Published in final edited form as:

Res Nurs Health. 2018 August ; 41(4): 336–345. doi:10.1002/nur.21880.

Identifying Phenotypes and Factors Impacting Outcomes in Older Adults with Asthma: A Research Protocol and Recruitment Results

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Abstract

Success in testing research outcomes requires identification of effective recruitment strategies in the targeted population. In this paper, we present the protocol for our NIH-funded study as well as success rates for the various recruitment strategies employed. This longitudinal observational study is: developing a phenotyping algorithm for asthma in older adults, exploring the effects of the asthma phenotype and of volatile organic compounds on asthma control, and developing a predictive model of asthma quality of life. A sub-aim is to characterize barriers to successful medication management in older adults with asthma. Individuals are eligible if they are ≥ 60 years, have a positive response to at least 1 of 6 asthma screening questions, non-smokers, and demonstrate bronchodilator reversibility or a positive bronchial challenge test with methacholine. Exclusion criteria are smokers who quit <5 years ago or with a >20 pack year smoking history, and those having other chronic pulmonary diseases. Participants (N=190) complete baseline pulmonary function testing, questionnaires, sputum induction, skin prick testing, and have blood drawn for Vitamin D and Immunoglobulin E. Home environmental assessments are completed including 24-hour particulate and volatile organic compound measurements. At 9-months post-

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The authors declare no conflict of interest.

baseline, home spirometry, medication assessment, and assessment of asthma quality of life and asthma control are assessed. At 18-months post-baseline, home spirometry, completion of baseline questionnaires, and a home environmental assessment are completed. We have employed multiple recruitment efforts including referrals from clinical offices, no-cost media events, flyers, and ads. The most successful efforts have been referrals from clinical offices and media events.

Keywords

Asthma; Older Adults; Environmental Exposures; Longitudinal Design; Recruitment Strategies

Introduction

Older adults comprise the fastest growing subset of the U.S. population (Williams, 2007) and the number of older adults affected by asthma rises annually (Gibson, McDonald, & Marks, 2010). Asthma is a common chronic inflammatory disorder of the small airways and is characterized by variable and recurring symptoms, airway inflammation, reversible airflow constriction, and bronchospasm (U.S. Department of Health and Human Services, 2007). Asthma is considered a collection of various phenotypes (characteristics) instead of a single disease (Lötvall et al., 2011) in which distinct entities (endotypes) may be present in a cluster of phenotypes each defined by a specific biological mechanism (Wenzel, 2006). The clinical features of asthma in older adults are distinct from its presentation in younger populations (Park et al., 2013). Understanding this unique pathophysiology is necessary for optimal, personalized treatment to improve patient outcomes. Comprehensive phenotyping specific to older adults with asthma that considers multiple factors relevant to the older individuals has not occurred.

Divergent asthma phenotypes and exposures to environmental triggers may impact asthma control in older adults. Older adults with asthma have high rates of medication non-adherence, emergency department visits, physician visits, hospitalizations for asthma exacerbations, and the highest mortality rate from asthma (51.3/million population) of any age group (Choi & Cho Chung, 2011; Dunn, Busse, & Wechsler, 2017; Moorman et al., 2007; Smith, Villareal, Bernstein, & Swikert, 2012; Tsai, Delclos, Huang, & Hanania, 2013). Environmental triggers such as volatile organic compounds (VOCs) in paint, air fresheners, pesticides, and other common household products can initiate acute asthmatic episodes in all ages (Crinnion, 2012; Ho & Kuschner, 2012; Institute of Medicine, 2000; Nurmatov, Tagiyeva, Semple, Devereux, & Sheikh, 2015). Older adults have been shown to be more susceptible to inflammation and respiratory complications due to natural and anthropogenic air pollution, as their inhaled particle clearance becomes less efficient with age, as well as impaired by other organ dysfunctions, and experience an increased risk of asthma exacerbations from exposure (Kurt, Zhang, & Pinkerton, 2016; Zhang, Li, Tian, Guo, & Pan, 2016). The relationships among asthma phenotypes in older adults and environmental exposures with asthma control have not been systematically explored.

Asthma impacts the physical and psychological well-being of older adults (O'Connor et al., 2017). Factors contributing to asthma quality of life (QOL) in the older adults are also not

well explicated (Hanania et al., 2011). Asthma QOL has been related to environmental triggers and to individual factors such as asthma self-efficacy, asthma knowledge, asthma control, and asthma phenotype (Choi & Hwang, 2009; Huss et al., 2001; Imhof, Naef, Wallhagen, Schwarz, & Mahrer-Imhof, 2012; Lavoie et al., 2008). Little research has focused on how these factors contribute to QOL in older adults with asthma. Research on asthma phenotyping and home environmental asthma triggers has largely focused on children and on distinct sub-sets such as those with severe asthma or distinct comorbid lung conditions (Sano et al., 2016; Welsh, Hasan, & Li, 2011; Wenzel, 2012). The increasing prevalence of asthma in older adults, the increasing elderly population, and the increasing potential for exposure to VOCs and other home environmental triggers warrants empirical attention. The long-term goal of this program of research is to develop personalized phenotype-driven management protocols for asthma in older adults that can be empirically tested.

The specific aims and hypotheses for this ongoing study are:

For older adults with asthma:

1. Develop and systematically implement a phenotyping algorithm.
2. Longitudinally investigate the effects of (a) asthma phenotypes and (b) VOC exposures on asthma control.

Hypothesis 1: Eosinophilic phenotypes are positively associated with accelerated loss of asthma control in older adults with asthma.

Hypothesis 2: Exposures to VOCs are positively associated with accelerated loss of asthma control in older adults with asthma.

3. Develop a predictive model of asthma quality of life.

Sub-aim: Characterize barriers to successful medication management in older adults with asthma.

Background

Older Adults with Asthma Have Higher Rates of Bronchial Hyperactivity and Asthma Symptoms

Only 20% of older adults with asthma have normal pulmonary function tests; another 20% show moderate to severe airflow obstruction (Forced expiratory volume in one second [FEV1] < 50% predicted) without structural changes seen in emphysema, indicating airway remodeling as the main cause (Reed, 1999). Lungs can lose more than 40% of capacity over a life-time, resulting in a decreased expiratory flow rate (Bom & Pinto, 2009), decreased capacity for activity, and reduced QOL. Older adults with asthma have been grouped into two functional categories: those with long standing asthma (LSA) (age of asthma onset < 40 years; represents about 60%), and those with late onset asthma (LOA) (age of onset > 40 years; represent about 40%) (Braman, 1993). LSA likely involves gene-environment interactions, rhinovirus, and respiratory syncytial virus (RSV) infections; it is driven by TH2 eosinophilic airway inflammation and enhanced allergen exposures (Hanania et al., 2011).

LOA likely involves epigenetic interactions, oxidative stress, and RSV infections; the inflammatory response appears to be driven by neutrophilic and/or eosinophilic innate immunity processes and related to environmental exposures. Asthmatics with eosinophilic inflammation have decreased asthma control (Miranda, Busacker, Balzar, Trudeau, & Wenzel, 2004; Wenzel, 2006). Given that most older adults spend the majority of their time indoors, those with specific Immunoglobulin E (IgE) antibodies to indoor allergens may be at increased risk for asthma exacerbations and thus increased loss of asthma control as they age (Bom & Pinto, 2009). Older adults with asthma have more steroid resistance, are less responsive to short acting beta agonists, have increased airway neutrophils, and increased co-morbidities with overlapping signs and symptoms (e.g., congestive heart failure, chronic obstructive pulmonary disease, and gastroesophageal reflux disease) (Banerji et al., 2006; Hanania et al., 2011). Remission from asthma in the older adults is uncommon (Birnbaum & Barreiro, 2007).

Chemical Emissions from Common Indoor Materials are Associated with Higher Risks of Asthma

Epidemiologic research has documented the association between residential chemical emissions and respiratory health, although most of these focused on children (Nurmatov et al., 2015). VOCs in cleaning products, room fresheners, polishes, carpets, solvents, floor adhesives, paints, and cigarette smoke in homes were significant risk factors for asthma in young children (< 3 years old), with the highest negative effect from benzene, ethylbenzene, xylenes, and toluene (Martins et al., 2012; Mendell, 2007; Rumchev, Spickett, Bulsara, Phillips, & Stick, 2004). Children were two to three times more likely to suffer from asthma when exposed to toluene and acetaldehyde—common indoor air pollutants. In the European Community Respiratory Health Survey, asthma in children was positively associated with the presence of higher indoor concentration of the VOCs acetaldehyde and toluene (Hulin, Caillaud, & Annesi-Maesano, 2010). Several reviews have concluded there is insufficient research to evaluate the impact of VOCs on asthma control (Canova, Jarvis, Walker, & Cullinan, 2013; Institute of Medicine, 2000; Nurmatov, Tagieva, Semple, Devereux, & Sheikh, 2013; Tagieva & Sheikh, 2014). The impact of VOCs on asthma control and quality of life in older adults has not been explored.

Older Adults with Asthma Experience Exacerbations Following Exposure to Environmental Asthma Triggers

At least one positive allergen test was found in 75–90% of older adults with asthma, with asthmatics having significantly higher rates of sensitization to mold, dog dander, and house dust mites (Busse, Cohn, Salo, & Zeldin, 2013; Huss et al., 2001; Lombardi et al., 2016; Ozturk, Ozyigit Pur, Kostek, & Keskin, 2015). Over 20% of the homes of older (55+) individuals with chronic respiratory disease - including asthma - had mold or water damage (Shendell et al., 2011). In homes of older adults with asthma, elevated levels of dust mites, cockroach, dog dander, and cat allergen were found; one-third had stuffed animals; 78% had bedroom temperatures > 70°F, and a third of the homes were categorized as untidy, sloppy, or dirty (Huss et al., 2001). Allergy to cockroaches was significantly related to lower QOL in New York adults after controlling for age, sex, asthma severity, and asthma regimen (Wisnivesky, Leventhal, & Halm, 2005). This study is uniquely exploring the role of home

environmental asthma triggers on outcomes such as pulmonary function, QOL, and asthma control in older adults.

Quality of Life is Significantly Lower for Older Adults with Asthma Compared to Non-Asthmatics

Quality of life is a multidimensional concept influenced by the health status of an individual. Presence of chronic respiratory disease is an important risk factor for lower QOL among older adults (Carreiro-Martins et al., 2016). Older adults with asthma have significantly worse general health and QOL compared to persons without asthma (Smith et al., 2012). Asthma control has both a positive direct (Eisner et al., 2002) and indirect relationship with QOL (Oh, 2008). The positive relationship between physical and mental functional status and asthma QOL has been well documented in cross-sectional studies; older adults with asthma reported limitations in activities of daily living (Woods et al., 2016), inability to sleep, going outside in hot weather, completing household chores, or performing other physical activities (Oh, 2008; Schneider et al., 2007). Lower QOL was also associated with lower self-efficacy, depressive symptoms, difficulty accessing care, lower socioeconomic status, and minority race/ethnicity (Lavoie et al., 2008; Trupin et al., 2013). Better asthma-related QOL has been longitudinally associated with lower healthcare costs (Eisner et al., 2002; Smith et al., 2012) further emphasizing the significance of longitudinally examining factors contributing to QOL in older adults with asthma.

Medication Use (or Misuse) Problems Add Substantial Costs to the Health Care System in Older Adults with Asthma

During 2008–2013, the incremental medical cost attributable to asthma has reached \$3,266 per-person per-year or a total of \$81.9 billion among of general population with asthma, which is more than twice the medical economic burden of people without this chronic condition, (Nurmagambetov, Kuwahara, & Garbe, 2018). The cost of medications (\$1,830) comprises the bulk of the medical costs of asthma (Nurmagambetov et al., 2018). One in six hospitalizations in older adults is due to adverse drug events, and for those 75 and over, it is one in three hospitalizations (Beijer & De Blaey, 2002; Page & Ruscini, 2006). Barriers to medication adherence and contributors to medication misuse include frequent hospitalization, depression, undocumented medication use, limited health literacy, cognitive impairment, and decreased self-efficacy (Rifkin et al., 2010). Contributors to adverse drug events include errors related to adherence, prescribing and monitoring, with missed monitoring being a significant factor (Budnitz, Lovegrove, Shehab, & Richards, 2011; Gurwitz et al., 2003). Comprehensive medication management applied to complex patients results in safe, appropriate, and effective medication use (Roughead et al., 2009), which yields a significant return on investment (ROI). The average ROI on comprehensive medication management ranges from 3:1–12:1 with an average of 5:1; this reflects a decrease in hospital admissions, physician visits, and emergency department admissions as well as reduction in unnecessary and inappropriate medications (Isetts et al., 2008). For improved asthma outcomes in older adults, it is imperative that the challenges of medication management due to age and medical complexity is explored (Melani, 2013). This study will fill that gap.

Research Design and Methods

Design and setting.—This study uses an observational longitudinal design with data collection occurring at baseline, 9-months, and 18-months post-baseline. Participants are recruited from the Louisville, Kentucky area. According to the American Lung Association, this area is ranked 13th for short-term particulate air pollution (out of 184 metropolitan areas) and 49th for high ozone days (out of 228 metropolitan areas) (American Lung Association, 2017). The study is approved by the University of Louisville Biobehavioral Institutional Review Board (IRB).

Instruments/measures.—The primary outcome measures used in this study are briefly described in Table 1. Self-reported demographics, health care utilization, health history, medications, tobacco use history, environmental tobacco smoke exposure, workplace exposures, influenza vaccine status, and known asthma triggers are also collected. Participants height and weight are measured, and blood is drawn to determine Vitamin D levels and total and specific IgEs.

Inclusion/exclusion criteria.—Participants are initially considered eligible if they are 60 years old, have a positive response to at least 1 of 6 asthma screening questions (U.S. Department of Health and Human Services, 2007), and have been diagnosed with asthma. Participants are enrolled in the study if they also demonstrate either: (1) a bronchodilator response showing a 12% or greater increase in FEV1 or FVC and an increase of 200 mL of lung volume in either measure following bronchodilator administration, or (2) a methacholine challenge test (MCT) result of PC20 $\leq$ 16 mg/dL (Crapo et al., 2000; A. Miller et al., 1992; M. R. Miller et al., 2005). Exclusion criteria are: a concurrent diagnosis of other chronic pulmonary diseases, residing in a skilled nursing facility, current smoker, smoker who quit $<$ 5 years ago, or $>$ 20 pack year smoking history, inability to perform pulmonary function testing maneuvers, and a Prognostic index score of $\geq$ 10 (Lee, Lindquist, Segal, & Covinsky, 2006). The Prognostic index was developed to determine 4-year mortality for community-dwelling older adults.

Recruitment and retention.—Participants are recruited from a wide range of settings including asthma clinics, pulmonologist and allergist offices, senior citizens centers, residential, independent and assisted-living facilities, and churches. Recruitment efforts have also included social media campaigns, media press releases, and placing ads/notices in newspapers, buses, newsletters, and church bulletins. Once enrolled, monthly contact with participants is maintained by letters/emails/text messages. The method of contact depends on participant's preference. Monthly contact includes a reminder about the next data collection time, birthday cards, and health and wellness information. Participants are asked to report change of residence or contact information and to provide the name and contact information of someone who will always know how to reach them.

Data collection.—At baseline, a trained research team member contacts a potential participant by email or phone to determine initial eligibility. Those determined to be potentially eligible after initial screening are scheduled for pulmonary function testing (PFT) at the University of Louisville Clinical Trials Unit to assess for bronchodilator reversibility.

Participants are instructed to hold bronchodilators for 6–24 hours before PFT, depending on the medication. Upon arrival to the Clinical Trials Unit, written informed consent is obtained. Participants then complete PFT, Fractional Exhaled Nitric Oxide (FENO) testing, and baseline questionnaires. Those meeting bronchodilator reversibility enrollment criteria complete sputum induction, skin prick testing (SPT) (if not contraindicated) and have blood drawn for Vitamin D and IgE analysis. Baseline data collection takes 4–5 hours. Parking vouchers for the adjacent parking garage and/or taxi/bus fares are provided. Those not meeting the bronchodilator reversibility requirements are offered the opportunity to return at a different date to the University of Louisville Physicians PFT lab for MCT or are considered to not meet inclusion criteria. This determination is based on participant PFT responses and clinical history. Potential participants not meeting final inclusion criteria receive an incentive payment of \$25.

Within 30 days of enrollment in the study, baseline home environmental data are collected in the participant's residence (Table 1). Home visits are conducted over 2 days. The first day includes surveying the home, completing the asthma Home Environment Checklist, and setting up monitors and pest traps. Monitors and pest traps remain in the participant's home for 24 hours. Data collection takes approximately 60–90 minutes on the first day and about 5 minutes to retrieve the instruments on the second day. Participants receive a \$150 gift card after the baseline home visit is completed.

Data collection at 9 months occurs in the participants' home by a trained registered nurse or respiratory therapist and includes the measures listed in Table 2. Each visit takes approximately 30 minutes. Participants receive the results of their baseline home environmental assessment with suggested action steps to assist in identifying and addressing home environmental asthma triggers, a \$25 gift card, and asthma trigger control supplies worth about \$25 (e.g., pillow covers). *Final data collection at 18 months* occurs in the participants' home and includes the measures noted in Table 2. Participants receive a \$25 gift card for completion of the 18-month data collection.

Power and sample size justification.—Identifying groups of elderly asthmatics that are similar to each other but different from other elderly asthmatics is a goal of the study. That is, we will identify clusters of elderly asthmatics who have similar habits, demographics and markers of disease. The term *cluster analysis* does not identify a particular statistical method. Typically, assumptions about the underlying distribution of the data are not assessed. Using cluster analysis, groups of related variables are formed, similar to factor analysis. Since cluster analysis requires a larger sample size, when compared with other dimension reduction methods (e.g., confirmatory factor analysis), sample size estimates were based on the cluster analysis with a small-to-medium intra-class coefficient (ICC) = 0.15. Although we anticipate two phenotypes, based on previous literature there may be as many as five phenotypes. An analytical sample of N=190 is needed to perform the cluster analysis, with an ICC = 0.15 if five clusters (phenotypes) exist, to achieve adequate power (80%). Since cluster analysis is not an inferential technique, *a priori* power was calculated for the inferential methods. Based on preliminary studies, we anticipated that 10% of all potential participants will not be eligible and/or willing to participate; and that 10% of the eligible/willing participants will be lost to follow-up. As such, power

calculations for the Generalized Linear Mixed-effects Models (GLMMs) (Aims 2 and 3) were based on the anticipated total sample size ($n = 152$) that will be available for complete analysis. Since Aim 3 requires the most saturated model and requires a larger sample size, power calculations were developed for Aim 3 given the sample size requirement from Aim 1. In Aim 3 we will develop a mixed-effects general linear models for quality of life. From the anticipated sample size ($n = 152$), the study has 87% power to detect a 10% main effect of each effect for each outcome. The estimated power for detecting a 5% interaction effect is 50%.

Statistical analytical plan.—Our initial goal (Aim 1) is to identify homogeneous groups of individuals with similar phenotypes that are useful and meaningful. Since we anticipate that only two phenotypes exist, we will first perform a confirmatory factor analysis (CFA) on phenotypes, to examine the assumed two-factor construct of phenotypes in elderly asthmatics. Convergent validity will be examined on phenotypes using Pearson's correlations. Assessment of discriminant validity will be done by using exact Mann–Whitney U tests. If the CFA suggests the two-factor construct is not valid, a cluster analysis, using traditional methods (e.g., non-hierarchical, hierarchical), will be used to derive a better fit in grouping individuals into phenotypes; such as a three-factor or five-factor construct that has been proposed in the literature (Moore, et al., 2010).

For Aim 2 we will longitudinally explore the effects of asthma phenotype (as determined in Aim 1) and exposure to VOCs in the home on asthma control. First, we will examine differences in demographics by phenotype. Analysis of Variance (ANOVA) will be used to test for difference among continuous variables, while Kruskal-Wallis, Fischer's Exact Tests and Wilcoxon methods will be used to test for differences among categorical variables. To examine asthma control scores over time, a generalized linear mixed-effects model (GLMM) will be developed. Phenotypes will be analyzed as fixed effects and time (month since enrollment) will be analyzed as a repeated measures effect. Traditional risk factors (e.g. age, ethnicity) will be incorporated as covariates. All main effects and all two-way interaction effects will be investigated for significance from the mixed-effects models developed.

For Aim 3, we will longitudinally determine if asthma quality of life for older adults is affected by environmental exposures, individual factors (e.g., asthma knowledge, asthma self-efficacy), and residence type while adjusting for traditional risk factors (e.g. age, ethnicity). In addition, the asthmatics will be stratified by phenotype. A comparison of groups will allow us to investigate the influence phenotype and residence type have on asthma control in isolation and in combination. Therefore, our study design allows us to perform the conventional analysis of variance of main effects as well as investigate interactions effects of residence and phenotype.

Discussion

Between May, 2015 and November, 2017 we enrolled 158 participants. Recruitment has been challenging and recruitment strategies have varied over the first three years of the study. Table 3 summarizes the success rates for the various recruitment strategies employed. Overall, we made initial contact with over 800 individuals. Initial inquiries consist of an

introductory letter explaining the study and contact information (phone, email, web page) for those wanting further information or are interested in participation. Most of our contacts (55%) are from clinical facilities that include primary care or specialist offices. Our waiver of HIPAA research authorization allows us to work with these offices to review electronic medical records and identify potential participants that meet our inclusion criteria. Of the 450 individuals identified from these medical offices, 67% (n=301) indicated they were not interested or did not reply to our initial inquiry. Unfortunately, smoking history is often inadequately or incorrectly recorded, and invitation letters are inadvertently sent to individuals who are not eligible due to their smoking history. Of the 149 individuals initially identified from a clinical office who indicated interest in the study, 78.5% (n=117) met the initial phone screening criteria, and 58% (n=68) of these were enrolled in the study. While we have had cooperation from many clinical offices, other offices have chosen not to assist our recruitment efforts. There have been instances where we received confirmation for cooperation from a physician, but the office gatekeeper has blocked access. In one instance a research team member brought donuts and a specialty coffee drink to the gatekeeper (paid for out of personal funds) that provided us the opportunity to further explain the study and gain access.

Recruitment efforts have also included no-cost media publicity. When the study was first funded, the university hosted a publicity event in which the project was introduced by the university's president. Members of the university community and the press were invited. This resulted in press releases to multiple media organizations, an article published in the local newspaper, and appearances on local radio shows. This initial publicity resulted in about 90 inquiries of interest. Subsequent appearances on local noon-day television programs resulted in 21 additional contacts. The local newspaper did a follow-up article specific to the home VOC assessments in 2017 that resulted in an additional 57 inquiries. Overall, recruitment efforts that involved the media resulted in 199 initial inquiries. Of those indicating interest in the study after further explanation of the study protocols (n=159), 80% (n=127) were initially screened eligible and 39.4% (n=50) were enrolled.

While referrals from clinical offices and media publicity were the most fruitful recruitment efforts, we also posted flyers and paid for ads placed in local and suburban newspapers, the radio, buses, and social media. Flyers were posted in places such as churches, local restaurants, libraries, and health centers. For about 5 months in early 2017 we employed a contract research organization to do a targeted and customized social media recruitment campaign. This organization provided a HIPAA compliant cloud-based management system that allowed us to do basic pre-screening (age, smoking history) online. We received 41 inquiries from this contracted social media campaign, of which 8 (19.5%) individuals were enrolled. Overall, the paid ads yielded 54 inquiries about the study resulting in 12 enrollees (22.2%). The average return on investment of the paid ads was \$698 per enrolled participant.

Recruitment efforts also included a variety of other miscellaneous approaches. For example, we provided asthma education to several community groups, senior centers, assisted living facilities, and community health fairs. While the education focused on asthma in older adults, we always included a summary of the study and distributed study flyers. Although these efforts resulted in only 10 initial contacts and 1 enrollee, they were considered a

community service and an opportunity to provide asthma education. For about six months we hired an individual to focus on recruitment of minorities. She employed some unique recruitment strategies ranging from going to local restaurants for several hours and chatting with customers about the study to sending flyers to local policy makers. Interested individuals were encouraged to contact our research office to determine eligibility. Unfortunately, her efforts resulted in only one enrollee at a cost of \$600. Many of the individuals she referred to the study were ineligible due to their smoking history. The most fruitful miscellaneous recruitment efforts were referrals from individuals enrolled in the study. These participants indicated they enjoyed being a part of a study, they received a great deal of information about their lung health and about their home environment, and were happy to refer others to our study without any financial incentive for themselves. We received 36 such referrals and 16 (44.4%) were enrolled in the study. Overall, miscellaneous recruitment strategies yielded 21 enrollees.

In summary, recruitment remains a challenging enterprise. Our recruitment challenges are compounded by the specificity of our inclusion/exclusion criteria, the need for participants to come to the university health science center in downtown Louisville, Kentucky to undergo testing and determine final eligibility, and the need for those not meeting bronchodilator response criteria to return to the health science center for MCT. Additionally, the longitudinal aspects of the study protocol that include three home visits, and 24-hour home environmental monitoring at baseline and 18-months are challenges. Our analysis of the various recruitment strategies employed indicates that most of our participants were identified from clinical offices and no-cost media outlets. Working with the environmental reporter in the local newspaper to assess his home (data not included in the study) from which he generated a front-page story and providing allergy prevention advice on a local noon television program that ended with the study's contact information displayed are examples of combining community education and information about the study. As we work to complete enrollment, recruitment efforts will focus on the two most successful strategies: clinical offices, and media outlets.

Acknowledgments

Funding: National Institutes of Health, National Institute on Aging. Research reported in this paper was supported by the National Institute on Aging under Award Number R01AG047297. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors would like to acknowledge the contributions of Ms. Diane Endicott, Ms. Carol Norton, and Ms. Paula Kingsolver in recruiting, enrolling, and retaining participants and in collecting data for this longitudinal study.

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Table 1

Study outcome measures

Measure	Description
Biophysical Measures	
Bronchodilator responsiveness	Pre-and post-bronchodilator (short acting beta agonist) are assessed (Miller et al., 2005). Spirometry is repeated at 30 minutes post-nebulizer. If 12% reversibility is not achieved spirometry is again repeated at 60 minutes.
Home spirometry	Provides precise volume and flow measurements and complies with American Thoracic Society standards for accuracy and reproducibility (+/- 3%) (Miller et al., 2005).
Fractional exhaled Nitric Oxide (FENO)	Nitric oxide (NO) is generated by inflammatory cells, primarily by airway eosinophils. An elevated level of exhaled NO is considered a marker of eosinophilic airway inflammation. (Dweik et al., 2011).
Bronchial hyperresponsiveness	Methacholine challenge test (MCT) is done to confirm asthma if there is no documented bronchodilator reversibility 5 years (Crapo et al., 2000).
Atopic skin prick testing (SPT)	SPT on the forearm with standardized extracts and bifurcated SPT devices for 13 common allergens (cat, dog, dust mite, German cockroach, Maple/Box elder, Oak mix, Kentucky bluegrass, Bermuda grass, short ragweed, English plantain, Lambs quarter, Alternaria, and Aspergillus). Positive SPT: wheal 3 mm than the saline control after 15 minutes (Smith et al., 2012).
Immunoglobulin E (IgE)	Total and specific serum IgE levels (IU/mL) are measured using commercially available assay.
Sputum Analysis	Sputum eosinophilic cationic protein is measured as a biomarker of eosinophilic inflammation in the asthmatic airway, urokinase plasminogen activator, and plasminogen activator inhibitor as these may have prognostic value for determining asthma severity. (Barck, Lundahl, Hallden, & Bylin, 2005; Haldar et al., 2008; Kowal, Zukowski, Moniuszko, & Bodzenta-Lukaszyk, 2008).
Self-Reported Measures	
Asthma Knowledge	24-item Self-Management Knowledge Questionnaire; $\alpha = .69$ (Schaffer & Yarandi, 2007)
Asthma Self-efficacy	12-item Self-Efficacy Scale; $\alpha = .86$ (Krieger, Takaro, Song, Beaudet, & Edwards, 2009)
Asthma control	5-item Asthma Control Test™ (ACT); $\alpha = .79-.84$ (M. Schatz et al., 2007; Schatz et al., 2006)
Asthma quality of life	15-item Mini Asthma Quality of Life Questionnaire; $\alpha = .95$ (Juniper, Buist, Cox, Ferrie, & King, 1999; Juniper, O'Byrne, Ferrie, King, & Roberts, 2000)
Functional and health status	12-item Short Form-12v2™; test-retest=.89 (Ware Jr, Kosinski, & Keller, 1996)
Nutritional status	5-item Mini Nutritional Assessment-Short Form®; $\alpha = .65$ (Kaiser et al., 2009),
Medication Risk Assessment	4 item Morisky Scale of medication adherence; $\alpha = .56-.62$ (Morisky, Green, & Levine, 1986) Health Literacy Single Item Screener (SILS); Specificity 83% (Morris, MacLean, Chew, & Littenberg, 2006) CLOX drawing; discriminated between those with Alzheimer's and elderly controls (Royall, Cordes, & Polk, 1998)
Home Environmental Measures	
Volatile Organic Compounds (VOCs)	24-hour sample taken in room that participant spends majority of time (e.g. bedroom) and outside their home. Indoor sample taken 1 meter off floor. Canisters use flow controllers to allow the pre-evacuated canister to fill slowly over a 24-hour period.
Air Particulates	24-hour sample taken in room that participant spends majority of time. Sample taken 1 meter off the floor. Laser particle counter counts particles in .01 cubic foot of air and is calibrated to count small (0.5 microns) and larger (2.5 microns) particles.
Moisture	On-site bathroom(s), kitchen and other areas are assessed as warranted.
Temperature and humidity	24-hour measure of temperature and humidity taken in room participant spends majority of time.
Pests	Visual inspections; traps placed based on visible observations of pest activity.
Home Environmental Checklist	Checklist of 149 items completed by trained observers assessing the building exterior, home interior, and room interior for dust, cleaning, ventilation, moisture, pets, pests, heating and cooling, and hobbies. Visual inspection of kitchen, living room, participant's bathroom, participant's bedroom, and basement (if available).

Table 2

Data collected at baseline, 9 and 18 months

	Baseline	9 months	18 months
ACT™, Asthma QOL, Spirometry; FENO	X ^a	X ^b	X ^b
Skin prick testing; Total and Specific IgE, Vitamin D, Height and weight; baseline demographics	X ^a		
Asthma knowledge; Asthma self-efficacy; SF-12v2; Mini-Nutritional Assessment; participant characteristics	X ^a		X ^b
VOCs; Air Particulates; Moisture; Humidity; Pests; Home Environment Checklist	X ^b		X ^b
Medication Risk Assessment		X ^b	X ^b

Data collection sites:

^aU of L Clinical Trials Unit;^bParticipants' home

Table 3

Recruitment outcomes by recruitment strategy

Recruitment strategy	Initial contacts ^a	Initially screened eligible	EV scheduled ^b	EV completed	Did not meet PFT ^c inclusion criteria	Enrolled	% Enrolled after initial contact ^h	% Enrolled of those initially screened eligible ⁱ
Clinical office referrals	450	117	94	88	20	68	15.1%	58.1%
Media ^d	199	127	101	92	42	50	25.1%	39.4%
Posted flyers	35	18	15	15	8	7	20.0%	38.9%
Paid ads ^f	54	27	21	19	7	12	22.2%	44.4%
Miscellaneous ^g	85	46	40	32	12	21	24.7%	45.7%
Total	823	335	271	246	89	158	19.2%	47.2%

^aIncludes introductory letter, email, phone call, or in-person contact^bEV=Enrollment Visit^cPulmonary Function Testing^dMedia includes press releases, newspaper articles, radio and TV appearances^fPaid ads include ads in newspapers, radio, buses, social media^gMiscellaneous includes referrals from multiple sources such as friends/family of enrolled participants, community health fairs, or unknown^h $\frac{\# \text{ Enrolled}}{\# \text{ Initial Contacts}} \times 100$ ⁱ $\frac{\# \text{ Enrolled}}{\# \text{ Phone Screened Eligible}} \times 100$