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Dyspepsia in the community: value of a community-based mailed survey to identify potential participants for a randomized clinical trial

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Abstract

Objective—To assess the usefulness of a community-based mailed survey to identify participants with functional dyspepsia (FD) for a clinical trial.

Material and Methods—In 2008, a valid self-report questionnaire of gastrointestinal (GI) symptoms required for diagnosis of FD was mailed to randomly selected cohorts of Olmsted County, Minnesota residents. From survey responses (54%), FD cases and controls were identified. Phone calls were completed in 2010 and 2011 to 54% of respondents offering participation to those meeting criteria.

Results—Of 937 people identified from the survey, 189 cases and 265 controls were contacted by phone using four questions similar to the written survey resulting in a moderate level of agreement (Kappa 0.43, 95% CI: 0.35 to 0.51; $p = 0.11$). The proportion reporting FD symptoms by survey was 42% while the proportion by phone was 38%. Comparing classification of cases and controls, 118 (62%) survey cases had dyspepsia symptoms on phone screening while 53 (20%) of the survey controls reported FD symptoms. Of 171 who had symptoms, 60 (35%) declined, 33 (19%) were over study age limit, 24 (14%) had inadequate symptom levels, and 36 (21%) had co-morbidities. Of survey respondents contacted, 6 (3%) people were enrolled with 2 screen fails resulting in 4 (1%) randomized.

Conclusions—Agreement between survey and phone questions was modest. Classifications between case and control changed. People eligible and willing to participate were a fraction of people reporting symptoms. People participating in clinical trials do not broadly represent those in the population.

Keywords

dyspepsia; epidemiology; prevalence; clinical trial; response rate

INTRODUCTION

Functional dyspepsia (FD) is a clinical syndrome characterized by one or more symptoms of epigastric discomfort or pain, postprandial fullness, and early satiety (1–6). Studies suggest that dyspepsia is very common in the United States (US) with as many as one in four reporting symptoms of dyspepsia (3, 7–9). Currently, effective treatment options are limited and outcomes are heterogeneous (2, 10–13). Pharmacological treatment often includes antisecretory agents or if available prokinetics, but results are often unsatisfactory leading to the use of largely unproven alternatives, including antidepressants (1, 11, 12).

Recruitment for a clinical trial evaluating effectiveness of two commonly used antidepressants (<http://clinicaltrials.gov/ct2/show/NCT00248651>) proved exceptionally challenging. That study was a randomized, multicenter, double-blinded, placebo-controlled trial evaluating 12 weeks of escitalopram vs. amitriptyline vs. placebo with a 6-month follow-up (14). While symptoms have been reported to be common, recruitment of FD patients to this clinical trial was slower than expected despite having eight research sites internationally (US and Canada). Recruitment was primarily through gastroenterology clinics at these referral sites rather than from the general population despite population-based recruitment efforts such as paper or radio advertisements. Recruitment of referred patients in specialty may result in a sample with refractory and more severe symptoms, and has implications for the generalizability of such trials.

In order to try and optimize recruitment, results of a population-based survey that collected gastrointestinal symptoms were used to identify community residents reporting symptoms of dyspepsia. In 2008, a valid, self-report abdominal symptom questionnaire (15) that recorded gastrointestinal symptoms required for diagnosis of FD was mailed to randomly selected residents (n=8006) of Olmsted County in southeastern Minnesota. Four of the questions used on this mailed survey were the same questions that were being used for telephone screening of patients for the clinical trial. To assess whether these community-based patients with dyspepsia symptoms would meet the criteria for the clinical trial and be potential participants, possible FD cases and controls were identified from the survey respondents. Those cases and controls were screened by phone for possible inclusion in the clinical trial. This study assessed the usefulness of identifying potential participants for this FD clinical trial using reported symptoms of dyspepsia from a mailed survey in a population-based setting.

METHODS

We were interested in evaluating how recruitment into a randomized trial matched a community sample who reported dyspepsia symptoms. The study was approved by the Mayo Foundation Institutional Review Board.

Subjects

Subjects for this study were selected from respondents to an abdominal symptom survey sent to randomly selected residents in Olmsted County, MN in 2008. Olmsted County was comprised of approximately 144,248 persons of whom 86% were Caucasian in the 2010

census (16). A comparison of Olmsted County to the entire United States (US) population (years 1970–2000), found the Olmsted County education level was slightly higher (91.1% vs 80.4% high school graduates) and households wealthier (\$51,316 vs \$41,994 median household income) (17). Age- and sex-specific mortality rates were reported as similar to other populations in the US (17).

The subjects included cohorts from a series of previous mailings (1988–2003) who were thought to still be alive and residents of the county. Specifically, surveys conducted from 1988 to 2003 were used to identify approximately 5000 people who were 35 to 90 years of age and had previously been mailed prior surveys. An additional randomly selected cohort of 4000 “new” people ages 25 to 75 years from Olmsted County were added to the original cohort for the 2008 survey to balance the age groups and provide additional younger aged subjects in the sample. The survey was sent to 8006 people with 3,831 responding (48%). Response bias in the survey was assessed in a random sample of 723 subjects through abstraction of medical records. The odds for response increased in those subjects with higher body mass index (BMI), more health care seeking behavior for non-GI problems and those who had responded to prior surveys. Response status was not found to be significantly associated with any GI symptoms or any GI or non-GI disease (18).

Subjects in the sample were mailed a validated gastrointestinal symptom questionnaire. A revised version of the previously validated Talley Bowel Disease Questionnaire© (BDQ) (15) was mailed to eligible subjects with an explanatory recruitment letter. The survey contained four questions that were used to screen for FD. The questions were based on Rome III criteria (see Table 1). The Rome classification defines functional dyspepsia as having one or more of the following: (i) bothersome postprandial fullness; (ii) early satiation; (iii) epigastric pain; and/or (iv) epigastric burning. For this study, cases were defined as those reporting a symptom frequency ≥ 1 day a week, or more frequently, to at least one question (Table 1). Controls were identified from those reporting none, or infrequent (< one day a week) occurrence of any of these four symptom questions. Controls were then randomly selected age and gender frequency matched to cases. This resulted in 937 people with 462 cases and 475 controls. The case vs. control status of potential candidates to be contacted was not provided to the callers to minimize potential biases arising from knowing possible symptoms prior to the calls.

Sampling, inclusion, and exclusion criteria of the clinical trial

The Functional Dyspepsia Treatment Trial (FDTT) was a double-blind randomized, placebo controlled clinical trial comparing the efficacy of escitalopram (10 milligrams), amitriptyline (50 milligrams) or placebo in patients with FD (14). This multi-site, international study had a recruitment goal of 400 participants. Inclusion criteria for the clinical trial included a diagnosis of functional dyspepsia with either ulcer-like with predominant epigastric pain or dysmotility-like with a predominant non-painful symptom such as early satiety, epigastric fullness, epigastric bloating, or nausea. Patients needed to have symptoms at least twice a week for the last 3 months. To rule out structural (e.g. peptic ulcers), patients had to have a negative esophagogastroduodenoscopy (EGD) within the past 5 years. A number of medications were prohibited during the trial including systemically acting cholinergics and

anticholinergics, prokinetics, macrolide antibiotics, aspirin (greater than 325 mg / day), non-steroidal anti-inflammatory drugs, and antidepressants other than study medications.

Subjects were excluded if there was any documented history of endoscopic esophagitis, predominant heartburn or acid regurgitation, adequate response to antisecretory therapy, or peptic ulcer disease. Those with a history of psychiatric treatment, depression or a positive screen for depression, or drug or alcohol abuse were also excluded as were patients with concurrent major physical illness (e.g. cardiac or liver disease, diabetes, etc.) or a history of major abdominal surgery. Pregnancy or refusal to apply adequate birth control excluded some women. Lastly, patients had to be literate in English to complete the required surveys in the trial.

Recruitment methods

Cases and controls were randomly sorted resulting in a list for use in contacting potential participants to the clinical trial. Letters were sent to the individuals informing them that someone from the study team would be contacting them by phone regarding the study. Individuals were required to actively decline participation to opt out of the phone call. Approximately two weeks after letters were sent, phone calls began. Using an approved script, two members of the clinical trial team made telephone calls to the cases and controls in the randomized order on the list. A maximum of three telephone call attempts could be made to reach an individual. Calls were attempted at various times of the day, evening, and weekends to maximize the ability to contact people. Responses from the calls were recorded on paper forms and then transferred to an electronic database. If patients gave permission for medical record review, their medical records were screened for exclusionary criteria at the time of the call. The assessment of potential bias in contacting subjects identified only SSC score to be significantly ($p=0.01$) associated with contact status (contacted vs. not contacted) with higher scores increasing the odds for contacting subjects.

Statistical analysis

The kappa coefficient (95% CI) for agreement (survey classification vs. phone follow-up classification) was calculated to estimate the reliability of identifying people meeting criteria for dyspepsia. The comparison of the proportion of those with dyspepsia by the survey response to the proportion by telephone interview was made using McNemar's test for paired binary responses.

RESULTS

Of the 937 cases and controls, 42 (4%) requested no call be made to them, 8 (1%) had died, and 52 (6%) had no active phone number. Phone contact was completed for 454 of the remaining 835 individuals, yielding a contact rate of 54% (Figure 1). Calls were made to 300 people but no contact was made. Due to institutional guidelines, the number of attempts were limited to 3. No calls were made to 41 individuals based on prior participation rates and call attempts were stopped.

The mean ($\pm$ SD) age of the total survey respondents was 63 (± 15) years and 54% were female compared to 63 (± 13) years old in those contacted by phone (63% female).

Agreement between survey response and phone interview was moderate ($\kappa = 0.43$ [0.35, 0.51]) with the overall proportion considered to have FD by the survey (42%) somewhat greater than those identified by phone interview (38%) to have FD ($p=0.11$, McNemar's test). Since the median time from survey to phone call was 234 days, agreement was compared for those individuals contacted > 234 days from survey ($\kappa = 0.42$ [0.31, 0.54]) and those < 234 days ($\kappa = 0.46$ [0.36, 0.57]). There was no significant difference between those called earlier or later after the survey.

A comparison of cases and controls indicated that 189 (52%) of the cases received phone calls and 265 (46%) of the controls received phone calls. Of the 189 cases identified by written survey, 118 (62%) people screened positive for dyspepsia by phone. In contrast, of the 265 controls who did not meet criteria for FD based on the mailed survey, 53 (20%) screened positive for FD in the phone survey (Figure 2).

A total of 171 of the phone contacted respondents screened positive for dyspepsia symptoms, however only 6 met pre-screening criteria and were willing to consider participation and thus were brought in for screening for the clinical trial. Of these only 4 of the 171 (2%) were randomized and participated in the trial. The majority (67% or 4 of 6) of those meeting pre-screening criteria were called after the median time of 234 days indicating the timing of the calls did not affect screening. Reasons for non-participation in the clinical trial included not willing to undergo screening in the clinical trial ($n=60$, 35%), age exclusion (>75 years of age) ($n=33$, 19%), inadequate symptom severity ($n=24$, 17%), co-morbidities or predominant symptoms indicated GERD ($n=16$, 9%) or irritable bowel syndrome (IBS) ($n=3$, 2%), or currently prescribed an antidepressant ($n=12$, 7%) (Table 2). For the clinical trial, a diagnosis of GERD or response to a proton pump inhibitor was an exclusion criteria, while abdominal pain below the umbilicus or relieved with passage of a bowel movement indicated IBS; these criteria were also used for screening in this study.

DISCUSSION

Agreement between the survey and the telephone call was modest, and classification of cases and controls changed based on the methodology. One reason for the lack of agreement may be a difference in response based on the methodology, paper vs. telephone. There was also a period of time (median time of 234 days) between the written survey and the use of the survey results for recruitment calls of the clinical trial. Symptoms may have changed over that time for a variety of reasons. Several noted resolution of symptoms with additions or changes in medications such as proton pump inhibitors or antidepressants or a change in other medications known to cause GI symptoms. Others noted that their symptoms had changed since they had completed the survey. Symptom severity needed to be moderate to severe; approximately 17% of subjects had dyspepsia symptoms but not of a frequency or severity to qualify for the clinical trial. For the trial medication to demonstrate adequate relief, a fairly consistent and moderate level of symptoms was required to avoid a floor effect.

Change of symptom status observed here are consistent with a study noting the transition of chronic GI symptoms in the general population on prospective follow-up (19). In validated

surveys mailed to a population-based cohort, the natural history of functional gastrointestinal diseases (FGIDs) was evaluated (19). Each subject completed at least 2 surveys over a 12 year period. Though the point prevalence was stable for FD (1.9 and 3.3%, respectively), approximately 20% of people with symptoms at baseline had the same symptoms at the later survey while 40% had no symptoms and 40% had different symptoms, indicating dyspepsia symptoms do change over time. In another study over a 10 year period in Iceland, findings were similar with the point prevalence relatively stable (13.9% and 17.6%) but major changes in symptoms occurred including alterations in the intensity and frequency of abdominal pain (5).

The overall recruitment yield for the clinical trial was a total of four randomizations (1% of those contacted) and two screen failures. Of those contacted, 35% declined participation for a number of reasons including possible reasons that would have excluded them. The Institutional Review Board required a question that asked whether the person would be interested in hearing about the trial as the first question. If they declined, the screening questions could not be asked nor the medical record reviewed for exclusionary factors. However, anecdotally several noted they were not interested as they did not have stomach problems any more, but because they declined interest in the trial that information could not be used. Lastly, a number of individuals had symptoms of dyspepsia but had not received that diagnosis or had received a diagnosis of gastroesophageal reflux disease (GERD) despite ongoing dyspepsia symptoms after treatment for GERD. The symptoms of FD can be nonspecific making the diagnosis of FD and differentiation from GERD potentially difficult (2, 6).

People in the clinical trial represent a small fraction of those people who identified dyspepsia symptoms in the community survey. There were several notable challenges to recruitment; the lack of recognition of the dyspepsia diagnosis, a need for people with moderate to severe symptoms in order to demonstrate significant changes in the treatment trial, other causes of dyspepsia other than FD, and a requirement of generally otherwise healthy individuals to reduce possible confounding and safety factors. While population-based epidemiological surveys indicated a potentially large population pool from which to draw for the clinical trial, the reality was that only 1% of those contacted qualified and were willing to participate in the study. The inclusion and exclusion criteria necessary for a well-designed clinical trial limit the potential pool of subjects from a community sample. This has implications for the number of sites and cost of such trials as well as generalizability to the population. While direct cost effectiveness of this method was not assessed, over 100 hours of phone calls were logged with a return rate of 4 patients. Within the clinical trial, it was determined that recruitment from the GI clinics was the most efficient method of recruitment.

We acknowledge the limitations of the study. The participants self-reported GI symptoms through a mailed survey. Participants were not examined or evaluated to exclude the possibility of organic disease. Their medical histories were reviewed if they agreed at the time of the interview but some participants had not been seen recently or had not sought care for their GI symptoms. Some of the changes in symptoms may have been due to participants seeking care or receiving therapy between the time of the written survey and the telephone

follow-up though this was a relatively short period of time. The definitions applied may have influenced the results. While Rome II criteria were used, minor changes in the definitions have the potential to affect the estimates of prevalence and transition. It should be noted that definitions however remained consistent between the mailed and telephone surveys. We recognize that variations in responses to repeated survey questions may be a measure of reliability or affected by the use of different methodologies. The Talley BDQ has been tested extensively and found to be reliable and valid (15). Sudman and Bradburn note mean effect differences of $-.01$ to $-.03$ using mail versus telephone survey methods respectively (20).

Additional limitations of this population-based are the response rate of just over 50% in the original mailed survey although we could not detect evidence of major response bias (18). Additionally, 85% of the county population is white which is similar to the state of Minnesota so our results may not apply to Hispanics and African Americans (17). The county's population is also slightly better educated with a slightly higher income level and more people working in health care than the general population (17).

In summary, these data suggest it is very difficult to recruit participants with FD from a community population despite the high population prevalence. Recruitment for the clinical trial has come primarily from tertiary referral GI clinics despite local advertisements in surrounding communities. The data also suggest changes in GI symptoms reported over time impair recruitment from the local population. More research is needed to understand the drivers into clinical trials and their representativeness.

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Figure 1.
Consort diagram of individuals surveyed and called.

Figure 2.
Breakdown and transition of cases and controls

Table 1

Screening Questions

Questions:	Response options
1. In the past 3 months, how often were you unable to finish a regular size meal?	0 Never 1 Less than once a month 2 One day a month 3 Two or three days a month
2. In the past 3 months, how often did you feel uncomfortably full after a regular-sized meal?	4 One day a week 5 More than one day a week 6 Every day
3. In the past 3 months, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?	
4. In the past 3 months, how many times have you had a feeling of wanting to throw up (nausea)?	

Table 2

Results of screening and enrollment

Outcome	Call case and Survey case (n = 118)	Call case and Survey control (n = 53)	Total (n = 171)
Declined	47 (40%)	13 (25%)	60 (35%)
Age > 75	22 (19%)	11 (21%)	33 (19%)
Inadequate Symptoms	10 (8%)	14 (26%)	24 (14%)
Medical History	15 (13%)	2 (4%)	17 (10%)
Gastroesophageal reflux disease	10 (8%)	6 (11%)	16 (9%)
Antidepressant Use	7 (6%)	5 (9%)	12 (7%)
IBS	3 (3%)	0 (0%)	3 (2%)
<i>Screen fail</i>	<i>2 (2%)</i>	<i>0 (0%)</i>	<i>2 (1%)</i>
<i>Randomized</i>	<i>2 (2%)</i>	<i>2 (4%)</i>	<i>4 (2%)</i>