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The online case-crossover study is a novel approach to study triggers for recurrent disease flares

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Abstract

Objectives: To evaluate the feasibility of conducting an online case-crossover study of triggers for recurrent disease flares.

Methods: We conducted an online case-crossover study of triggers for recurrent flares using gout as a paradigm. We constructed a Web site and recruited individuals with history of gout via the Internet. We confirmed gout diagnosis by reviewing each subject's medical records. We collected via the Internet exposure information during the intercritical period using a scheduled Control-period Questionnaire, and prior to recurrent gout attacks using a Hazard-period Questionnaire.

Results: Over 10 months we recruited 197 subjects with a history of gout from 41 states and the District of Columbia. We obtained medical records from 172 subjects. All participants had experienced at least one recurrent attack and filled out required questionnaires. The median time between the date of an attack and the date of logging on to the Web site was 2 days. The incidence rate of recurrent gout attacks was 1.03 per person-year. Longer disease duration and presence of comorbidities appeared to increase the risk of recurrent flares.

Conclusion: The results of this study demonstrate that a case-crossover study can be successfully conducted through the Internet. This approach has broad applicability to other diseases typified by recurrent attacks.

Keywords: Internet; Case-crossover study; Triggers; Recurrent attacks; Epidemiological methods; Gout

1. Introduction

Many chronic diseases are characterized by recurrent flares or attacks. The recurrent attacks may be attributed to precipitating factors that immediately precede the disease flares (i.e., triggers). However, identifying these triggers and assessing their effects are challenging because traditional research designs are ill suited to investigating recurrent attacks.

For example, in a case−control study, selection of a control group poses a serious problem because neither healthy subjects from the community nor patients with other diseases from a hospital are optimal comparison groups for cases with recurrent attacks of a particular disease. Ideally, the control group should be selected from subjects who have a history of the disease of interest and are currently in remission. However, few, if any, subjects would seek health care in the absence of a recurrent attack, and thus identification and recruitment of such subjects are difficult. Another approach would be to assemble a group of subjects with a history of the diagnosed disease of interest, and then follow-up on them for the recurrence of flares of the disease under investigation. However, because the investigators are interested in risk factors triggering unpredictable recurrent acute events within a short latency period, they would have to assess exposures repeatedly on all cohort members. The cost would be high and the respondent burden considerable.

We developed a methodology that enabled us to examine the effects of triggers on the risk of recurrent attacks. The proposed method combined two approaches: the case-crossover study design and the Internet. The case-crossover study uses each case as its control and is ideal for assessing effects of triggers on recurrent flares [1], whereas the Internet is a powerful technological resource for participant recruitment and

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data collection [2,3]. We tested the feasibility of this method using gout as a paradigm.

In this article, we shall demonstrate how a case-crossover study can be designed to benefit from the unique advantages of the Internet: access to a large number of interested subjects with a disease, and opportunity to capture exposure and disease attacks in real time. We will also show how large numbers of appropriately verified cases can be recruited with relatively low cost and effectively followed over time.

2. Materials and methods

2.1. Web site construction

We constructed a Web site for this study (https://dcc2.bumc.bu.edu/GOUT) on an independent secure server within the Boston University Medical Center domain. Files stored on the server are protected by electronic ''firewalls'' that allow access only to authorized users. Study participants accessed the Web site by means of unique login names and passwords.

The study Web site provided information about the study, invited applicants to participate, administered a screening questionnaire, linked eligible respondents to an online consent form, and posed additional questionnaires to assess risk factors and features of the recurrent attacks. To promote participation and minimize loss to follow-up, a system of e-mail reminders and prompts for follow-up Web site visits was used. The information submitted by participants in the questionnaires, the IP address of the computer submitting the information, and the date and time of log on to the Web site were automatically obtained and saved in the server database. The Web site also performed real-time monitoring of data quality, such as logic and error checking. All data were electronically encrypted using Secure Socket Layering (SSL) technology.

2.2. Subject recruitment

We advertised the study on the Google search engine (www.Google.com) by linking an advertisement to the search term ''gout.'' When a subject conducted a search on Google containing the keyword ''gout,'' the study advertisement appeared on the screen, often among other advertisements associated with the search term. Interested individuals who clicked on the box containing our specific advertisement were immediately redirected to the study Web site.

Upon entering the study Web site, subjects could view informational pages about gout and the general description of the study, and were invited to complete an online Eligibility Screening Questionnaire. To be eligible for the study, a subject had to report a diagnosis of gout by a physician, have had an attack within the prior 12 months, be at least 18 years old, reside in the United States, be willing to release his or her medical records pertaining to his or her gout diagnosis and treatment, and consent to participating in the study.

2.3. Subject consent and authentication

Immediately following submission of the screening questionnaire, eligible subjects were asked to read an online Consent Form. Subjects were able to electronically consent by clicking on a box on the form. The Boston University Institutional Review Board approved the use of electronic consent, rather than requiring collection of a signed, paper consent form, based on the minimal risk posed and the Internet design of this study. Each subject who electronically consented for the study was then asked to enter an e-mail address and to select a username and password for the study.

Upon submission of this information, an automated e-mail was sent to the e-mail address provided by the subject containing a Uniform Resource Location (URL) link to the questionnaire page. Study subjects were unable to proceed without this URL link. When subjects visited the Web site using the URL link, they were asked to complete the Socio-demographic Questionnaire. We also mailed each subject paper copies of the Consent Form, Health Insurance Portability, and Accountability Act (HIPAA) Authorization Form, a Medical Record Release Form, and a copy of the Hazard-period Questionnaire to the home address provided in the Socio-demographic Questionnaire. The Medical Record Release and HIPAA forms enabled us to request documentation of subjects' gout diagnosis from their physician or hospital.

2.4. Study questionnaires

Study questionnaires were developed based on previously validated instruments [4–6]. The questionnaire was partitioned into five modules to reduce respondent burden.

The online questionnaires consisted of five modules: (1) *Eligibility Screening Questionnaire*: US residency, diagnosis of initial gout attack, and a history of gout attack in the last 12 months; (2) *Socio-demographic Questionnaire*: name, age, gender, home address, home and work phone number, e-mail address, date of birth, years of education, household income, and type of Internet connection; (3) *Medical History Questionnaire*: medication use, self-reported comorbidities, age of gout onset, medication use for treatment of gout, and history of gout attacks; (4) *assessment of risk factors*: frequency and quantity of potential risk factors occurring over the intercritical gout period (control period, thereafter referred to as Control-period Questionnaire) and within the 48 hours prior to the time of recurrent gout attack (hazard period, thereafter referred to as Hazard-period Questionnaire); and (5) *ascertainment of recurrent gout attack*: the date of recurrent gout attack, clinical symptoms, and medication used to treat the recurrent gout attack. Using the information from the medical

charts and/or physician's checklists (a checklist form that listed possible clinical symptoms of gout disease), as well as data collected from their Medical History and Gout Attack questionnaires, we were able to confirm the history of gout diagnosis according to the Criteria for the Classification of Acute Gouty Arthritis [7].

2.5. Assessment of risk factors during the control period

Approximately 1 week after subjects submitted their Socio-demographic Questionnaire, an e-mail was sent asking the subjects to log on to the Web site and complete a Control-period Questionnaire. This questionnaire assessed the occurrence of risk factors for each day over the preceding 2-day period and was administered at study entry, and in months 3, 6, and 9 of the follow-up period. If a subject had a recurrent gout attack during the follow-up period, then the next control period assessment of risk factors would occur 3 months after the onset date of the recurrent gout attack.

Subjects were asked to complete the Control-period Questionnaire every 3 months. Approximately 10 days prior to the scheduled time of submitting the Control-period Questionnaire, we sent an e-mail reminder to subjects asking them to submit their Control-period Questionnaire. Repeated reminders (up to 10) were sent every 3 days until the subject either completed the scheduled control visit or was withdrawn from the study.

2.6. Assessment of risk factors during the hazard period

Subjects were instructed to log on to the Web site and complete a Hazard-period Questionnaire as soon as they experienced a recurrent gout attack. The questions included in the Hazard-period Questionnaire were the same as those used in the Control-period Questionnaire. However, in the Hazard-period Questionnaire, participants were specifically instructed to respond to the questions with reference to the 24- and 48-hour period prior to the *onset of the current attack*. Subjects also completed a Recurrent Gout Attack Questionnaire, which enabled us to characterize the recurrent gout attacks, including the time and date of the attack, the joint(s) involved, symptoms, medication use, and whether a physician was consulted for the attack.

Considering that a participant might have limited access to the Internet during a recurrent gout attack, we also sent a paper copy of the Hazard-period Questionnaire to each participant so that he or she could complete it during a gout attack without delay. During the study period, only two subjects used a paper copy of the Hazard-period Questionnaire.

2.7. Promotion of participation and protocol adherence

To ensure that subjects with recurrent gout attacks visited our study Web site and completed an online Hazard-period Questionnaire promptly, we sent an e-mail to each participant every 3 weeks reminding him or her to report a recurrent gout attack as soon as it occurred. E-mails were also sent reminding subjects when it was time to complete the Control-period Questionnaire. If a subject did not complete the questionnaire on the scheduled date, a reminder e-mail was automatically generated every 3 days for 4 weeks. After 4 weeks of reminders we sent a personal e-mail, signed by the study clinician, encouraging the subject to log on and complete the questionnaire. If the subject still did not comply, a final e-mail was sent to inform the subject that he or she had been withdrawn from the study. E-mail reminders were also sent to subjects who did not fully complete a visit, asking them to log on and finish the questionnaire module.

Upon completing the study, subjects were given $5.00 for the Socio-demographic Questionnaire and each Control-period Questionnaire submitted and an additional $5.00 for returning a signed Medical Record Release Form. Subjects received only a single $5.00 payment for completing the Hazard-period Questionnaires, irrespective of the number of Hazard-period Questionnaire they actually completed to limit the potential for payment as an incentive for reporting more recurrent attacks than actually occurred.

2.8. Statistical analysis

We estimated the incidence rate of first recurrent gout attack over the study period. We examined the relation of age, sex, highest education level attained, body mass index, duration of gout, and self-reported comorbidities (high blood pressure, diabetes, renal disease, and congestive heart failure) to the risk of first recurrent gout attacks using the proportional hazards model.

3. Results

We launched the study Web site on February 16, 2003. Over a 10-month period of recruitment (February 2003–December 2003), our study advertisement on Google was displayed 866,703 times. Potential subjects clicked on the advertisement and were directed to the study Web site link 57,627 (6.6%) times. The total advertising cost of the study was $9,339.

Two thousand eight hundred fifty-seven subjects completed the Eligibility Screening Questionnaire, and 2,064 (72.2%) met the preliminary screening criteria. Of those, 772 consented electronically; all but 30 provided valid e-mail addresses. Over the 1-year follow-up period, 197 participants completed Socio-demographic, Control-period, and Hazard-period Questionnaires.

The median time between the date of the gout attack and logging on to the Web site for the subjects who completed all three types of questionnaires was 2 days (range: 0–24 days). We received Medical Record Release forms from 186 (94.4%) subjects and obtained 172 subjects' medical records (or checklists) from their physicians. We were able to confirm physician-diagnosed gout in 165 (95.9%) subjects,

and of those, 119 subjects fulfilled the Criteria for the Classification of Acute Gouty Arthritis. Among the 25 subjects whose medical records or checklists were unavailable, seven (28%) subjects fulfilled the Criteria for the Classification of Acute Gouty Arthritis.

The characteristics of participants are presented in Table 1. The majority of the participants (80.2%) were men, and 50% were under age 52. Eighty-eight percent of subjects were white, and just over half (57.3%) were college graduates. The participants resided in 41 states and the District of Columbia (Fig. 1), with the majority of participants coming from the Northeast and California.

During the follow-up period, 321 recurrent attacks occurred among 197 subjects. Of these attacks, 152 (47.4%) involved a single joint; in 236 (73.5%) attacks, subjects reported pain occurring from none to maximal within 24 hours, and in 209 (65.1%) attacks, the painful joint was red. The incidence rate of first recurrent gout attack was 1.03 per person-year.

Table 2 displays the distribution of the days of the week for which information about risk factors during control and hazard periods is available. Overall, 32% of the data for the control period contains information about the risk factors that occurred during the weekend, i.e., Saturday and Sunday, whereas 68% contains information about risk factors that occurred during the weekdays. Consistent with the fact that there was less control period information available for Fridays (Table 2), subjects were less likely to log into the Web site and fill in the control period questionnaire on Saturdays (9.3%) and Sundays (3.9%).

As shown in Table 3, no apparent association was found between risks of recurrent gout attacks with age, sex, education level, or obesity. Risk of recurrent gout attacks appeared to be higher among subjects with longer disease duration (relative risk [RR]: 1.3, 95% confidence interval [CI]: 0.8–2.0) and presence of comorbidities (RR: 1.4, 95% CI: 0.9–2.0), although none of these effect estimates was statistically significant owing to the relatively small sample size in this feasibility study.

Table 1
Characteristics of participants in the Internet-based case-crossover study of gout, 2003–2004

	Number of subjects	Percent, mean, or median
Sex (%)		
Men	158	80.2
Women	39	19.8
Age (median, range)	197	52 (29–83)
Education (%)		
High school graduate/GED	14	7.1
Some college/technical school	70	35.5
College graduate	43	21.8
Completed professional or graduate school	70	35.5
Household income (%)		
<25,000	10	5.1
25,000–49,999	42	21.3
50,000–74,999	42	21.3
75,000–99,999	30	12.2
>100,000	54	27.4
Missing	19	9.6
Race (%)		
Black	2	1.0
White	174	88.3
Other	16	8.1
Missing	5	2.5
Number of days between attack date and logon (median, range)[a]	321	2 (0–24)
Years of disease duration (median, range)[b]	196	5 (0–36)

[a] Three hundred twenty-one hazard visits contributed by 197 subjects.
[b] One subject did not provide the data on years of disease duration.

4. Discussion and conclusion

Using gout as a paradigm, we demonstrated that a case-crossover study can be conducted over the Internet. This approach allowed us to access a large number of potential subjects, coordinate rapid interaction between researchers and participants, collect data quickly and uniformly, and evaluate incoming data in real time. We showed that a large number of verified cases can be recruited for minimal cost through the Internet and that these subjects can be efficiently followed over time.

Many chronic diseases are characterized by recurrent attacks. These recurrent attacks often have triggering events. However, assessment of the effects of these triggers is challenging. In the early 1990s, Maclure [1] proposed a new epidemiologic design, the case-crossover study, to evaluate the effect of a transient exposure as a trigger for acute disease onset. The case-crossover study uses each subject as his or her own control and compares the frequency of exposure to a suspected precipitating factor immediately prior to disease onset (hazard period) to that during the control periods. Self-matching of each subject eliminates the bias in control selection and removes the confounding effects of the factors that are constant over time. Thus, it is an optimal study design for examining the effect of risk factors triggering recurrent attacks, such as recurrent gout attacks. Nevertheless, two challenges remain—how to recruit a sufficient number of intercritical individuals, and how to capture data on risk factors and recurrent attacks in real time.

The use of the Internet as a platform for conduct of the case-crossover study addresses these two challenges. As Rothman et al. [2] stated, "We now have the potential to conduct a cohort study of users of the World Wide Web… and can have people recruit themselves, enter their own data into our computers, and provide for fast, convenient electronic follow-up." Florey et al. [3] further advocated using the Internet to advertise a study and to invite volunteers to take part by completing an online questionnaire. Several Internet-based

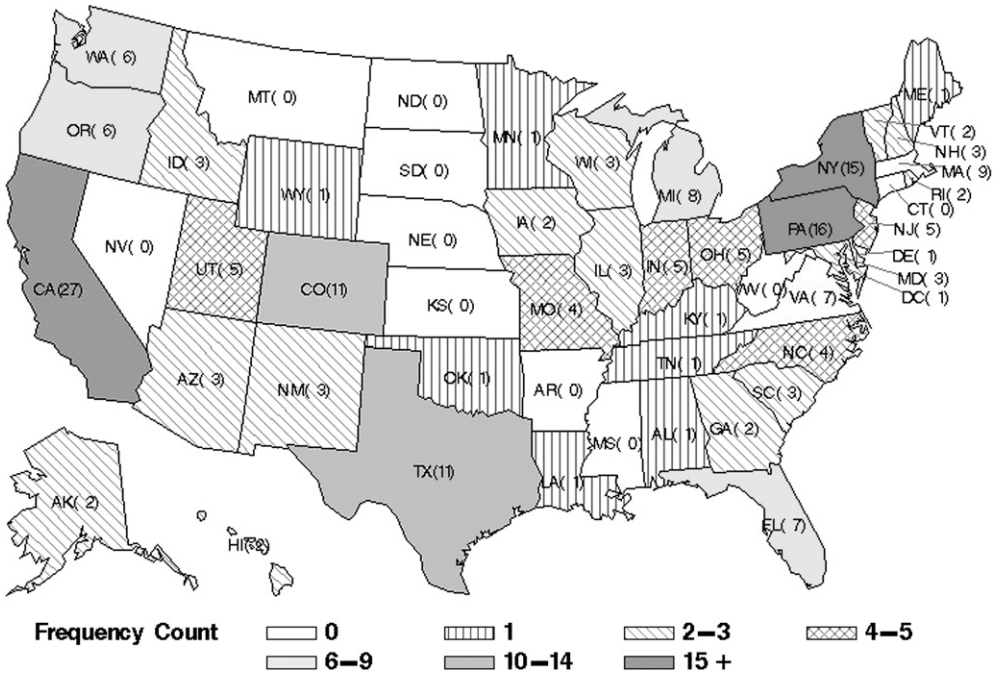

Fig. 1. Geographic distribution of 197 participants in the Internet-based case-crossover study of gout, 2003–2004.

epidemiologic studies [8–13] have shown that the Internet is an efficient way to recruit participants and to collect information in real time. In this study, we also demonstrated that using Internet technology, we were able to recruit a sufficient number of subjects with intercritical gout during a short period of time and with a relatively low cost, and to capture both risk factors and recurrent gout attacks in real time.

However, several issues may impede Internet-based epidemiologic studies. First, security is a major concern in conducting an Internet-based study. We took several measures to prevent the possible interception of information posted electronically and outside interference with Web site programming and data stored on the server. Such measures included SSL encryption of data submitted, protecting files stored on the servers with electronic ''firewalls,'' and using unique login names and passwords so that only designated users could access the study Web site.

The second issue is the authentication of study subjects and their responses. In our study, subjects were required to sign HIPAA Research Authorization and Medical Record Release forms, and mail them back to the investigators. Although the primary purpose of collecting the signed forms was to obtain information on gout diagnosis, it also served to further authenticate each applicant's identity. In this study, no envelope was returned to us as ''undeliverable'' by the US Postal Service after it was mailed to the address provided by the subject. Each subject was also required to provide a valid e-mail address before proceeding to the study questionnaires. Immediately after a subject submitted his or her e-mail through the Web site, an automated e-mail containing the URL link to the questionnaire page was dispatched to the e-mail address provided. A subject was unable to proceed unless this link was received. The study Web site also had functions to check the internal consistency of responses. For example, we asked some questions several times in different ways (e.g., age and date of birth) to identify inconsistent responders.

Third, verification of disease diagnosis is particularly challenging given the general anonymity of the Internet. Participants in this study were asked to sign a Medical Record Release Form and to provide us with their physicians' names and addresses. Physicians were given the option of mailing either copies of all records pertaining to a subject's gout diagnosis and treatment or a signed checklist confirming a diagnosis of gout and gout episode features. This documentation was available on all but 25 subjects, and only seven records did not contain a confirmed diagnosis of gout by the subjects' own physicians. Of those 25 who did not provide medical records, seven met the American College of Rheumatology Criteria for self-reported gout. This suggests that with an

Table 2
Availability of risk factor information during control and hazard periods, by days of the week

Days of week	Control period, no. of days (%)		Hazard period, no. of days (%)	
Monday	163	18.5	96	15.0
Tuesday	148	16.8	101	15.7
Wednesday	131	14.9	87	13.6
Thursday	100	11.4	83	12.9
Friday	58	6.6	95	14.8
Saturday	105	11.9	92	14.3
Sunday	175	19.9	88	13.7

Table 3
Baseline characteristics of participants in relation to the risk of recurrent gout attacks

Risk factors	No. of gout flares	Person-years	Incidence rate (per person-years)	Rate ratio (95% CI)
Age (years)				
<60	43	38.60	1.11	1.0 (referent)
⩾60	64	65.05	0.98	0.9 (0.6–1.4)
Sex				
Women	20	21.87	0.91	1.0 (referent)
Men	87	81.79	1.06	1.2 (0.5–1.4)
Education				
High school/some college	40	43.53	0.92	1.0 (referent)
College graduate	67	60.13	1.11	1.2 (0.8–1.7)
Body mass index (kg/m^2)				
<30	50	54.47	0.92	1.0 (referent)
⩾30	57	49.19	1.16	1.0 (0.7–1.4)
Disease duration (years)[a]				
<1	27	30.37	0.89	1.0 (referent)
⩾1	79	72.73	1.09	1.3 (0.8–2.0)
Presence of self-reported comorbidities				
No	56	59.29	0.94	1.0 (referent)
Yes	51	44.36	1.15	1.4 (0.9–2.0)

[a] One subject did not provide the data on years of disease duration.

appropriate case confirmation approach, a large number of valid cases can be verified in an Internet-based epidemiologic study.

Finally, while the case-crossover study eliminates the bias in control selection and removes the confounding effects of the factors that are constant over time, sampling referent periods, i.e., control periods, is a critical issue because the case-crossover study is sensitive to the effects of time-varying risk factors [14]. In the current study, although we asked each subject to complete the Control-period Questionnaire at 3-month intervals, we did not require subjects to submit their Control-period Questionnaires on a specific day. Subjects may prefer to fill in the Control-period Questionnaire on the certain days of the week, for example, on weekdays rather than on weekends. If a potential risk factor for recurrent gout attacks, such as alcohol consumption or diuretic use, varies by day of the week, this could potentially introduce bias in the effect estimate for such a risk factor. Thus, when the effect of a specific time-varying risk factor is assessed in our study, we should be aware that potential bias could occur in the effect estimate and an appropriate analytic approach, such as time-stratified analysis (e.g., by days of the week, weekdays vs. weekends, or by seasons) be considered.

Although this study is aimed at testing a novel methodological approach to assess risk factors triggering recurrent gout attacks, this approach has broad applicability to other diseases typified by recurrent attacks, such as migraines, epilepsy, and ulcerative colitis. Identification of factors that trigger recurrent flares not only helps elucidate disease etiology, but can also reveal preventive measures to reduce morbidity and improve quality of life.

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