]. *Arch Gen Psychiatry* 1990;47:980.

13. Gorenstein C, Lotufo-Neto F, Melo M, Lauriano V. Untreated psychopathology of candidates to "normal volunteers." *J Clin Psychopharmacol* 1997;17:238-239.

14. Skinner NF. Personality characteristics of volunteers for painful experiments. *Bull Psychonomic Society* 1982;20:299-300.

15. Lasagna L, von Felsinger JM. The volunteer subject in research. In: Newman R, Ladimer I (eds). *Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects*. Boston, MA: Boston University Law-Medicine Research Institute, 1963:440-445.

16. Hersen M, Barlow DH. *Single Case Experimental Designs*. New York, NY: Pergamon, 1976.

17. Robins LN, Helzer JE, Weissman M, Orvaschel H, Gruenberg E, Burke JD Jr, et al. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry* 1984; 41:949-958.

18. Thacker J. Working through groups in the classroom. In: Jones N, Fredrickson N (eds). *Refocusing Educational Psychology*. Education and Alienation Series. London, England: Falmer Press/Taylor & Francis, 1990:68-83.

19. Adebimpe VR. Race, racism, and epidemiological surveys. *Hosp Community Psychiatry* 1994;45:27-31.

20. Allen TJ, Dougherty D, Rhoades HM, Cherek DR. A study of male and female aggressive responding under conditions providing an escape response. *Psychol Rec* 1996;46:651-664.

21. Robins LN, Helzer JE, Weissman M, Orvaschel H, Gruenberg E, Burke JD, et al. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry* 1984; 41:949-958.