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Extended diagnostic criteria used for indirect challenge testing in elite asthmatic swimmers.

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Published in:
Respiratory Medicine

DOI:
10.1016/j.rmed.2011.09.011

2012

Variability and direct positivity in provocation testing of elite asthmatic swimmers.

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Keywords: Adolescence, Exercise, Swimming, Questionnaire, Asthma, Respiratory symptoms, Mannitol provocation test, Exercise provocation test.

Acknowledgements: This study was supported by funding from Skane county council´s research and development foundation and independant grants from Astra-Zeneca, Schering-Plough and MSD. Following companies providing material for the study; Niigard Pharma (Mannitol tests), Airocrine (NO measurement), Medikro (Spirometers), ALK (Skin prick test). The authors are truly grateful for the tremendous work done by Caroline Silwer, Ann-Mari Ohrberg, Boel Diwall. A special thanks to the swimmers and leaders from MKK, RAN and VNSK.

Author contributions: KR contributed to the design of the study, data collection, data interpretaton and writing the manuscript. ET contributed to the design of the study, data interpretation, and writing the manuscript. LB contributed to the design of the study, data interpretation and writing the manuscript

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Abstract

The **aim** of the study was to investigate the prevalence of asthma with or without exercise induced symptoms among elite swimmers and to compare sport specific exercise provocation with mannitol provocation. **Methods:** 101 adolescent swimmers were investigated with mannitol provocation and sport specific exercise challenge test. Mannitol positivity was defined as either direct FEV_1 PD15 (ordinary criteria) or as β_2- reversibility $\geq$15% after challenge (extended criteria). A direct positive exercise test was defined as a drop in FEV_1 of 10% (ordinary criteria) or a difference in FEV of $\geq$15% either spontaneous, variability, or with β2-agonist, reversibility (extended criteria). **Results:** We found a high prevalence of mannitol and/or exercise positivity. Twenty-six swimmers were mannitol direct positive and 14 were direct exercise positive using ordinary criteria. Using extended criteria 43 were mannitol positive and 24 were exercise positive. When including reversibility and variability to define a positive test the sensitivity for current asthma with or without exercise induced symptoms increased while the specificity remained roughly unchanged. Direct positivity for mannitol and exercise poorly overlapped using ordinary criteria but improved using extended criteria. **Conclusion:** We found a high prevalence of asthma among elite swimmers. The use of variability and reversibility (liability) as additional criteria to define a positive test provided to our mind relevant information and should be considered.

Introduction

Asthma and allergies are common diseases and have increased during the last four decades especially among children and adolescents([1]).Strenuous physical exercise on elite level may represent a risk factor for asthma development([2]). The degree of risk is intimately connected to the type of exercise and the environmental factors connected to the particular form of sport. It has been shown that swimming represents a significant risk for asthma development([3]) and large number of swimmers develop increased bronchial hyperresponsiveness to methacholine([4],[5]). The chlorinated pools and exposure to chloramines is believed to be one important pathogenetic factor and there is a clear association with degree of and duration of exposure to chloramines and hyperresponsiveness and inflammation of the lower airways([6],[7]).It is also known that swimmers have an increased susceptibility to airborne allergens([8]).

The diagnosis of asthma in athletes have been under debate during the last years. The use of indirect tests has been advocated as it is believed that indirect provocation tests, in contrast to direct tests like methacholine, better reflects airway inflammation. On one hand, test sensitivity and specificity has been questioned, especially as many athletes that are well controlled with their asthma medication do not respond to exercise or dry air provocation. On the other hand, a positive methacholine challenge test does not predict that the subject necessarily benefit from anti-asthma treatment. In a study on skiers with asthma symptoms and positive methacholine test, three months on Budesonide (800µg per day) had no effect on the disease([9]). Thus asthma in different athlets may have a different pathophysiology, i.e different endotypes([10]) and it is thus necessary to identify those that may benefit from antiinflammatory treatment. Exercise challenge test has earlier been shown to identify exercise-induced asthmatic patients that benefit from anti- inflammatory treatment. The degree of fall in the test was proportionate to the inflammation intensity in induced sputum([11]). Recently, mannitol challenge has been proposed as an alternative indirect test to confirm the presence of exercise induced asthma([12])and studies of elite summer athletes and skiers have been performed ([13],[14]). Whether the test is suitable as a diagnostic tool in all kind of athletes with an aetiology different than allergy still has to be studied.

The aim of this study was to investigate the freqency of exercise induced bronchoconstriction in elite aspiring swimmers. A second aim was to compare indirect testing with mannitol to a sport specific exercise challenge test. The aim was also to relate these results to symptoms and disease history.

Materials and Methods

Subjects

In 2008, swimmers were recruited from elite groups in the southwestern part of Sweden. 101 swimmers, 55 male and 46 female, 13-24 years, training volume 10-30 h/week were included in the study.(Table 1)

Study design

The swimmers were tested at two different days at least one week apart. During the first day, the subjects answered a questionnaire and a physical examination including skin prick test, FENO was done. The mannitol provocation test was perfomed during the fist test day and the sport specific exercise test on the second.

Questionaire: The swimmers were asked about presence of respiratory symptoms, allergic symptoms and life style factors as previously described[3]. The questionaire was self filled in and complemented by an interview.

Exercise induced symptoms was defined as dyspnea, wheezing or severe cough adjacent to physical activity.

Current asthma was defined as report of symptoms such as wheezing and/or nocturnal symptoms without respiratory infection during the past 12 months.

Current asthma with exercise induced symptoms was defined as current asthma with wheezing or coughing and chest tightness adjacent to physical activity.

Exacerbations was defined as either emergency room visits or periods with more accentuated symptoms that required an increase in medication durring the last 12 motnhs.

Current rhinitis was defined as report of symptoms as sneezing, runny, or blocked nose without concommitant respiratory infection.

Rhinitis with impact on daily living was defined as a current rhinitis which affected the swimmers in their daily lives.

Allergy testing: All subjects were skin prick tested with a panel of airborn allergens, i.e pollen (birch, timothy, mugwort), pets (cat, dog, horse), mould (*Claudosporium and Alternaria*) and house dust mite *(D. pteronyssinus and D. Farinae)*. A test was considered positive if the weal was ≥ 3 mm.

Exhaled Nitric Oxide was measured by a handheld device (NIOX Mino, Aerocrine, Sweden) according to the ATS and ERS recommendations with an exhaled flow rate of 50 ml/s([15]).

Mannitol challenge test: The test was performed in all subjects in the swimming pool arena. Mannitol (Aridol™, Pharmaxis®) was inhaled in incremental doses until a maximal cumulative dose of 635 mg was reached or a drop in FEV_1 of 15%. A flow volume spirometry (Spira2000, Finland) was performed at baseline and 60 s after each dose. After 30 minutes a new spirometry was done and the swimmers inhaled terbutaline (1 mg) followed by a spirometry after another 30 minutes. A positive test, $PD15_{Mann}$, was defined as a drop in FEV_1 of ≥15% of baseline. $PD15_{Mann}$ was defined as the cumulative dose of mannitol giving rise to a 15% fall in FEV_1. Positive reversibility was defined as an increase in FEV_1 ≥15% compared to FEV_1 after provocation.

Exercise challenge test: For the sport specific exercise test both males and females were swimming 600 m during 6-8 minutes. During the first 2 minutes a pulse rate of about 150 was held, and during the remaining 4-6 minutes a pulse rate ≥90% of maximal capacity was aimed. The pulse was checked during the race by a Polar water-proof puls watch (Polar RS 400) and checked manually after 300m, 400m, 500m and at the end of the test. Flow-volume spirometry measuring FEV_1 and FVC was performed before the start. FEV_1 was meassured immediately after finishing the lap (about one minute after the exercise) and then 5, 10, 15, and 30 minutes after the race. The subjects then inhaled 1 mg terbutalin and a new spirometry was performed after another 30 minutes. A positive test was defined as a drop in FEV_1 of ≥10% from baseline (=Exerc 10%). A positive variability was defined as drop of FEV_1 from the highest FEV_1 ≥ 15% and a positive reversibility was defined as an increase in FEV_1 ≥15% compared with the lowest value after provocation.

The Trichloramine content of the air was measured ([16],[17]) at two different occasions both at 50 cm above water line and in the surrounding area in the swimminghall.

Statistics

SPSS (SPSS Inc., Chicago, IL) was used for statistical analysis. All data is given as median (IQR), unless otherwise stated. Chi-square test was used for group comparisons. Spearmans correlation was used for relationship between the various tests concerning both direct fall and reversibility. A p-value of <0.05 (two tailed) was considered significant.

RESULTS

Study population

Study population is described in Table 1. Fifty-four swimmers were skin prick test positive, 13 were positive to a single antigen and the others had multiple sensitizations.

Swimmers with a training history more than 6 years were more likely to have a physician diagnosed asthma ($p=0.028$).

Mannitol provocation test

The mannitol provocation test was performed on all 101 swimmers. Twenty-six subjects had a positive test defined as a drop in FEV_1 of ≥15%. After inhalation of terbutaline, 41 of the swimmers were reversible ≥15% compared to their lowest value post mannitol (Fig 1). When the criteria for a positive test was extended and defined as a drop of 15% compared to baseline ($PD15_{Mann}$) and/or a reversibility in FEV_1 of ≥15% from the lowest to the highest value after terbutaline post challenge ($PD15_{Mann}$ +Rev 15%) an additional 17 swimmers had a positive test, giving a total of 43 swimmers with a positive test with extended criteria. (Table 2)

The swimmers with a positive mannitol provocation test under ordinary criteria ($PD15_{Mann}$), had significantly more current asthma ($p=0.010$), current asthma with exercise induced symptoms ($p=0.02$) and rhinitis with impact on daily living ($p=0.048$). When extending the criteria and comparing swimmers with a positive mannitol provocation test and/or reversibility ($PD15_{Mann}$ +Rev 15%) with those who had a negative test there was a significant difference in current asthma ($p=0.008$), current asthma with exercise induced symptoms ($p=0.005$) and rhinitis with impact on daily living ($p=0.005$). Regarding exacerbations and respiratory symptoms during exercise there were no significant differences. When using 20% as reversibility as extended criteria the significance stayed, current asthma ($p=0.004$), current asthma with exercise induced symptoms ($p=0.004$) and rhinitis with impact on daily living ($p=0.024$). (Table 3)

Exercise challenge test

The exercise test was performed by 97 of the swimmers. Fourteen subjects had a 10% drop of FEV_1 compared to baseline during the first 30 minutes after the exercise (Exerc 10%). After inhalation of terbutaline, 17 of the swimmers improved FEV_1 ≥15% compared to their lowest value post exercise (referred to as reversibility, Fig 2). Six of the swimmers had a higher FEV_1 just after the exercise test and then dropped ≥15% compared to the highest value (referred to as variability, Fig 2). When criteria for a positive test was extended and defined as either a drop of 10% compared to baseline, and/or a reversibility and/or variability of ≥15% (Exerc 10%+Rev 15%), a total of 24 subjects had a positive challenge test. (Table 4)

When comparing the swimmers with a positive exercise (Exerc 10%), ordinary criteria, with the swimmers who had a negative test there were no significant differences between the groups. When comparing swimmers with a positive exercise test due to extended criteria with those who had a negative test, there was a significant difference for current asthma (p=0.026) and for current asthma with exercise induced symptoms (p=0.007) but no other significant difference.(Table 5)

When using reversibility 20% instead of 15% as extended criteria, there was no significant difference for current asthma between the swimmers with only a direct fall (Exerc 10%) to those who had a positive test due to extended criteria (Exerc 10%+Rev 20%).

Sensitivity and specificity of mannitol test vs clinical characteristics (Fig 3)

When using ordinary criteria to define a positive test ($PD15_{Mann}$) the sensitivity of the test for detecting current asthma and asthma with exercise induced symptom was 35.0 and 35.2. When using extended criteria ($PD15_{Mann}$+Rev 15%) the sensitivity increased to 53.3 and 61,1. The specificity drops for current asthma from 80.8 to 74.4 and nothing at all for asthma with exercise induced symptoms. When comparing ordinary ($PD15_{Mann}$) to extended criteria ($PD15_{Mann}$+Rev 15%) the sensitivity for exacerbations increased from 29.4 to 53.0. The specificity was low and increased from 19.2 to 20.9.

For detecting current rhinitis the sensitivity of the test was low 31.1 with ordinary criteria and increased to 46.7 when using extended criteria while the specificity dropped from 53.9 to 48.8. For detection of rhinitis with impact on daily living the sensitivity of the test was also low 36.8 when using extended criteria ($PD15_{Mann}$+Rev 15%) the sensitivity increased to 60.5 and the specificity remained the same.

The sensitivity for detecting a FENO-value ≥20 was increased from 31.6 to 52.6 when using extended criteria instead of ordinary criteria while the specificity stayed the same. Using reversibility 20% instead of 15% made only marginal difference in specificity but lowered the sensitivity in all parameters.

Sensitivity and specificity of exercise test (fig 4)

When using ordinary criteria to define a positive test (Exerc 10%) the sensitivity of the test for detecting current asthma and exercise induced symptoms was even lower 17.2 and 17.0. When using extended criteria (Exerc 10%+Rev 15%) the sensitivity increased to 32.8 and 32.1) while the specificity increased for current asthma from 66.7 to 79.2 and for asthma with exercise induced symptoms from 64,3 to 70.8.

Both the sensitivity and specificity for exacerbations were low and using extended criteria made no significant difference. The sensitivity for the tests increased from 23.5 to 29.4 while the specificity dropped from 28.6 to 20.8. For detection of current rhinitis and rhinitis with impact on daily living both the sensitivity and specificity were low, 18.6 and 57.1 respectively 16.7 and 42.9, and increased only marginally when using the extended criteria.

The sensitivity, 5.3 and specificity, 7.1 for detecting a FENO-value ≥20 were very low in the exercise test. When using extended criteria the values were still very low but increased to 16.7 for sensitivity and 21.1 for specificity.

Using reversibility 20% instead of 15% as extended criteria made no difference compared to using reversibility 15% in any of the parameters.

Mannitol vs Exercise challenge (Fig5)

Ninety-seven of the 101 subjects performed both provocation tests. When using the ordinary criteria ($PD15_{Mann}$ and Exerc 10%) only five of the swimmers were positive in both tests (Fig 4a). When using extended criteria ($PD15_{Mann}$+Rev15% and Exerc 10%+Rev15%), eight of the swimmers were positive in both tests (Fig 4b). When using ordinary criteria for both tests ($PD15_{Mann}$+Exerc 10%), 34 of the swimmers with current asthma were not identified (Fig 4c). Eight of those were on regular treatment with ICS. Nine of 33 swimmers had a positive test (five in mannitol provocation test and four in exercise test) without having current asthma. When using extended criteria ($PD15_{Mann}$ +Rev15% and Exerc 10%+Rev15%) among subjects with current asthma, 14 were positive in both tests, but 20 current asthma subjects were not identified (Fig 4d). Also in this group eight were treated with ICS regularly, and 15 of 53 with a positive test did not have current asthma.

There was a significant correlation between $PD15_{Mann}$ value and the degree of reversibility in both mannitol provocation test ($p<0.001$, $r=0.525$) and exercise test ($p=0.035$, $r=0.216$) among all the swimmers. The FEV_1 drop in the exercise test also had a significant correlation to the degree of reversibility in the exercise test ($p<0.001$, $r=0.492$), but not in the mannitol provocation test ($p=0.12$). However, there was a significant correlation between the degree of reversibility in the mannitol provocation test and degree of reversibility in the exercise test ($p=0.003$, $r=0.298$).

Relation to atopy

In the exercise test nine out of fourteen who were positive with ordinary criteria were atopic and with extended criteria the number was 16 out of 24. In the mannitol test there were no significant difference in atopy, for ordinary criteria, 14 out of 26 and for extended criteria 25 out of 43 were atopic. The swimmers with a positive skin prick test had a significant higher FENO level ($p=0.021$).

Trichloramine measurement

The trikloramine values were independent of if the measurements were made just above the water surface or if they were taken at some distance from the poolside. The values were also similar when comparing the test day (330, 290 ug/m^3) to a normal training day (320, 300 ug/m^3).

Discussion

The main finding in this study is the high frequency of positive provocation tests, more frequent for the mannitol provocation test than for the exercise test. Despite the relatively high frequency of positive tests many of the swimmers with asthma symptoms were test negative when ordinary criteria for mannitol provocation test and a drop of FEV_1 ≥10% for exercise provocation test were used.

The swimmers have a high frequency of asthma as previously shown ([3]). One underlying cause is chloramine. In our study all the swimming pools were chlorinated and the swimmers spent a lot of time in this special environmental also besides training hours. The quality of the air in the swimming pool arena together with the hyperventilation during long training sessions leads to a great burden on the respiratory epithelium. Exposure to a chlorinated pool environment is known to increase the risk of asthma development ([6]). Tri-chloramine, a highly volatile product, reacts with the respiratory epithelium disturbing the integrity of the respiratory mucosa ([18]) This is indicated by reduced serum Clara Cell protein (CC16) levels which has been reported not only from active swimmers, but also pool-workers spending their time in the pool arenas ([19]). In a previous paper we have discussed the increased excretion of Clara cells protein during exercise test suggesting an epithelial stress not found during the mannitol provocation test ([20]).

Earlier studies have previous shown a mismatch between reported symptoms of breathing problems related to exercise and outcome of challenge tests under laboratory conditions([21,22]). Contributing factors to this could be difficulty to reach sufficient load during the tests due to both poor running technique and the athlete's high level of fitness. The environment in which tests are performed is also not consistent with the athlete's training surroundings and may also influence the results.

Our goal of this study was to conduct exercise tests in the swimmers training environment and compare it with a mannitol provocation a challenge test that is easy to conduct in primary care settings and does not require expensive investments. The mannitol provocation test has the advantage of being a standardized test and easy to perform. However, it might have the disadvantage that it does not take into account the athlete special environment, which is however done in this study.

In our study both the exercise and the mannitol provocation showed little overlap with reported exercise induced respiratory symptoms (EIS). This is also in agreement with other studies. In a study by Parson on 107 college athletes they found 39% hade a positive EIB response after euchapnic hyperventilation (EVH). No association was found between EIS and EIB in there study ([23]). One contributing factors to these observations could be that the symptoms reported are not only caused by asthma but also due to other causes such as exercise induced laryngeal obstruction (EILO), hyperventilation and training above or at their maximum capacity. In both tests the conformity was better both for current asthma and current asthma with exercise induced symptoms.

The exercise test in our study showed, compared to the mannitol test, lower frequency of positive exercise test, defined as exercise induce bronchoconstrion (EIB), and less consistency with current asthma and current asthma with exercise induced symptoms. One explanation is the favorable environment in the swimming pool area. It is well established that inhalation of warm moist air protects against bronchoconstriction ([24]). Other explanations may be the breathing pattern. Some of the swimmers had a somewhat different lung function response after the exercise test, compared to what is usually seen after a common treadmill provocation. Some swimmers do not hyperventilate during their training or race. The breathing pattern is more like intermittent deep inspirations and they start to hyperventilate after exercise. Fifty-four of the swimmers had a FEV1 higher after provocation, median 7.5 (IQR 4-12), giving rise to a variability but only one had a variability >15% without having a reversibility >15%. When performing the test in the pool there is a difficulty in obtaining sufficiently high work load and keep it for a sufficiently long time. When interviewing the swimmers, they reported they often use their legs only during the start, the turns and finish, even during competition, not to get to much lactic acid, and might therefore not get sufficiently high load due to using mainly their arms during the test. We aimed to ensure a sufficient a work load by using Polar® waterproof pulse watch during the race and regularly checking pulse rate each 100 m. Seventy-five procent of the swimmers reached 90% of their HRmax or more (median 190, IQR184,195)

Both the mannitol tests and especially the exercise test showed a low sensitivity to detect swimmers with asthmatic symptoms. One way to increase the tests ability to relate to swimmers with current asthma and other factors associated with disease activity could thus be the use of reversibility and/or variability as complementary test criterias. This was most clearly shown for the mannitol provocation test where the sensitivity for detecting current asthma, asthma with exercise induced symptoms and rhinitis with impact on daily living increased while the specificity decreased only slightly or remained unchanged. The difference for the exercise test was not as obvious. This can partly be exlained by the assumed lower sensitivity in our study with overall fewer positive tests. There were no differences in the clinical characteristics between the swimmers who were mannitol or exercise positive and those who were reversible 15% in the different tests. The swimmers positive in both tests with extended criteria were the swimmers with most pronounced symptoms. A much higher agreement between the two tests was achieved when reversibility and/or variability were included in the criteria, and even more pronounced among the swimmers with current asthma.

When only using ordinary criteria defined as a direct bronchoconstricitve response either as $PD15_{Mann}$ or Exerc 10%, there is a high risk of not detecting patient with clinically relevant asthma symptoms and missing the patients who could benefit from a proper diagnosis and treatment. In this age group there is a high risk of developing asthma and in our study we found a tendency for the swimmers to misinterpret their symptoms. Despite that several of the swimmers have asthmatic symptoms and positive tests they did not report and understand that their breathing difficulties were symptoms of asthma but thought it was due to lesser physical fitness. Other swimmers symptoms of asthma but had negative tests. For eight of the swimmers this was probably due to their regular treatment with inhaled corticosteroids (ICS).

In clinical work with athletes in terms of both exercise and elite activities, it is important that we have the tools that are sensitive enough to capture the asthmatics that would benefit from asthma treatment. We also have to inform and to educate the trainers and teachers so they are aware of the different ways of expression of asthma related problems since some of the athletes do not recognize the symptoms. It is also important to capture those whose respiratory symptoms are not due to asthma and to help them with proper treatment. This area requires more research.

In this study the swimmers had a lower FENO than one would expect regarding their sensitization rate and their symptoms. This has earlier been reported in studies including swimmers and an epithelial damage has been discussed as a possible cause (**Error! Bookmark not defined.**). Another explanation could be that high FENO usually is associated with an eosinophilic airway inflammation while swimmers have been reported to have a more neutrophilic inflammation. ([25]).

In summary, using the ordinary criteria, there is a risk of missing patients with asthma symptoms who could benefit from a proper diagnosis and treatment. Using extended criteria in the interpretation of the tests gives us greater ability to detect asthma in elite swimmers while the increased risk of misdiagnosis stays low.

A high number of our swimmers had one or two positive challenge tests and the majority were symptomatic. This clearly show that swimming at least in a chlorinated pool environment is a definite risk factor for asthma development. It is thus very important to carry out regular controls of the pool environement and to reduce future risk exposure.

Figure legends

Figure 1

Illustration of direct positivity after mannitol provocation defined as a drop in FEV_1 of ≥15% from baseline after inhalation of cumulative doses of mannitol ≤ 635 mg (ordinary criteria) vs reversibility defined as an increase ≥15% from lowest to highest FEV_1 value after inhalation of 1 mg terbutalin (extended criteria).

Figure 2

Illustration of direct positivity after exercise challenge defined as a drop in FEV_1 of ≥10% from baseline (Exerc 10%; ordinary criteria). Reversibility; an increase ≥15% from lowest to highest FEV_1 value after inhalation of 1 mg terbutaline and variability; a drop ≥15% from highest to lowest FEV_1 value (extended criteria).

Figure 3

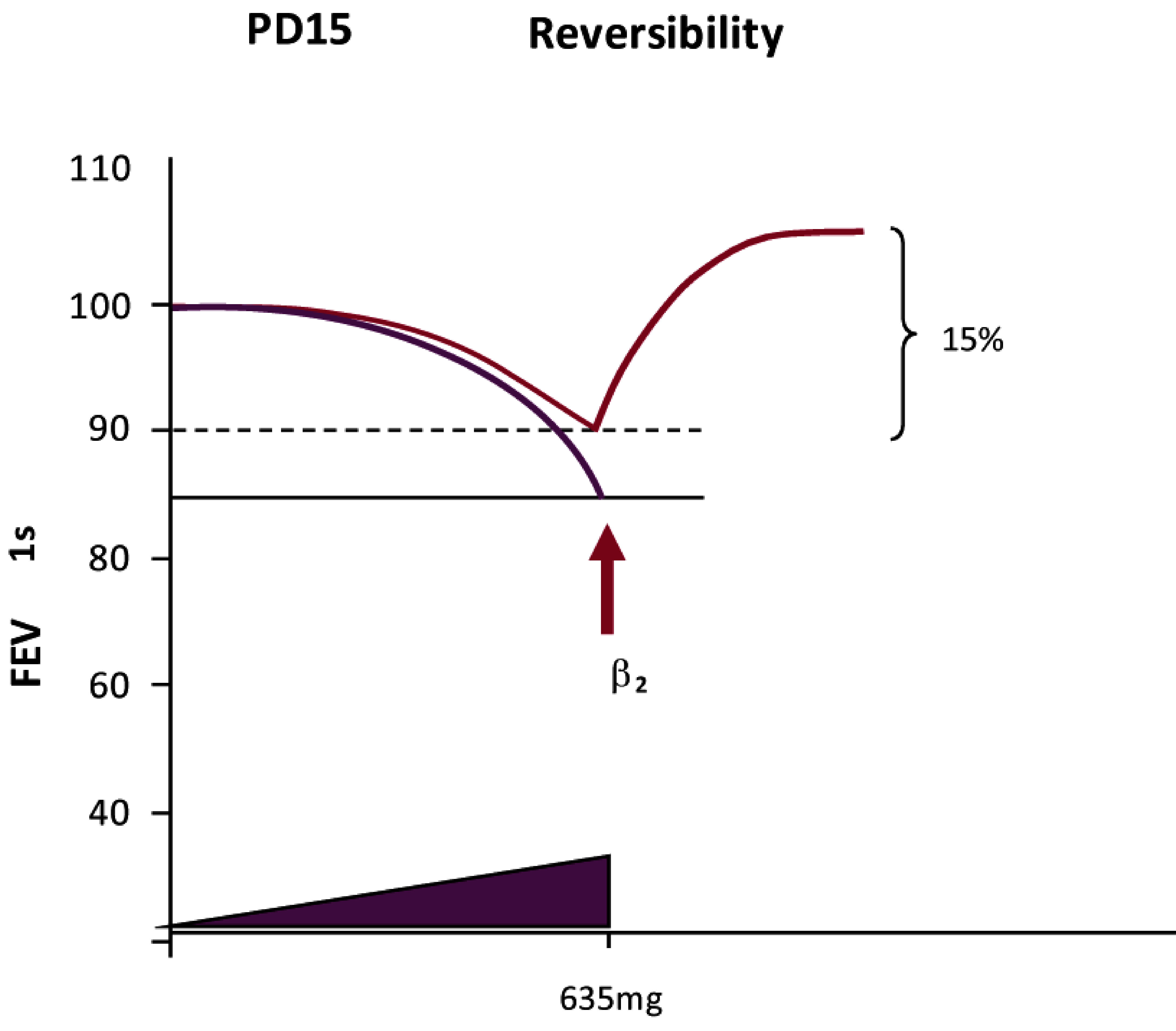
Sensitivity and specificity when different critias were used to define a positive mannitol test.

Figure 4

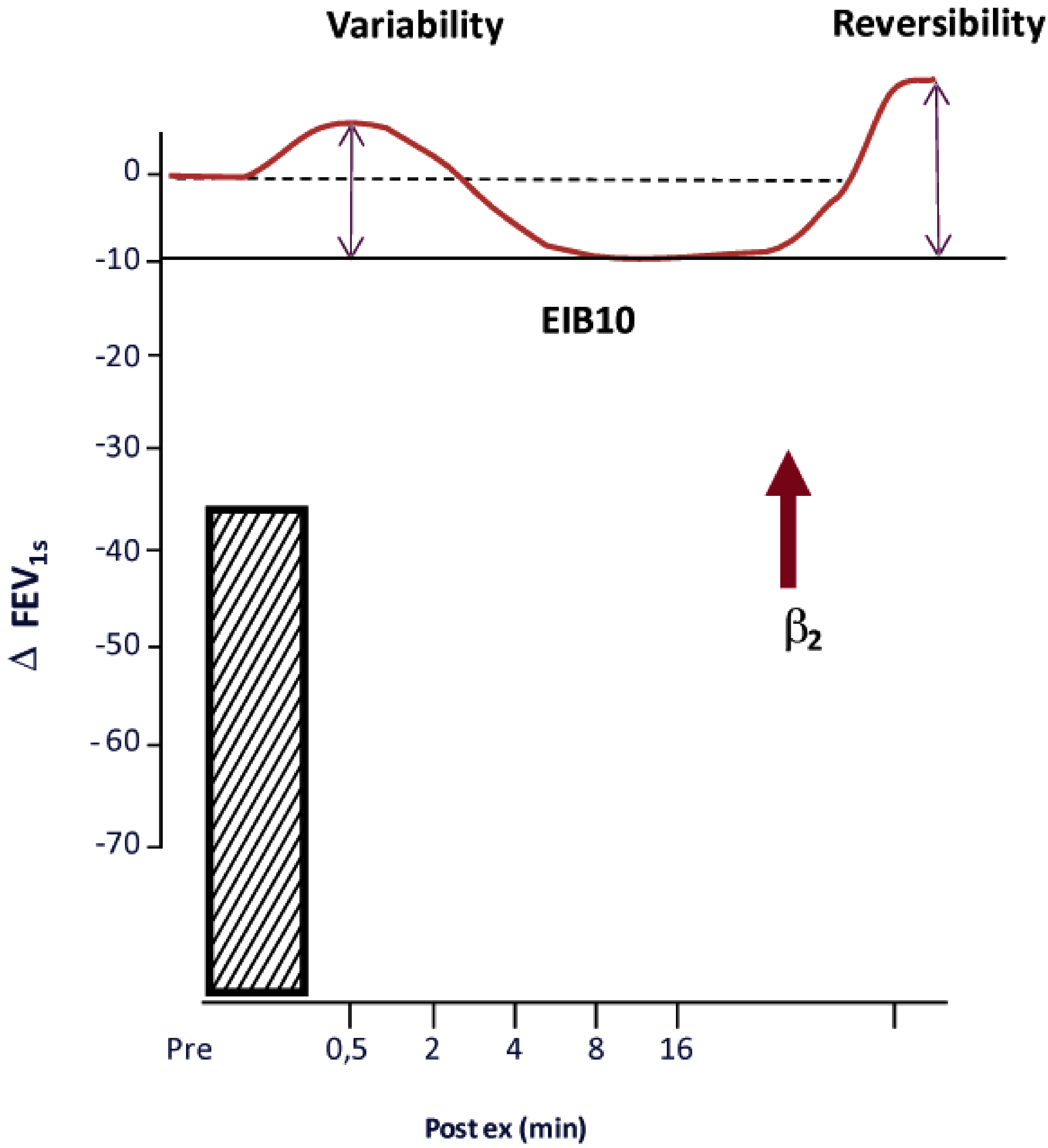
Sensitivity and specificity when different critias were used to define a positive exercise test.

Figure 5

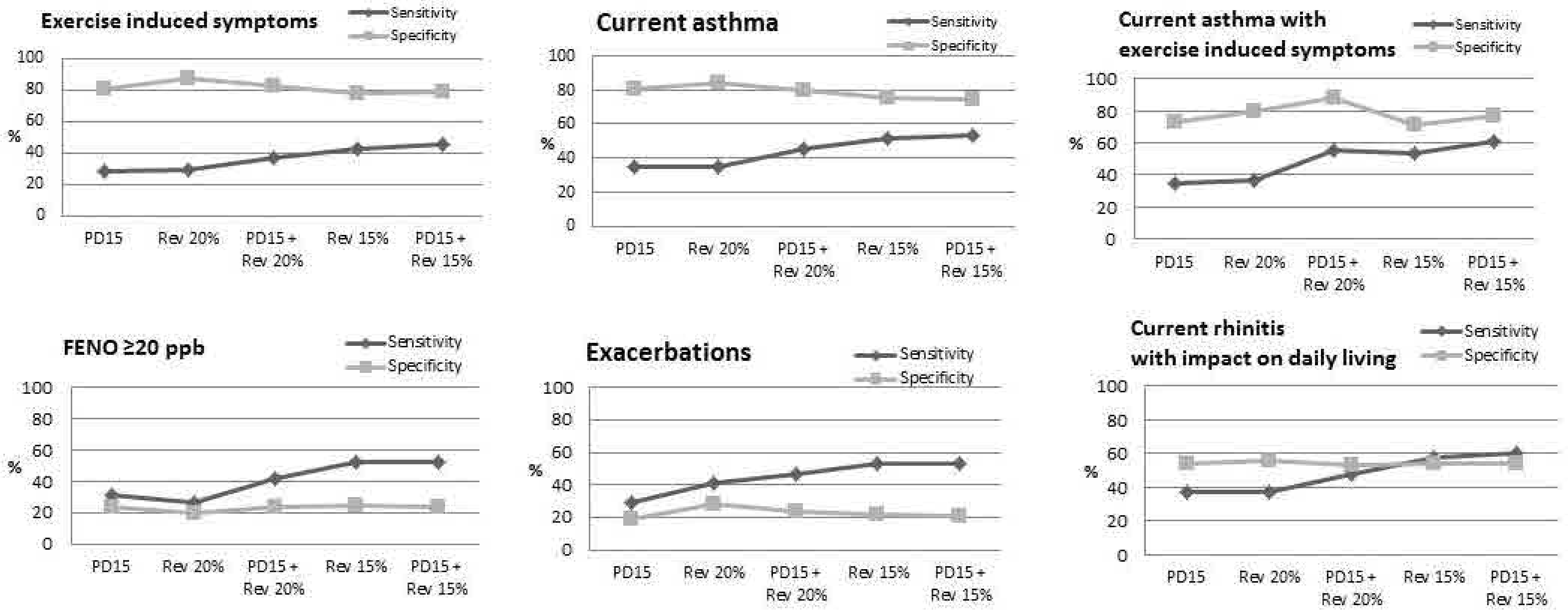
Number of provocation test positive subjects among 97 tested swimmers where different criterias were used for to define a positive test. (A,C) Ordinary criteria; $PD15_{Mann}$ defined as a drop in FEV_1 of ≥15% from baseline after inhalation of cumulative doses of mannitol ≤ 635 mg. Exerc 10% defined as a drop in FEV_1 of ≥10% from baseline after exercise challenge. (B,D) Extended criteria with mannitol provocation test; defined as $PD15_{Mann}$ positive and/or reversibility ≥15%, exercise provocation test; defined as Exerc10 and/or reversibility ≥15% and/or variability of ≥15%. (A,B) in all swimmers, (C,D) in subjects with current asthma, defined as report of symptoms such as wheezing and/or nocturnal symptoms without respiratory infection during the past 12 months.



PD15
Reversibility
110
100
90
80
60
40
FEV 1s
15%
β2
635mg



Variability
Reversibility
0
-10
-20
-30
-40
-50
-60
-70
EIB10
Δ FEV1s
β2
Pre
0,5
2
4
8
16
Post ex (min)


Exercise induced symptoms
Current asthma
Current asthma with exercise induced symptoms
FENO ≥20 ppb
Exacerbations
Current rhinitis with impact on daily living
Sensitivity
Specificity
%
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PD15
Rev 20%
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Rev 15%
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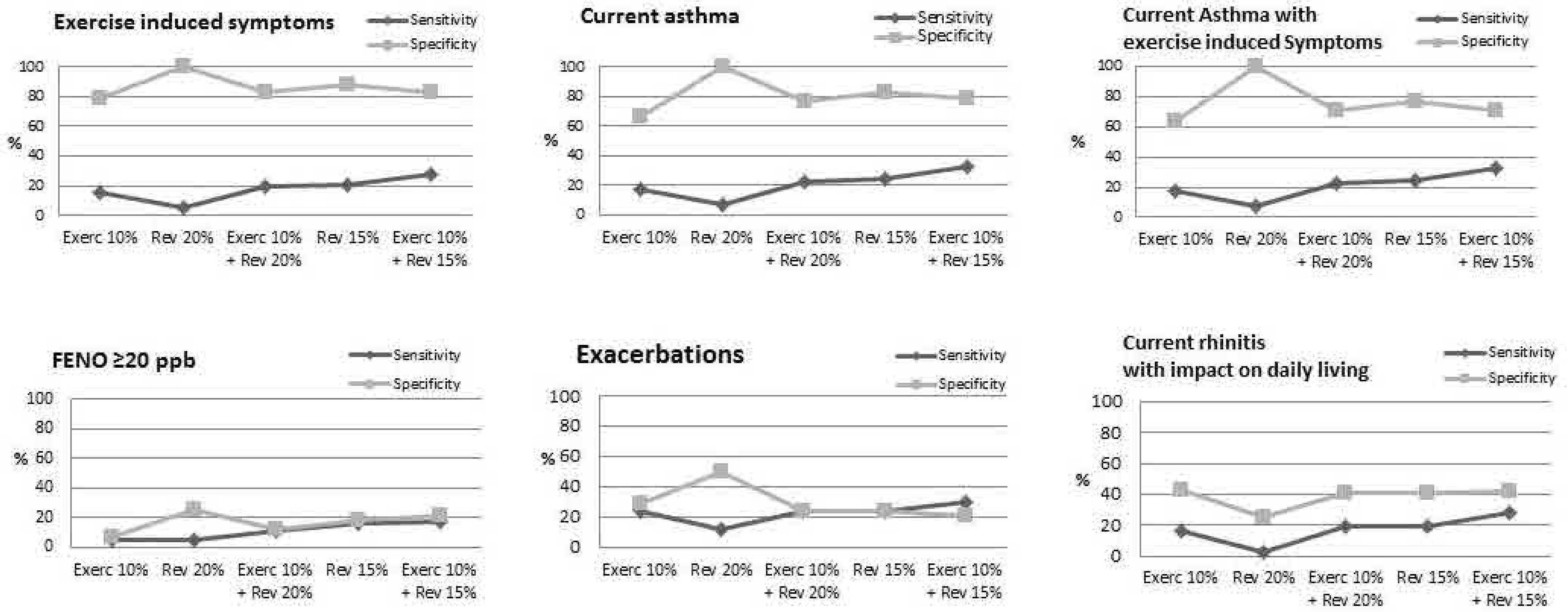

Exercise induced symptoms
Current asthma
Current Asthma with exercise induced Symptoms
FENO ≥20 ppb
Exacerbations
Current rhinitis with impact on daily living
Sensitivity
Specificity
%
0
20
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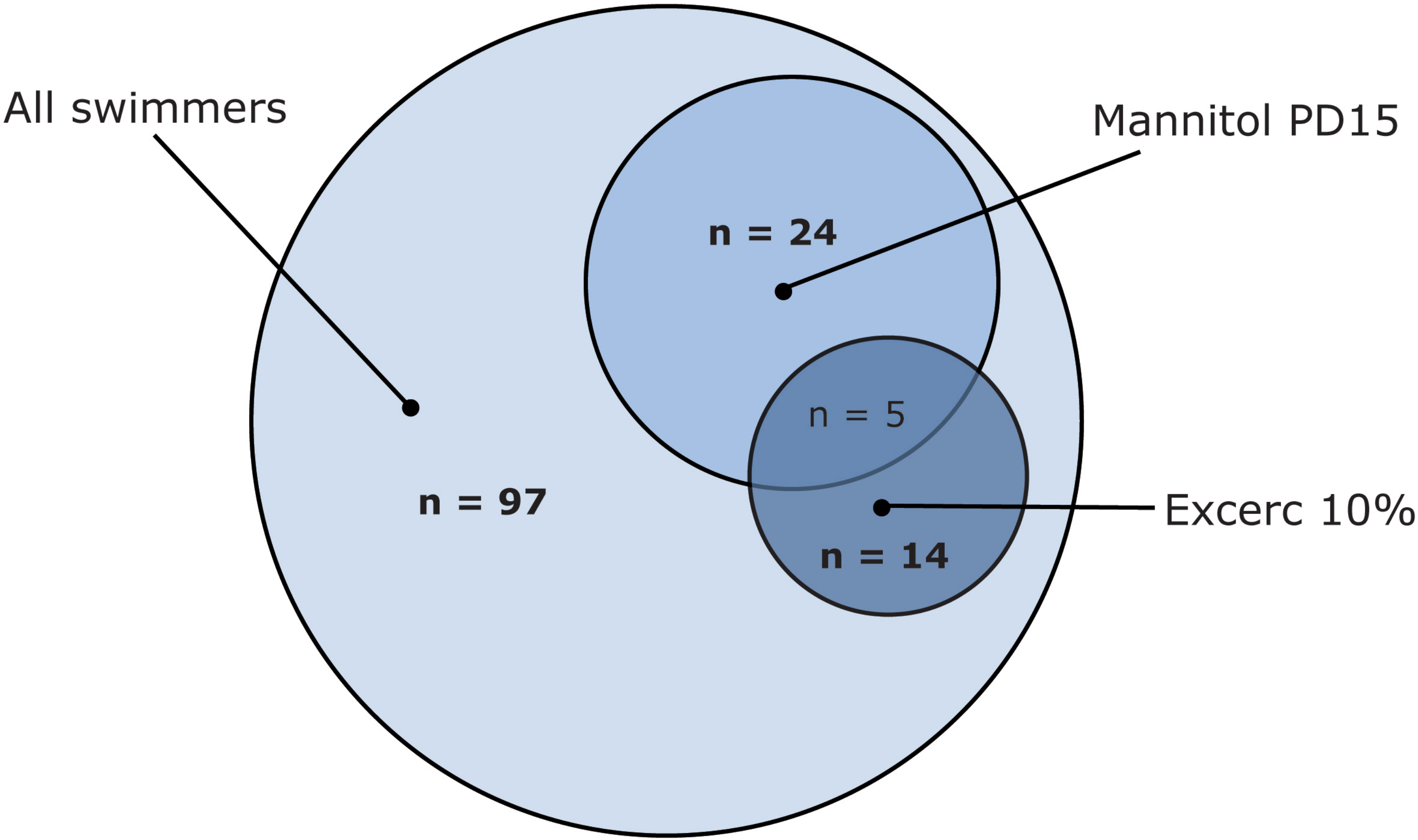
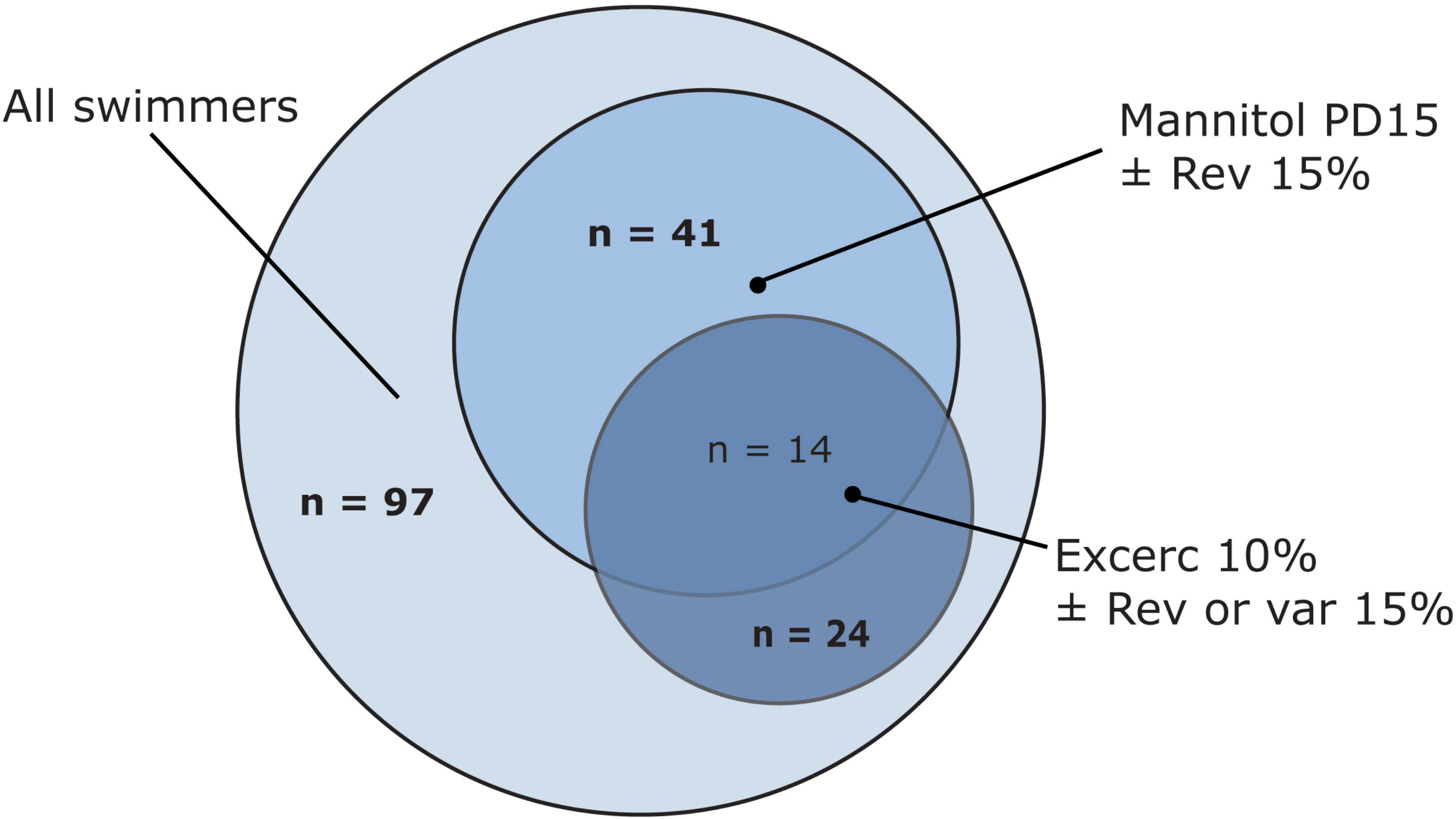
80
100
Exerc 10%
Rev 20%
Exerc 10% + Rev 20%
Rev 15%
Exerc 10% + Rev 15%

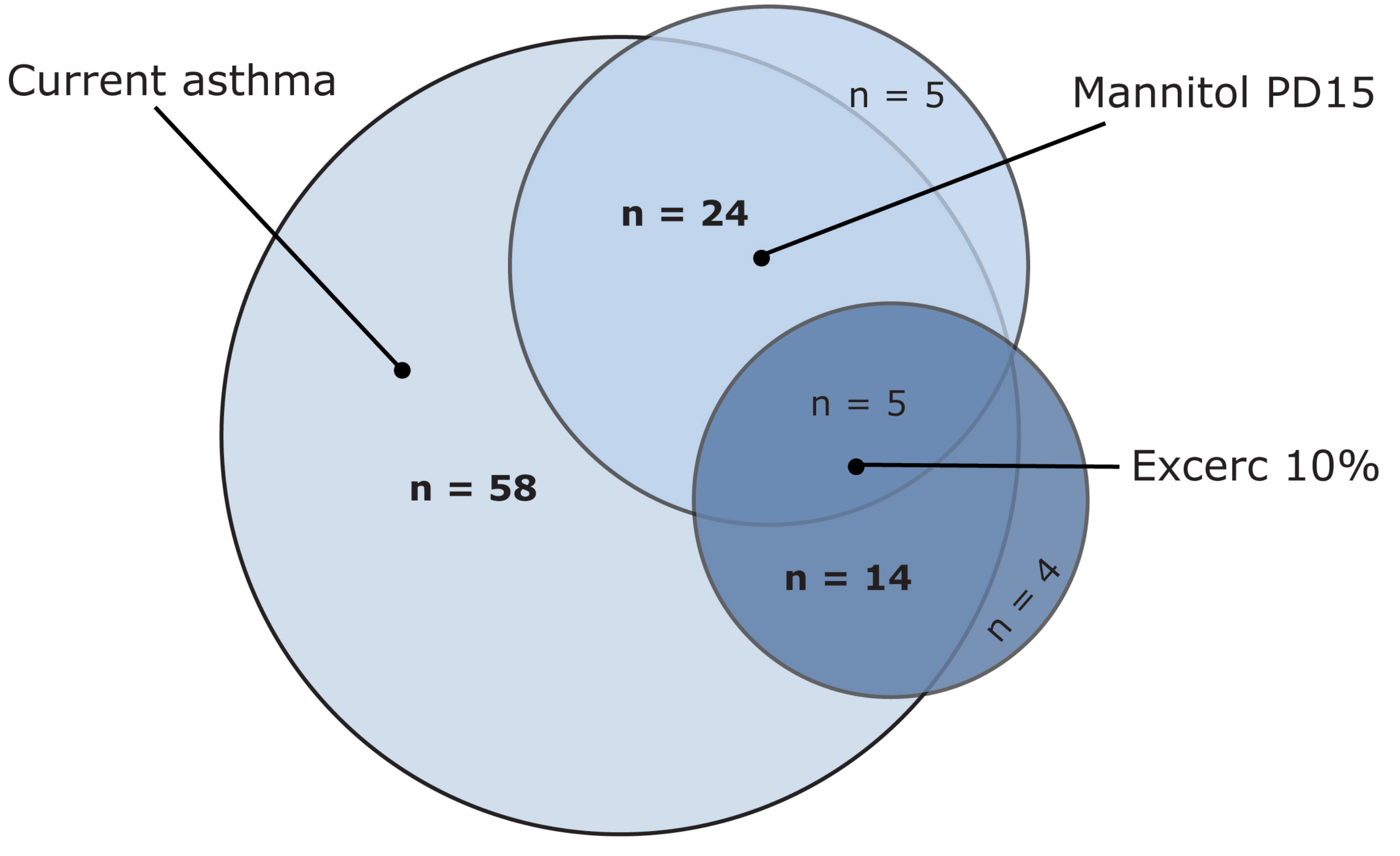
Ordinary criteria



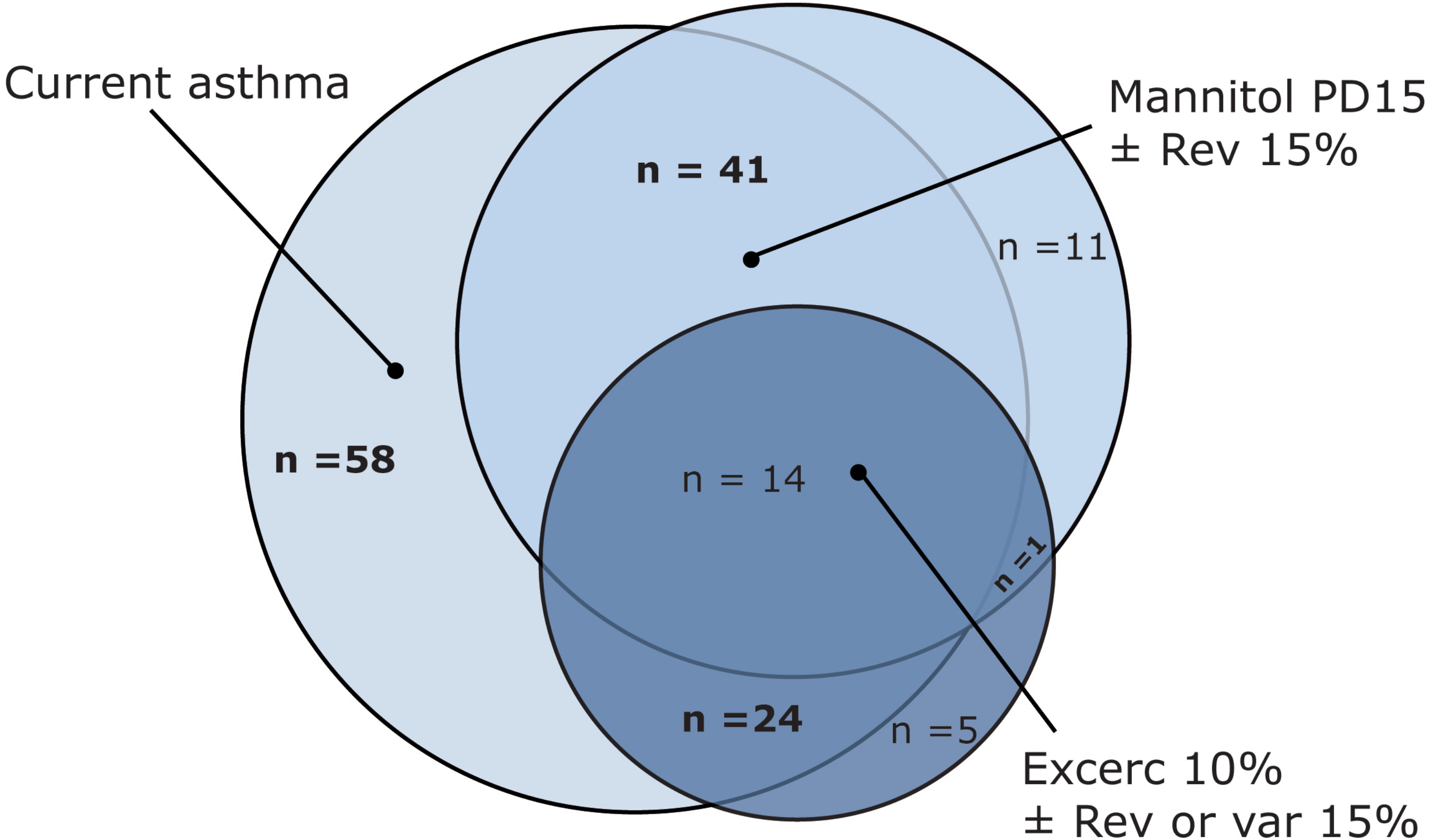
Extended criteria



Ordinary criteria



Extended criteria



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