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**EXTERNAL VALIDITY OF RANDOMISED CONTROLLED TRIALS IN
ASTHMA:
TO WHOM DO THE RESULTS OF THE TRIALS APPLY?**

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ABSTRACT

Background: Asthma is a heterogeneous disease with a wide range of clinical phenotypes, not all of which may be encompassed in the subjects included in randomised controlled trials (RCTs). This makes it difficult for clinicians to know to what extent the evidence derived from RCTs applies to a given patient. We have calculated the proportion of individuals with asthma who would have been eligible for the major asthma RCTs from the data of a random community survey of respiratory health.

Methods: A postal survey was sent to 3500 randomly selected individuals aged 25 to 75 years. Respondents were invited to complete a detailed respiratory questionnaire and pulmonary function testing. Subjects with current asthma were assessed against the eligibility criteria of the 17 major asthma RCTs cited in the Global Initiative for Asthma (GINA) guidelines.

Findings: A total of 749 subjects completed the full survey of whom 179 subjects had current asthma. A median 4% of subjects with current asthma (range 0 to 36%) met the eligibility criteria for the included RCTs. A median 6% (range 0 to 43%) of subjects with current asthma on treatment met the eligibility criteria.

Interpretation: This study demonstrates that the major asthma RCTs on which the GINA guidelines are based may have limited external validity as they have been performed on highly selected patient populations. The majority of subjects with current asthma on treatment in the community would not have been eligible for these RCTs.

Keywords: asthma, randomised controlled trial, external validity, inclusion criteria, exclusion criteria.

INTRODUCTION

In recent years, clinical decision making has been directed away from the doctor's clinical experience towards a paradigm based on the evidence from randomised controlled trials (RCTs). The results of large RCTs have been translated into guidelines containing evidence-graded recommendations which clinicians are encouraged to accept as the basis of good clinical practice. However RCTs are only able to guide clinical decision making when trials are well designed, have clinically relevant outcome measures and the subjects in the trial are representative of the range of real-life patients managed by the doctor.¹ This last requirement is not always met and it is recognized that older adults, women and ethnic minorities may be underrepresented in RCTs.²⁻⁵ Design considerations often lead to RCTs that are performed in highly selected patient populations such as those with the most typical features of a disease, or those most likely to respond to the intervention being studied. This may be necessary to initially assess the efficacy of an intervention, for example in a phase II clinical trial. However, when these same design considerations are applied to phase III and IV clinical trials, they may result in the exclusion of many subjects in whom treatment may be potentially useful,¹ thereby restricting the generalisability of the trial results.

Asthma is a heterogeneous disease with a wide range of clinical phenotypes⁶ so it is not surprising that there is evidence that many individuals with asthma are not eligible for RCTs due to highly selective inclusion and exclusion criteria.^{7,8} This makes it difficult for clinicians to know to what extent the evidence for the safety and effectiveness of an intervention applies to a given individual. The proportion of individuals with asthma who are eligible for the major asthma RCTs from which the clinical evidence is derived is not known. In this population-based survey of respiratory health, we have determined the proportion of individuals with asthma who would have met the eligibility criteria for the RCTs that form the basis of asthma consensus guidelines.

METHODS

Subjects

Subject data were obtained from the results of the Wellington Respiratory Survey, a detailed survey of respiratory health performed between the years of 2002 and 2005 in Wellington, New Zealand.⁹ Subjects were recruited from a postal questionnaire sent to 3500 individuals randomly selected from the electoral register. Random selection was performed so that equal numbers of questionnaires were sent to men and women within each of five decade age groups between the ages of 25 and 75 years. Subjects who responded to the postal questionnaire were invited to undertake the full survey which included a detailed, interviewer administered questionnaire, pulmonary function tests, chest CT scan, skin prick tests to common allergens, blood tests for eosinophil count and serum immunoglobulin E and a one week peak flow diary.

Pulmonary function testing

Pulmonary function tests were carried out using two Jaeger Master Screen Body volume constant plethysmography units with a pneumotachograph as described previously.⁹ Static and dynamic lung volumes were measured before and after the administration of 400µg of salbutamol via a spacer device. Peak flow readings were recorded by subjects twice daily over a one week period following instruction in the use of a Breath Alert™ peak flow meter (Medical Developments International, Melbourne, Australia). Subjects were not tested within 3 weeks of an upper or lower respiratory tract infection. The survey was approved by the Wellington Ethics Committee and written informed consent was obtained from each subject.

Identification of current asthma

Subjects were identified as having “current asthma” if they

- ♦ reported a doctor diagnosis of asthma and either symptoms of asthma or asthma medication use in the previous 12 months, and/or
- ♦ demonstrated an increase in the forced expiratory volume in one second (FEV_1) $\geq 15\%$ compared to baseline after bronchodilator administration, and/or
- ♦ documented diurnal peak flow variation $\geq 20\%$ in any of the first seven days of recordings.

Symptoms of asthma were wheeze, shortness of breath and wheeze at night or chest tightness at night. A subject with current asthma was identified as having “current asthma on treatment” if they reported use of asthma medication in the previous 12 months.

Identification of RCTs

Asthma RCTs were identified in a systematic manner.¹⁰ To qualify as a trial forming the basis of consensus guidelines, a RCT had to be cited as a reference accompanying a level A or B evidence-graded treatment recommendation in the Global Initiative for Asthma (GINA) Workshop Guideline ‘Global Strategy for Asthma Management and Prevention: 2005 Update’ Chapter 7 part 4A ‘Establish Medication Plans for Long-Term Asthma Management in Adults’.¹¹ Trials had to be RCTs of drug therapy for asthma in adults with at least 400 subjects randomised and have been published in the last 30 years. References were assessed independently by two reviewers (JT, BC). Inclusion and exclusion criteria were obtained from the full text of all qualifying trials.

Analysis

The proportion of subjects with current asthma who met the eligibility criteria for each of the identified RCTs was determined. Where we were unable to determine from our survey data whether a subject met a particular RCT eligibility criterion, the subject was considered to meet that criterion. For example, a RCT may have a criterion that subjects be exacerbation free in the previous two months when our survey recorded only that subjects were exacerbation free in the last three weeks. In this case, all subjects who were exacerbation free for three weeks were considered to meet this criterion and remain potentially eligible.

The sponsor had no involvement in the study design, collection, analysis or interpretation of data, the writing of the report or the decision to submit for publication.

RESULTS

A total of 2319 subjects responded to the postal survey, representing a response rate of 78%. Of these respondents, 749 subjects completed the detailed questionnaire and satisfactory pulmonary function testing and form the study group (Figure 1). Compared to the 1570 survey respondents who were not included in the study group, the study group had a higher rate of physician diagnosed asthma (23.1% vs. 17.3%), were more likely to be male (53.7% vs. 44.3%) and ex-smokers (41.4% vs. 35.3%). There were no significant differences in the prevalence of physician diagnosed chronic bronchitis or emphysema.

Of the 749 subjects in the study group, 179 (24%) met our criteria for current asthma and 127 (17%) met our criteria for current asthma on treatment. Amongst the 179 subjects with current asthma, there were 67 who also met the criteria for chronic obstructive pulmonary disease (COPD) defined as an FEV₁/FVC ratio <0.7 post-bronchodilator.¹² Of these 67 subjects, 29 had a tobacco cigarette history of >10 pack years. The characteristics of the subjects with current asthma are presented in Table 1.

TABLE 1:
Characteristics of subjects with current asthma (n=179)

	Mean (SD)
Age	55.2 (13.6)
FEV ₁ pre bronchodilator as a percentage of predicted	77.8 (21.8)
	N (%)
Female sex	87 (49)
Smoker*	54 (30)
Doctor diagnosis of asthma	137 (77)
Current symptoms [†]	122 (68)
Any asthma medication use in the previous 12 months	127 (71)
Inhaled corticosteroid use in the previous 12 months	93 (52)
Inhaled short acting beta agonist use in the previous 12 months	114 (64)
Chronic obstructive pulmonary disease [‡]	67 (37)
Peak flow variability ≥20%	61 (34)
Bronchodilator reversibility ≥15%	43 (24)

FEV₁: forced expiratory volume in one second

* Current or ex smoker with more than 10 pack-years cigarette smoke exposure.

[†] Wheeze, shortness of breath and wheeze at night or chest tightness at night in the last year.

[‡] Defined as a FEV₁/forced vital capacity ratio <0.7 after bronchodilator.¹²

There were 215 individual references in the relevant chapter of the GINA guidelines from which 17 qualifying RCTs were identified and included in the analysis (Figure 2).¹³⁻²⁹ The characteristics of the included RCTs are given in Table 2. The number of subjects screened was stated in 8 of the 17 RCTs included in the analysis.

**TABLE 2:
Characteristics of included RCTs**

Reference	Year	Number of subjects screened	Number of subjects randomised	Age range (years)	Interventions
13	1994	Not stated	429	18+	salmeterol/BDP vs. higher-dose BDP
14	1996	990	738	17+	salmeterol/BDP (2 different salmeterol doses) vs. higher BDP
15	1997	1114	852	18-70	formoterol/budesonide vs. budesonide (2 different budesonide doses in each group)
16	1998	Not stated	473	18-70	budesonide (4 different doses) vs. placebo
17	1998	Not stated	747	6-65	BDP vs. theophylline
18	1998	Not stated	539	12+	salmeterol vs. albuterol
19	1999	Not stated	642	15+	montelukast/BDP vs. montelukast vs. BDP vs. placebo
20	2000	592	451	12+	fluticasone vs. zafirlukast
21	2000	Not stated	447	15+	salmeterol/fluticasone vs. montelukast/fluticasone
22	2001	Not stated	525	12-75	omalizumab vs. placebo
23	2001	Not stated	948	15+	salmeterol vs. montelukast
24	2001	2525	1970	12+	formoterol/budesonide vs. budesonide vs. placebo and formoterol/budesonide vs. budesonide (2 different budesonide doses in each group)
25	2003	494	467	15+	formoterol/budesonide vs. higher-dose budesonide
26	2003	Not stated	7241	5-66	budesonide vs. placebo
27	2003	1192	889	15-75	montelukast/budesonide vs. higher-dose budesonide
28	2003	1168	806	15+	salmeterol/fluticasone vs. montelukast/fluticasone
29	2003	846	639	18-70	montelukast/budesonide vs. budesonide

BDP: Beclomethasone dipropionate

Inclusion criteria used in all 17 RCTs were: a diagnosis of asthma, age greater than a lower age limit and bronchodilator reversibility. Other inclusion criteria were: a specified FEV₁ range in 16, specified inhaled corticosteroid use in 12, specified symptoms or rescue medication use in 9, age less than an upper age limit in 7, peak flow variability in 4 and other inclusion criteria in 4 RCTs. Exclusion criteria used were: recent respiratory tract infection or asthma exacerbation in 13, potentially confounding medication use in 11, comorbid conditions in 9, more than a specified amount of smoking in 7, pregnant or lactating female subjects in 5 and other exclusion criteria in 6 RCTs.

The proportion of subjects with current asthma who met the eligibility criteria for these 17 RCTs ranged from 0 to 36% with a median of 4% (Table 3). The proportion of subjects with current asthma on treatment who met the eligibility criteria for these trials ranged from 0 to 43% with a median of 6% (Table 3).

TABLE 3:
Percentage of individuals who potentially meet eligibility criteria for included asthma RCTs

RCT reference	Current asthma (%) n=179	Current asthma on treatment (%) n-127
13	5	7
14	7	10
15	6	9
16	6	8
17	0	0
18	4	6
19	2	3
20	1	1
21	7	9
22	8	11
23	7	9
24	36	43
25	2	2
26	1	0
27	1	2
28	2	3
29	3	5

The proportion of subjects with current asthma who did not meet common eligibility criteria is shown in Table 4. The most selective criterion was bronchodilator reversibility which excluded either 71% or 76% of subjects with current asthma, depending on whether 12% or 15% reversibility in FEV₁ was required. The requirement for peak flow variability of $\geq 20\%$ resulted in the exclusion of 66% of subjects with current asthma.

TABLE 4:
Selectivity of eligibility criteria

Criterion	Percentage of subjects with current asthma excluded (%)
Bronchodilator reversibility $\geq 15\%$	76
Bronchodilator reversibility $\geq 12\%$	71
Peak flow variability $\geq 20\%$	66
FEV ₁ $\geq 50\%$ and $< 80\%$ of predicted	61
Inhaled corticosteroid use	48
Less than 10 pack-years cigarette exposure	31
Active symptoms or use of rescue medication	20
FEV ₁ $\geq 50\%$ of predicted	12

DISCUSSION

This study demonstrates that the major asthma RCTs have been performed on highly selected patient populations with a median of only 4% of subjects with current asthma in our community being eligible. Similarly, a median of only 6% of subjects with current asthma on treatment would have been eligible for these RCTs. These findings suggest that although the treatment recommendations of major asthma guidelines have a strong scientific evidence base, they may be limited with respect to the external validity of the RCTs from which they are derived.

We made no attempt to perform a complete search of the asthma literature and it is likely that RCTs have been reported elsewhere that are more inclusive of subjects with current asthma than those examined. However the RCTs selected here are those that provide the evidence for the treatment recommendations of the GINA guidelines¹¹ so have a direct impact on asthma management worldwide. Using actual RCTs rather than a hypothetical 'typical' RCT⁷ has allowed a realistic estimate of the degree of selectivity of existing asthma trials. It also allows comparison of the degree of selectivity between different asthma medications or medication indications. For example, there was only one qualifying RCT comparing theophylline to another agent for which none of the 179 subjects with current asthma in our study were eligible.¹⁷

We were not always able to determine from our survey data whether a subject with asthma met a particular criterion or not as many trials used criteria for exacerbations, symptom scores and measures of medication use that we were not able to duplicate. Where this occurred, subjects were deemed to remain eligible by the criterion we could not assess. Hence our estimates of the proportion of subjects with asthma eligible for a given trial are maximum values and the true degree of selectivity of these RCTs is probably greater than we have shown.

Our definition of asthma did not exclude those with concomitant COPD, defined as a post-bronchodilator FEV₁/FVC <0.7.¹² About a third of the asthma subjects met these criteria, most of whom did not have a significant smoking history. As a result it is likely that this group with concomitant COPD was predominantly made up of subjects with asthma who had developed an irreversible component to their airways obstruction. Importantly, they represented a group of subjects that had mostly received a doctor's diagnosis of asthma and had been prescribed asthma treatment based on trials that largely excluded them.

The most common reason subjects with current asthma were not able to meet RCT eligibility criteria was the need to demonstrate bronchodilator reversibility. Application of this criterion resulted in only about a quarter of subjects with current asthma in our survey being eligible for the RCTs included in the study. This proportion was greater than that observed from a similar study from Australia in which only 7 to 18% of subjects with current asthma demonstrated bronchodilator reversibility depending on the criteria used.³⁰ These observations are likely to be due to the widespread use of inhaled corticosteroid therapy, resulting in good asthma control and associated reduction in lung function variability in asthma. The use of bronchodilator reversibility criteria in asthma RCTs may be justified on the basis that it provides the greatest opportunity to determine the maximum efficacy of a therapeutic agent. It also identifies individuals who do not have optimal asthma control, and as a result could be considered suitable for the addition of another

therapeutic agent. This has led to novel study designs in which subjects reduce or withdraw their inhaled corticosteroid therapy to demonstrate unstable asthma and its associated lung function variability.^{31,32}

Other eligibility criteria, such as the requirement that subjects be non-smokers, also tend to produce a more homogenous study population. This has the advantage of reducing the likelihood of a subject having concomitant COPD and limiting the number of variables aside from the RCT intervention, again maximizing the likelihood of demonstrating a therapeutic effect specific to asthma. However, the criterion that subjects be non-smokers resulted in the exclusion of 30% of the subjects with current asthma in our study, representing a major group in which drug efficacy would not have been assessed. The importance of this limitation is evident from the experience with inhaled corticosteroids in asthma where the studies showing a reduced efficacy of inhaled corticosteroids in smokers were not undertaken until more than 25 years after the introduction of these agents.^{33,34}

In our study group, the prevalence of wheezing and physician diagnosed asthma was relatively high, with rates of 28.8% and 23.1% respectively. These findings reflect the high prevalence of asthma in the New Zealand population, consistent with previous surveys which have reported rates of wheezing between 26 and 30%.³³⁻³⁵ Due to the high survey response rate and the similarity between survey responders and the study group which undertook the investigative procedures, any effect of non-response bias is likely to be small.

In summary, we conclude that the degree to which the results from asthma RCTs apply to individual patients cannot be assessed directly and the clinician can not assume that their patient will respond to a medication in the same way as trial subjects. As a result, clinicians should consider that the treatment recommendations of major asthma guidelines may be limited with respect to the external validity of the RCTs on which they are based. This does not mean that the results of these RCTs are not generalisable to the wider community of individuals with asthma, but rather that the degree of generalisability is uncertain. We encourage the inclusion of a wider range of subjects with asthma in future clinical trials.

Conflict of Interest

Richard Beasley is a member of the GINA Assembly.

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FIGURE 1: Flow diagram for the Wellington Respiratory Survey

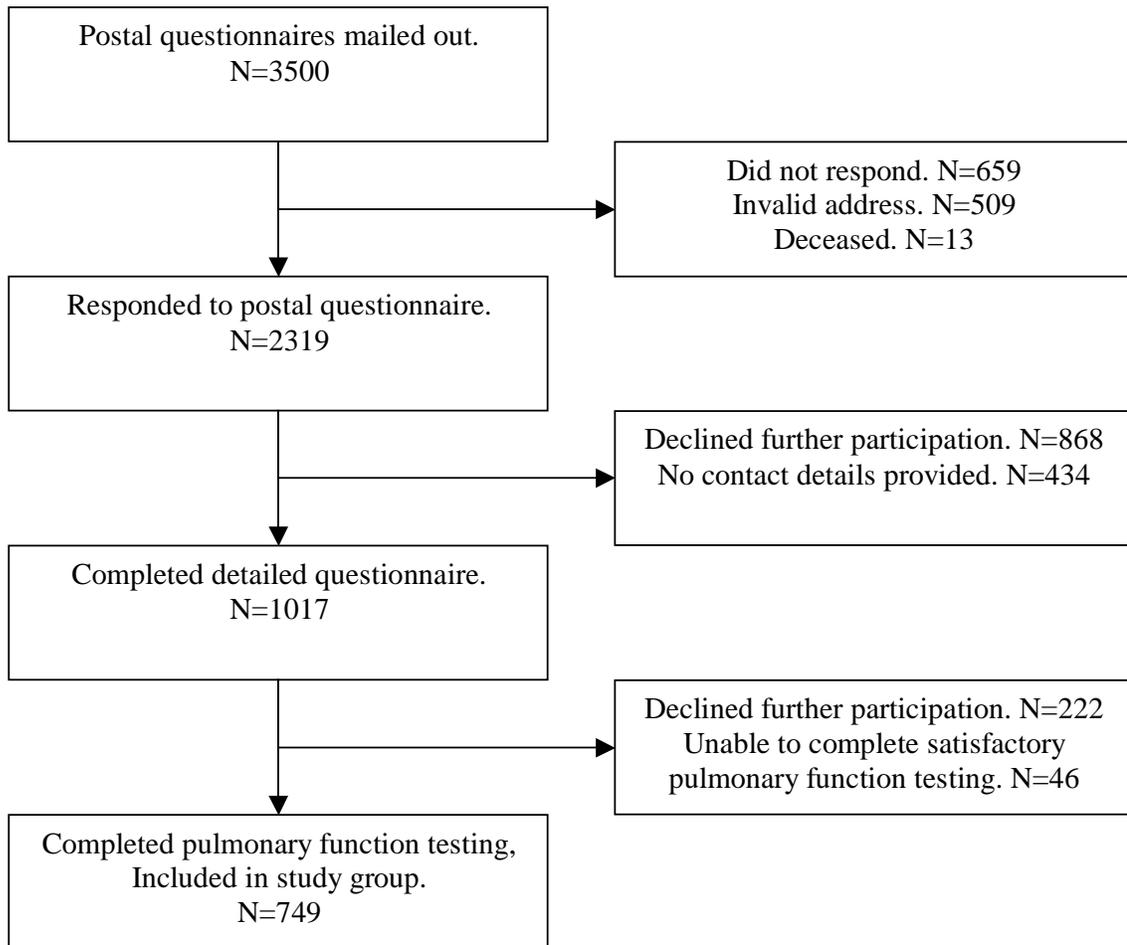
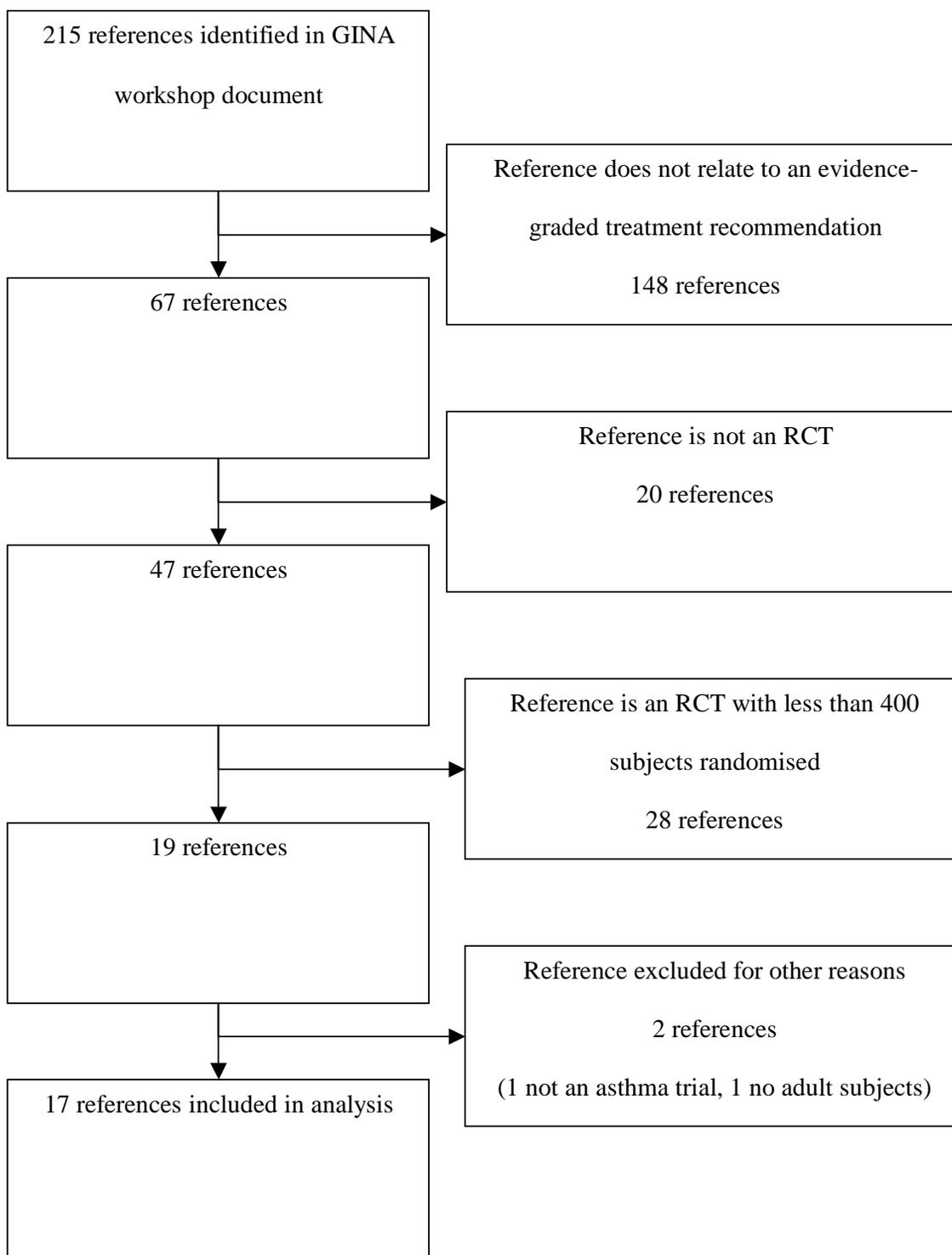


FIGURE 2: Flow diagram for selection of RCTs



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Figure 1: Flow diagram for the Wellington Respiratory Survey

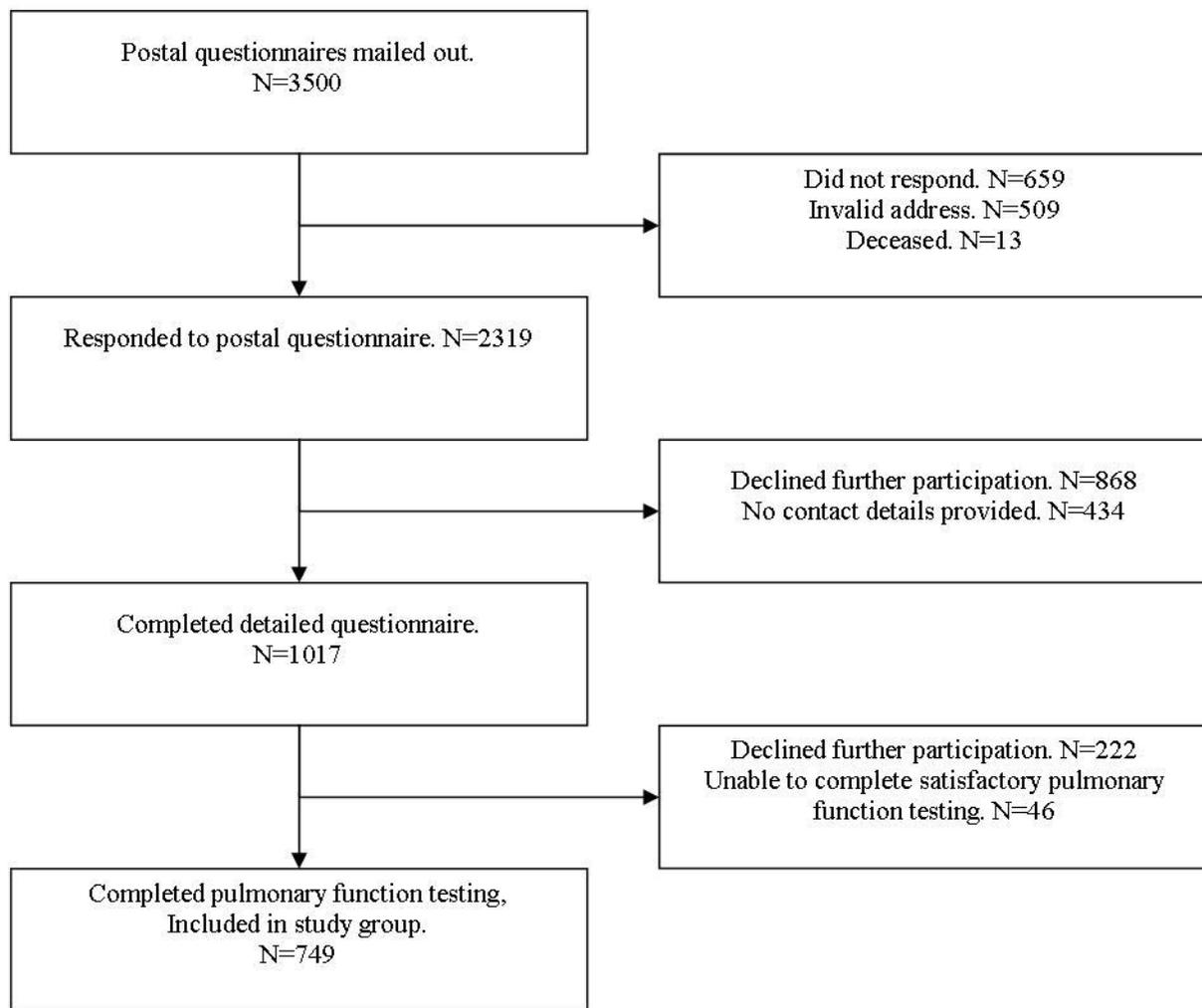


Figure 2: Flow diagram for selection of RCTs

