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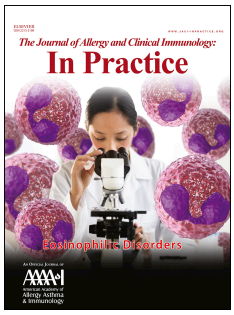

Reported symptoms differentiate diagnoses in children with exercise-induced respiratory problems: findings from the Swiss Paediatric Airway Cohort (SPAC)

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Reported symptoms differentiate diagnoses in children with exercise-induced respiratory problems: findings from the Swiss Paediatric Airway Cohort (SPAC)

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Dr. Singer reports personal fees from Novartis, personal fees from Vertex, outside the submitted work. All other authors declare that they have no competing interests.

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Word count

Abstract: 246 words

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Abstract (246 words)

Background: Exercise-induced breathing problems with similar clinical presentations can have different etiologies. This makes distinguishing common diagnoses such as asthma, extrathoracic and thoracic dysfunctional breathing (DB), insufficient fitness, and chronic cough difficult.

Objective: We studied which parent-reported, exercise-induced symptoms can help distinguish diagnoses in children seen in respiratory outpatient clinics.

Methods: This study was nested in the Swiss Paediatric Airway Cohort (SPAC), an observational study of children aged 0-17 years referred to pediatric respiratory outpatient clinics in Switzerland. We studied children aged 6-17 years and compared information on exercise-induced symptoms from parent-completed questionnaires between children with different diagnoses. We used multinomial regression to analyze whether parent-reported symptoms differed between diagnoses (asthma as base).

Results: Among 1109 children, exercise-induced symptoms were reported for 732 (66%) (mean age 11 years, 318 of 732 [43%] female). Among the symptoms, dyspnea best distinguished thoracic DB (relative risk ratio [RRR] 5.4, 95%CI 1.3-22) from asthma. Among exercise triggers, swimming best distinguished thoracic DB (RRR 2.4, 95%CI 1.3-6.2) and asthma plus DB (RRR 1.8, 95%CI 0.9-3.4) from asthma only. Late onset of symptoms was less common for extrathoracic DB (RRR 0.1, 95%CI 0.03-0.5) and thoracic DB (RRR 0.4, 95%CI 0.1-1.2) compared with asthma. Localization of dyspnea (throat vs. chest) differed between extrathoracic DB (RRR 2.3, 95%CI 0.9-5.8) and asthma. Reported respiration phase (inspiration or expiration) did not help distinguish diagnoses.

Conclusion: Parent-reported symptoms help distinguish different diagnoses in children with exercise-induced symptoms. This highlights the importance of physicians obtaining detailed patient histories.

Highlights box

1. What is already known about this topic?

Experts suggest that information about the symptoms and their onset and duration can assist accurate diagnosis of children with exercise-induced respiratory problems, but no original studies have tested this.

2. What does this article add to our knowledge?

Exercise-induced symptoms reported by parents and further information about their onset, triggers, and effects of treatment help differentiate diagnoses in children with exercise-induced respiratory problems.

3. How does this study impact current management guidelines?

Our results emphasize the importance of taking detailed symptom histories of children with exercise-induced problems, and suggest which questions are most helpful.

Key words

Exercise-induced, ILO, asthma, childhood, adolescents, dysfunctional breathing

List of abbreviations

BMI	Body mass index
DB	Dysfunctional breathing
FeNO	Fractional exhaled nitric oxide
ILO	Inducible laryngeal obstruction
RRR	Relative risk ratio
SPAC	Swiss Paediatric Airway Cohort

96 **Manuscript: 2592 words**

97 **Introduction**

98 Exercise-induced respiratory symptoms are common in childhood. But their underlying
99 causes can be difficult to identify because the clinical presentation of exercise-induced
100 symptoms of different etiologies can overlap (1-3). Exercise-induced symptoms are most
101 often caused by asthma, extrathoracic or thoracic dysfunctional breathing (DB), insufficient
102 fitness, and nonspecific chronic cough (4, 5). Even though clinical presentations can be
103 similar, certain symptoms are typically associated with specific diagnoses (6-8). Knowing
104 which symptoms are particularly characteristic of different underlying causes may help
105 physicians to make a diagnosis, in addition to formal exercise testing (4, 6, 9). For example,
106 expiratory wheeze, cough, and shortness of breath are typical for asthma with symptoms
107 lasting from minutes to hours that usually peak after exercise (10, 11). Inspiratory problems
108 with stridor, throat tightness, and shortness of breath are more typical for extrathoracic DB
109 with symptoms that last only a few minutes and peak during exercise (10, 12). Typical
110 symptoms for thoracic DB are shortness of breath, sighing, dizziness, and symptoms can last
111 from minutes to hours and peak during exercise (9). Tingling in fingers or lips is typical for
112 thoracic DB with hyperventilation.

113

114 A few studies have examined the association of diagnoses with typical symptoms. However,
115 exercise-induced symptoms have been reported only for specific diagnostic groups such as
116 children with asthma (13), or no more than two diagnostic groups have been compared (14-
117 16). If we better knew which symptoms most usefully distinguish diagnoses, then
118 misdiagnoses in children with exercise-induced symptoms, such as extrathoracic DB
119 misdiagnosed as asthma, might be reduced (17-19). We therefore studied children visiting

120 pediatric respiratory outpatient clinics in Switzerland to investigate which symptoms
121 reported by parents are most useful to distinguish different diagnoses of exercise-induced
122 symptoms.
123

124 **Method**

125 **Study design**

126 We used cross-sectional data from the Swiss Paediatric Airway Cohort (SPAC), a multicenter
127 study of children referred to pediatric respiratory outpatient clinics in Switzerland (20). The
128 SPAC study includes children aged 0-17 years who were referred for respiratory problems
129 such as wheeze, cough, dyspnea, or symptoms related to sleep or exercise, and who spoke
130 sufficient German to participate. At the time of the visit, the physicians explained the SPAC
131 study to the families. Parents completed a questionnaire before or shortly after the visit that
132 inquired about symptoms, medication, environment, and health behaviors. After the visit,
133 the SPAC study team collected the outpatient clinic letters that had been sent back to the
134 referring pediatrician with information on diagnosis, diagnostic investigations, and
135 treatment. We entered questionnaire responses and information from outpatient clinic
136 letters into a Research Electronic Data Capture (REDCap) database (21). Recruitment for
137 SPAC started in July 2017 and is ongoing. At the time we extracted data for this analysis,
138 eight pediatric respiratory outpatient clinics in Switzerland were participating. Among 2971
139 children invited, 1838 (62%) agreed to participate (December 1, 2019).
140 The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale
141 Ethikkomission Bern 2016-02176). Written informed consent was obtained from parents and
142 patients older than 13 years. This article follows the STROBE reporting recommendations
143 (22).

144

145 **Inclusion criteria**

146 We included children aged 6-17 years with a completed questionnaire and an available
147 outpatient clinic letter with information on diagnosis. We restricted the population to
148 schoolchildren because nearly all children referred for exercise-induced symptoms to
149 respiratory outpatient clinics are older than 5 years. The question used to identify children
150 with exercise-induced symptoms was "Does your child sometimes experience breathing
151 problems during exercise?"

152

153 **Parent reported exercise-induced symptoms (EIS)**

154 The questionnaire was completed by parents at the first visit to the clinic and inquired about
155 symptoms that included exercise-induced wheeze, cough, dyspnea, tingling sensations in
156 fingertips/lips, and other symptoms that could be reported in a free-text field. It also asked
157 about characteristics of symptoms that included trigger factors (running, bicycle riding,
158 intensive sport games, swimming), localization of dyspnea (chest, throat, or both),
159 respiration phase (inspiration, expiration), onset of symptoms (during or after exercise),
160 duration of symptoms, and whether a short-acting bronchodilator helped to relieve
161 symptoms. **Table E1** reproduces English translations of the questions about exercise-induced
162 symptoms in the German language questionnaire. Parental questionnaires were not
163 disclosed to outpatient physicians.

164

165 **Diagnosis**

166 Diagnosis was taken from the outpatient clinic letter that the hospital pulmonologists sent
167 back to the referring physician. We distinguished six diagnoses: asthma, extrathoracic DB,

168 thoracic DB, asthma plus DB, chronic cough, and other (including insufficient fitness level,
169 exercise-induced symptoms of unknown etiology, allergic rhinoconjunctivitis, recurrent
170 respiratory infections, and rare pulmonary diseases). Exact definitions of diagnoses are in
171 **Table E2**. The diagnosis given at the clinic was made by the attending pediatric
172 pulmonologist and supported by at least one pulmonary function test such as spirometry,
173 bodyplethysmography, measurement of fractional exhaled nitric oxide (FeNO), direct or
174 indirect bronchial provocation tests. Some children were seen more than once in the
175 outpatient clinic, and we took the diagnosis from the outpatient clinic with the latest date. If
176 a child had more than one diagnosis listed in the letter, we used the diagnosis listed first,
177 except in children who had asthma and any type of DB. In these children we created a
178 separate category (asthma plus DB) because we believed that symptoms might differ
179 between children with asthma, DB, and both occurring together. Outpatient clinic physicians
180 were blinded to the parent completed questionnaire when giving the final diagnosis.
181
182 **Other variables**
183 Age, sex, height, and weight were taken from the outpatient clinic letter. We calculated
184 body mass index (BMI) as weight/height^2 (kg/m^2) and calculated age-adjusted BMI z-scores
185 based on Swiss reference values (23), defining overweight as BMI z-score > 1. We obtained
186 information on symptoms not induced by exercise from the questionnaire including parental
187 education, environmental factors, and physical activity.
188
189 **Statistical methods**
190 We compared proportions of exercise-induced symptoms by diagnosis categories: asthma,
191 extrathoracic DB, thoracic DB, asthma plus DB, chronic cough, and others using chi-square

192 and Fisher's exact tests. We studied which symptoms were most useful to distinguish
193 diagnoses using multinomial logistic regression. We defined diagnosis as outcome and
194 asthma as the reference category, and studied each explanatory variable in turn, adjusted
195 for age and sex. For the multinomial regression, due to the sample size we grouped chronic
196 cough with other diagnoses. Overall, we had little missing information in the questionnaire
197 replies (<7%) apart from the question about the respiration phase when symptoms are
198 worst (inspiration or expiration) for which 14% were missing. Children with missing data
199 were excluded. We used STATA version 14 for statistical analysis.
200
201 **Results**
202 Of the 1109 children aged 6-17 whose parents completed the questionnaire and for whom
203 we had information about diagnosis, 732 (66%) reported exercise-induced symptoms in the
204 questionnaire (**Figure E1).** On average, children were 11 years old (SD 3.2), 318 (43%) were
205 female (**table 1**). Children with reported exercise-induced symptoms were older and more
206 often female than children without reported exercise-induced symptoms. Among these
207 children with exercise-induced symptoms, 549 (75%) were diagnosed with asthma, 38 (5%)
208 with extrathoracic DB, 30 (4%) with thoracic DB, 43 (6%) with asthma plus DB, 21 (3%) with
209 chronic cough, and 51 (7%) received other diagnoses. Overall, more boys than girls were
210 diagnosed with asthma (63% boys) whereas more girls than boys were diagnosed with
211 extrathoracic DB (62% girls), thoracic DB (59% girls), and asthma + DB (61% girls), data not
212 shown.
213
214 Symptoms differed between diagnostic groups (**figure 1, table 2, figure 2**). Results from our
215 multinomial regression analysis (adjusted for age and sex) showed that wheeze was

216 reported less often for children with other diagnoses (relative risk ratio [RRR] 0.2, 95% CI
217 0.1-0.4) than for children with asthma. Cough was less common in children with thoracic DB
218 (RRR 0.3, 95% CI 0.2-0.7) and asthma plus DB (RRR 0.3, 95% CI 0.2-0.6) than in children with
219 asthma alone. Dyspnea was reported more often for children with thoracic DB (RRR 5.4, 95%
220 CI 1.3-23.1) and asthma plus DB (RRR 4.9, 95% CI 1.5-16.2) than in children with asthma
221 alone. A tingling feeling in fingertips or lips was more common in children with thoracic DB
222 (RRR 3.0, 95% CI 1.2-7.3) than in children with asthma.
223
224 The type of physical activity reported to trigger exercise-induced symptoms differed
225 between diagnostic groups (**table 2**, **figure 3**). Compared to children with asthma, swimming
226 was more commonly reported as trigger in children with thoracic DB (RRR 2.9, 95%CI 1.3-
227 6.2), asthma plus DB (RRR 1.8, 95%CI 0.9-3.4), and other diagnoses (RRR 2.1, 95%CI 1.2-3.4).
228 Bicycle riding was reported more often for children with extrathoracic DB (RRR 2.0, 95%CI
229 1.0-4.2), and intensive sports games were more often reported for children with asthma plus
230 DB (RRR 2.4, 95%CI 1.0-5.8).
231
232 The characteristics of exercise-induced symptoms differed between diagnostic groups (**table**
233 **2, figure 4**). Late onset (after exercise) of symptoms was rarely reported for extrathoracic DB
234 (RRR 0.1, 95% CI 0.03-0.5) compared to asthma. A long duration of symptoms (more than 10
235 minutes) was reported more often for thoracic DB (RRR 4.8, 95% CI 1.4-16.8) than asthma.
236 For localization of dyspnea, throat was reported more often than chest for children with
237 extrathoracic DB (RRR 2.3, 95% CI 0.9-5.8) than for children with asthma. Respiration phase
238 (inspiration or expiration) did not differ between diagnostic groups. Use of a bronchodilator

made symptoms disappear in 172 (43%) children with asthma in contrast to 2 (14%) children with extrathoracic DB and 1 (8%) child with asthma plus DB (**table 2**).

Discussion

Parent-reported symptoms can distinguish different diagnoses in children with exercise-induced symptoms referred to pediatric outpatient clinics. We observed that especially reported exercise-induced cough, dyspnea, and tingling sensation in fingers or lips differed between diagnostic groups. Of the physical activities triggering symptoms, intensive sport games and swimming best distinguished diagnosis groups. Additionally, onset of symptoms, duration of symptoms, and effect of a short-acting bronchodilator differed between the diagnostic groups. Respiration phase (inspiration or expiration) was less helpful.

Strengths and limitations

Information about exercise-induced symptoms and activities that trigger them has not previously been reported in such detail. The comparison of questionnaire-reported exercise-induced symptoms and diagnostic groups, which included asthma, extrathoracic DB, thoracic DB, and the combination of asthma and DB, is this study's major strength. The level of detail afforded examination of how activities trigger different exercise-induced problems. In addition, our study was nested in SPAC, a real-life prospective observational clinical cohort which is representative of children referred to pediatric respiratory outpatient clinics for respiratory problems. We therefore believe our findings can be broadly generalized to children seen by respiratory physicians for exercise-induced symptoms.

262 A limitation of the study is that we did not analyze if results from diagnostic tests can help
263 distinguish diagnoses additionally to reported symptoms. The SPAC study is embedded in
264 routine care, and therefore some tests (e.g., exercise challenge tests) were performed by
265 indication and therefore not done in all children, and including these results in our analyses
266 would have introduced selection bias. Another limitation is that the questionnaire was
267 addressed to the parents rather than the children themselves. However, we encouraged
268 parents to fill in the questionnaire together with their child, which increases validity of
269 reported symptoms (24, 25). Our questionnaire included the set of questions usually asked
270 by physicians during the consultation. However, physicians might have worded some
271 questions differently, addressed them to the child rather than the mother, simulated
272 respiratory sounds such as wheeze or stridor, or provided additional explanations. So,
273 although collected at the same time, the replies in the parental questionnaire, used for the
274 analysis, might not always mirror the information retrieved by the physician who took the
275 history. Our limited sample size for some diagnostic categories (thoracic DB, n=30) led to
276 wide confidence intervals, and we could not investigate combinations of reported
277 symptoms. Still, our study is the largest of its kind. A further limitation is that the final
278 diagnosis was made by different pulmonologists and not based on a standardized,
279 predefined diagnostic algorithm specific for this study. However, all pulmonologists were
280 board-certified and diagnoses were based on clinical history and standardized objective
281 diagnostic test results representative of typical situations in a tertiary care clinic.
282

283 **Comparison with other studies**

284 A few studies have presented questionnaire-reported symptoms for children or adolescents
285 with exercise-induced symptoms. A Swedish population based study in children aged 12-13

286 years reported exercise-induced symptoms for 128 children with an asthma diagnosis (13).
287 Exercise-induced wheeze was reported for 76 (59%), cough for 81 (63%), and chest tightness
288 for 56 (44%); throat tightness also was reported for 63 (49%), and inspiratory stridor for 47
289 (37%). We saw higher prevalence of symptoms overall because our study included
290 respiratory outpatients and not children from the general population.
291 In a case series study of 12 adolescent athletes seen for suspected exercise-induced
292 laryngeal obstruction (EILO) (15), dyspnea during inspiration was reported by all (100%) and
293 dyspnea during expiration by 8 (67%), and throat tightness was reported more frequently
294 (50%) than chest tightness (25%). A Danish study that compared 42 adolescents with EILO
295 with 16 adolescents diagnosed with airway hyper-responsiveness (AHR) similarly found that
296 all reported wheeze and stridor, but those with EILO mostly reported cough and throat
297 tightness while those with AHR reported mostly dyspnea (14). Our results and those from
298 previous studies emphasize that no symptom is uniquely reported for single diagnostic
299 groups among children with exercise-induced symptoms, but some symptoms are reported
300 more frequently for certain diagnoses than others.
301
302 **Interpretation**
303 Cough, dyspnea, and tingling sensation in fingers or lips better distinguished thoracic DB
304 from asthma than extrathoracic DB from asthma. This partly explains why extrathoracic DB
305 can be misdiagnosed as asthma (17, 19). Onset of symptoms during exercise was strongly
306 associated with extrathoracic DB, while onset after exercise was associated with asthma.
307 This finding is in line with the literature and could help physicians distinguish extrathoracic
308 DB from asthma (7, 26, 27). We found that of the different triggers, swimming best
309 distinguished diagnoses. Swimming has been reported as a trigger of bronchoconstriction in

310 children with asthma (28). It was therefore surprising that children with thoracic DB more
311 often reported swimming as a trigger of symptoms than children with asthma. We found no
312 other studies that reported on triggers of exercise-induced symptoms in children with
313 dysfunctional breathing. An explanation could be that children with thoracic DB have
314 difficulties with their breathing patterns and might therefore find swimming especially
315 difficult as correct breathing is a requirement during swimming. We found no evidence that
316 the distinction between inspiration and expiration helped to distinguish diagnoses. Most
317 parents reported that their child's symptoms occur during inspiration (n=298, 47%) or during
318 inspiration and expiration (n=276, 44%) rather than during expiration alone (n=54, 9%).
319 Results from other studies confirm that adolescents with exercise-induced symptoms rarely
320 only report symptoms during expiration alone but usually report symptoms during
321 inspiration or both inspiration and expiration (14, 15). Therefore, although asthma is
322 associated with expiratory airway obstruction, most adolescents report symptoms during
323 inspiration and expiration. While physicians are trained to distinguish inspiratory sounds
324 from expiratory sounds during auscultation, this might be more difficult for parents and
325 children (7, 29). This feature might therefore be useful for clinical examination but not for
326 interpretation of patient-reported symptoms. We also did not see any difference in the
327 duration of symptoms between diagnostic groups. It might be difficult for parents in a
328 stressful moment to judge whether the child's symptoms lasted a few minutes, between 5-
329 10 minutes, or longer unless they observed their child at the time of an attack.
330
331 Diagnosing children with exercise-induced symptoms is not easy and requires a thorough
332 diagnostic work up including objective diagnostic tests. Our study confirms that parent-
333 reported symptoms can help to distinguish different diagnoses in children with exercise-

induced symptoms. This highlights the importance of physicians taking detailed symptom histories.

Ethics approval and consent to participate

The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176). Written informed consent was obtained from patients' parents and directly from patients older than 13 years.

Author's contributions

EP and CK made substantial contributions to the study conception and design. EP, CdJ, and MCM collected and prepared data from the SPAC study. EP drafted the manuscript. EP, CdJ, CA, MCM, JB, CC, KH, AJ, AM, DM, NR, FS, MG, and CK critically revised and approved the manuscript.

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Availability of data and material

The SPAC dataset is available on reasonable request by contacting Claudia Kuehni by email: Claudia.kuehni@ispm.unibe.ch .

356 **References**

357 1. Connett GJ, Thomas M. Dysfunctional Breathing in Children and Adults With
358 Asthma. Frontiers in pediatrics. 2018;6:406.
359 2. Johansson H, Norlander K, Berglund L, Janson C, Malinovschi A, Nordvall L, et
360 al. Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal
361 obstruction in a general adolescent population. Thorax. 2015;70(1):57-63.
362 3. Fretzayas A, Moustaki M, Loukou I, Douros K. Differentiating vocal cord
363 dysfunction from asthma. Journal of Asthma and Allergy. 2017;10:277-83.
364 4. Barker N, Everard ML. Getting to grips with 'dysfunctional breathing'. Paediatric
365 respiratory reviews. 2015;16(1):53-61.
366 5. Depiazzi J, Everard ML. Dysfunctional breathing and reaching one's
367 physiological limit as causes of exercise-induced dyspnoea. Breathe (Sheffield, England).
368 2016;12(2):120-9.
369 6. Kenn K, Hess MM. Vocal Cord Dysfunction: An Important Differential Diagnosis
370 of Bronchial Asthma. Deutsches Ärzteblatt International. 2008;105(41):699-704.
371 7. Roksund OD, Heimdal JH, Clemm H, Vollsaeter M, Halvorsen T. Exercise
372 inducible laryngeal obstruction: diagnostics and management. Paediatric respiratory
373 reviews. 2017;21:86-94.
374 8. Roksund OD, Heimdal JH, Olofsson J, Maat RC, Halvorsen T. Larynx during
375 exercise: the unexplored bottleneck of the airways. European archives of oto-rhino-
376 laryngology : official journal of the European Federation of Oto-Rhino-Laryngological
377 Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and
378 Neck Surgery. 2015;272(9):2101-9.
379 9. Niggemann B. How to diagnose psychogenic and functional breathing disorders
380 in children and adolescents. Pediatric allergy and immunology : official publication of the
381 European Society of Pediatric Allergy and Immunology. 2010;21(6):895-9.
382 10. Liyanagedara S, McLeod R, Elhassan HA. Exercise induced laryngeal
383 obstruction: a review of diagnosis and management. European archives of oto-rhino-
384 laryngology : official journal of the European Federation of Oto-Rhino-Laryngological
385 Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and
386 Neck Surgery. 2017;274(4):1781-9.
387 11. Chiang T, Marcinow AM, deSilva BW, Ence BN, Lindsey SE, Forrest LA. Exercise-
388 induced paradoxical vocal fold motion disorder: diagnosis and management. The
389 Laryngoscope. 2013;123(3):727-31.
390 12. Olin JT. Exercise-Induced Laryngeal Obstruction: When Pediatric Exertional
391 Dyspnea Does not Respond to Bronchodilators. Frontiers in pediatrics. 2019;7:52.
392 13. Johansson H, Norlander K, Hedenstrom H, Janson C, Nordang L, Nordvall L, et
393 al. Exercise-induced dyspnea is a problem among the general adolescent population.
394 Respiratory medicine. 2014;108(6):852-8.
395 14. Christensen PM, Thomsen SF, Rasmussen N, Backer V. Exercise-induced
396 laryngeal obstructions: prevalence and symptoms in the general public. European archives of
397 oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-
398 Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-
399 Laryngology - Head and Neck Surgery. 2011;268(9):1313-9.
400 15. Shembel AC, Hartnick CJ, Bunting G, Ballif C, Shaiman S, de Guzman V, et al.
401 Perceptual Clinical Features in Exercise-Induced Laryngeal Obstruction (EILO): Toward

402 Improved Diagnostic Approaches. Journal of voice : official journal of the Voice Foundation.
403 2018.
404 16. Nielsen EW, Hull JH, Backer V. High prevalence of exercise-induced laryngeal
405 obstruction in athletes. Medicine and science in sports and exercise. 2013;45(11):2030-5.
406 17. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children
407 and adolescents: if not asthma then what? Annals of allergy, asthma & immunology : official
408 publication of the American College of Allergy, Asthma, & Immunology. 2005;94(3):366-71.
409 18. Khan DA. Exercise-induced bronchoconstriction: burden and prevalence.
410 Allergy and asthma proceedings. 2012;33(1):1-6.
411 19. Seear M, Wensley D, West N. How accurate is the diagnosis of exercise induced
412 asthma among Vancouver schoolchildren? Archives of disease in childhood. 2005;90(9):898-
413 902.
414 20. Pedersen ESL, de Jong CCM, Ardura-Garcia C, Barben J, Casaulta C, Frey U, et al.
415 The Swiss Paediatric Airway Cohort (SPAC). ERJ open research. 2018;4(4).
416 21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research
417 electronic data capture (REDCap)--a metadata-driven methodology and workflow process for
418 providing translational research informatics support. Journal of biomedical informatics.
419 2009;42(2):377-81.
420 22. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP.
421 The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
422 statement: guidelines for reporting observational studies. Journal of clinical epidemiology.
423 2008;61(4):344-9.
424 23. Van den Broeck J, Willie D, Younger N. The World Health Organization child
425 growth standards: expected implications for clinical and epidemiological research. European
426 journal of pediatrics. 2009;168(2):247-51.
427 24. Braun-Fahrlander C, Gassner M, Grize L, Minder CE, Varonier HS, Vuille JC, et al.
428 Comparison of responses to an asthma symptom questionnaire (ISAAC core questions)
429 completed by adolescents and their parents. SCARPOL-Team. Swiss Study on Childhood
430 Allergy and Respiratory Symptoms with respect to Air Pollution. Pediatric pulmonology.
431 1998;25(3):159-66.
432 25. Olson LM, Radecki L, Frintner MP, Weiss KB, Korfmacher J, Siegel RM. At what
433 age can children report dependably on their asthma health status? Pediatrics.
434 2007;119(1):e93-102.
435 26. Griffin SA, Walsted ES, Hull JH. Breathless athlete: exercise-induced laryngeal
436 obstruction. British journal of sports medicine. 2018;52(18):1211-2.
437 27. Hall A, Thomas M, Sandhu G, Hull JH. Exercise-induced laryngeal obstruction: a
438 common and overlooked cause of exertional breathlessness. The British journal of general
439 practice : the journal of the Royal College of General Practitioners. 2016;66(650):e683-5.
440 28. Romberg K, Tufvesson E, Bjermer L. Asthma symptoms, mannitol reactivity and
441 exercise-induced bronchoconstriction in adolescent swimmers versus tennis players. Journal
442 of Asthma and Allergy. 2017;10:249-60.
443 29. Liyanagedera S, McLeod R, Elhassan HA. Exercise induced laryngeal
444 obstruction: a review of diagnosis and management. European archives of oto-rhino-
445 laryngology : official journal of the European Federation of Oto-Rhino-Laryngological
446 Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and
447 Neck Surgery. 2017;274(4):1781-9.
448

453 **Figure legends**
454
455 Figure 1: Type of exercise-induced symptoms in children referred to paediatric respiratory
456 outpatient clinics, displayed by diagnosis group (n=732)
457
458 Figure 2 Comparison of type of exercise-induced symptoms between diagnosis groups using
459 multinomial regression models adjusted for age and sex
460
461 Figure 3 Comparison of activities triggering exercise-induced symptoms between diagnosis
462 groups using multinomial regression models adjusted for age and sex
463
464 Figure 4 Comparison of exercise-induced symptom characteristics (localization of dyspnea,
465 respiratory phase, onset, and duration of symptoms) between diagnosis groups using
466 multinomial regression models adjusted for age and sex
467

468 **Table 1 Comparison of characteristics, respiratory symptoms and diagnoses between**
469 **included patients with and without exercise-induced symptoms (EIS) (N=1109)**

	Yes to EIS in questionnaire	**No to EIS in questionnaire**
	N=732	N=377
Characteristics	n(%)	n(%)
Demographic and socioeconomic characteristics		
Age (years), mean (SD)	11.0 (3.2)	9.5 (3.1)
Sex (female)	318 (43)	132 (35)
BMI z-score, mean (SD) (n=1091)	0.3 (1.2)	0.2 (1.2)
Overweight (BMI z-score >1) (n=1094)	177 (26)	76 (23)
Sports apart from at school (n=1056)	566 (78)	257 (70)
Swiss nationality	609 (83)	309 (82)
Parental education		
Mother, tertiary[a] (n=1071)	259 (37)	114 (31)
Father, tertiary[a] (n=1056)	315 (45)	142 (39)
Parental smoking		
Mother, current smoking (n=1090)	114 (16)	49 (14)
Father, current smoking (n=1046)	174 (25)	80 (23)
Respiratory symptoms in the past 12 months		
Cough apart from colds, yes often (n=1096)	88 (12)	55 (15)
Cough at night apart from colds (n=1079)	329 (46)	151 (41)
Wheeze (n=1086)	452 (63)	168 (46)
>3 attacks of wheeze (n=1086)	216 (30)	48 (13)
Rhinitis apart from colds (n=1100)	479 (66)	213 (57)
Eczema ever (n=1090)	215 (30)	102 (28)
Diagnosis given at outpatient clinic		
Asthma	549 (75)	276 (73)
Extrathoracic dysfunctional breathing	38 (5)	1 (0)
Thoracic dysfunctional breathing	30 (4)	7 (2)
Asthma + any DB	43 (6)	1 (0)
Chronic cough	21 (3)	35 (9)
Other	51 (7)	57 (15)

470 [a] Degree from university of applied sciences or university. Abbreviations: EIS, exercise induced symptoms

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Table 2 Reported exercise-induced symptoms (EIS) by diagnosis group in children who reported exercise-induced respiratory symptoms in the questionnaire (n=732)

Baseline questionnaire	Asthma N=549 N (%)	DB extra-thoracic N=38 N (%)	DB thoracic N=30 N (%)	Asthma + any DB N=43 N (%)	Cough N=21 N (%)	Other N=51 N (%)	P-value
Type of EIS (n=732)[a]							
Wheeze	329 (60)	20 (53)	15 (52)	27 (63)	9 (43)	9 (18)	<0.001
Cough	390 (71)	21 (55)	13 (43)	17 (40)	18 (86)	32 (63)	<0.001
Dyspnea	376 (68)	32 (84)	28 (93)	40 (93)	10 (48)	29 (57)	<0.001
Tingling feelings in finger or lips	53 (11)	6 (16)	8 (30)	10 (24)	0 (0)	10 (21)	0.002
Other symptoms	50 (9)	5 (13)	7 (23)	7 (16)	4 (19)	8 (16)	0.016
Trigger activities (n=697)							
Run short (50-100 m)	327 (63)	27 (71)	19 (66)	29 (69)	14 (70)	34 (71)	0.730
Run far (>1 km)	402 (77)	32 (84)	22 (76)	35 (83)	13 (65)	35 (73)	0.522
Cycle	254 (50)	27 (75)	19 (68)	23 (59)	9 (50)	24 (53)	0.034
Intensive sport games[#]	396 (75)	27 (71)	23 (77)	37 (86)	13 (65)	34 (71)	0.453
Swim	162 (31)	13 (34)	17 (59)	20 (48)	8 (40)	24 (50)	0.002
Localization of dyspnea (n=496 of 515 with dyspnea)[b]							
Chest	189 (52)	15 (47)	13 (46)	19 (50)	3 (30)	19 (70)	0.187
Throat	47 (13)	9 (28)	6 (21)	6 (16)	3 (30)	4 (15)	
Chest and Throat	125 (35)	8 (25)	9 (32)	13 (34)	4 (40)	4 (15)	
Respiration phase[c] (n=628)							
Inspiration	214 (46)	19 (51)	12 (44)	27 (64)	9 (60)	17 (44)	0.271
Expiration	45 (10)	0	2 (7)	2 (5)	0	5 (13)	
Inspiration and Expiration	209 (44)	18 (49)	13 (48)	13 (31)	6 (40)	17 (44)	
EIS start[d] (n=677)							
During exercise	344 (69)	36 (95)	24 (86)	33 (81)	9 (43)	29 (60)	<0.001
After ending exercise	156 (31)	2 (5)	4 (14)	8 (19)	12 (57)	19 (40)	
Duration of EIS[e] (n=648)							
1-2 minutes	189 (37)	13 (34)	5 (20)	14 (34)	8 (38)	21 (45)	0.503
5-10 minutes	268 (53)	22 (58)	14 (56)	23 (56)	10 (48)	22 (47)	
Longer than 10 min	48 (10)	3 (8)	6 (24)	4 (10)	3 (14)	4 (9)	
Used asthma-spray before or during exercise?[g] (n=712)	41 (77)	15 (39)	14 (47)	37 (88)	13 (62)	21 (43)	<0.001
Effect of asthma-spray[h] (n=494 of 511 who used asthma spray)							
EIS disappear	172 (43)	2 (14)	2 (14)	9 (25)	1 (8)	3 (17)	*
EIS are reduced	204 (51)	8 (57)	9 (64)	18 (50)	8 (62)	11 (61)	
No effect	23 (6)	4 (29)	3 (21)	9 (25)	4 (31)	4 (22)	

This table displays n(%) with column percentages.
EIS: exercise-induced symptoms
[a]Which symptoms does your child have during exercise?
[b]If reported dyspnea: Where is the sensation of symptoms felt the strongest?
[c]When are the symptoms worst?
[d]When do the symptoms begin?
[e]After ending the exercise, how long do the symptoms usually stay?
[f]Does your child sometimes get a tingling sensation in fingertips or around the mouth during the EIS?
[g]Has your child ever used an asthma inhaler during exercise?

[h]How well does this asthma inhaler help?
*Too few observations in single cells to calculate Fisher's exact

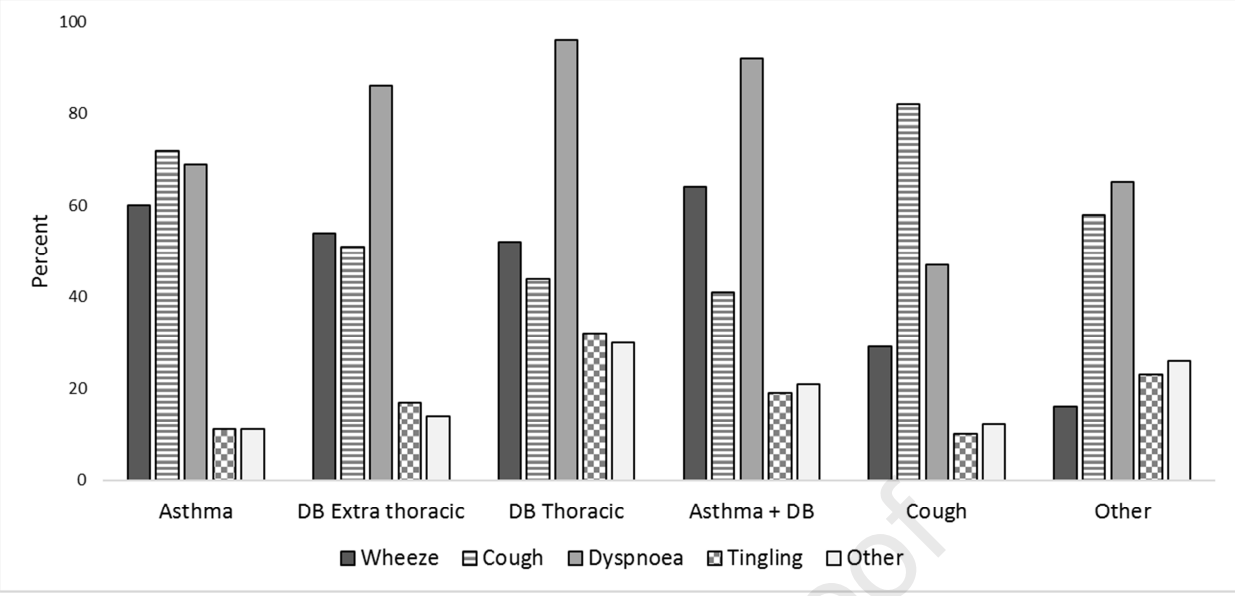
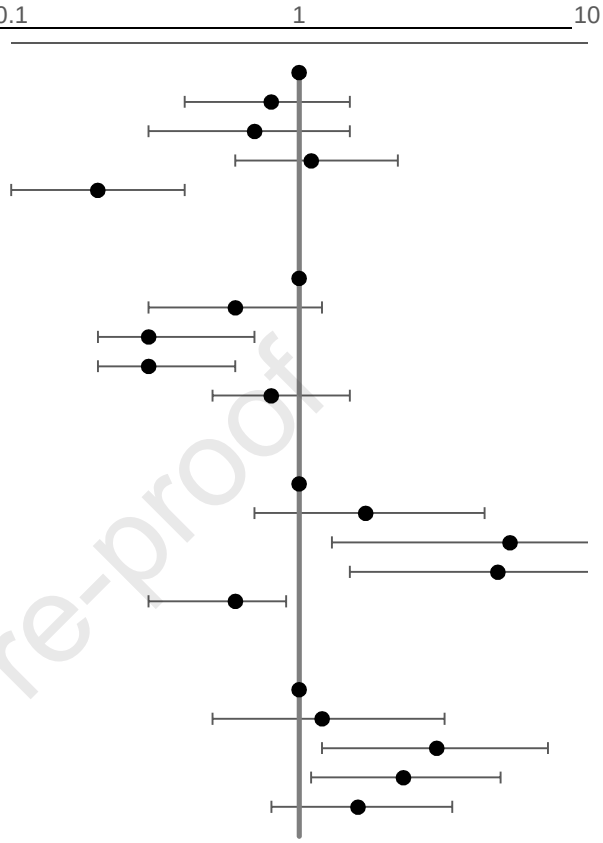


Figure 2 Comparison of type of exercise-induced symptoms between diagnosis groups using multinomial regression models adjusted for age and sex

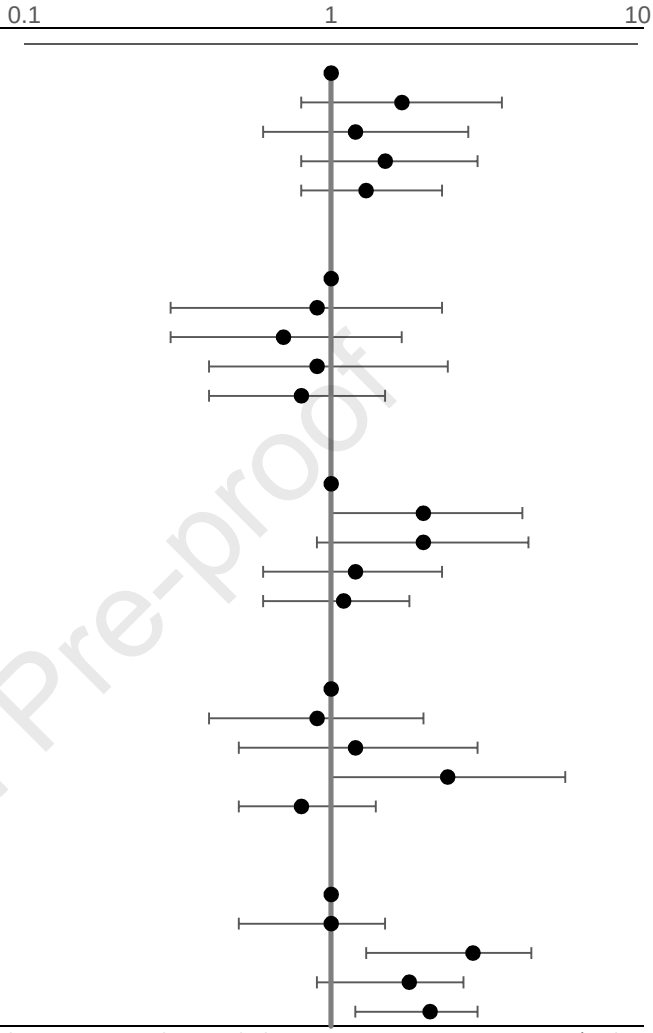
	RRR	95%CI
Wheeze		
Asthma (base)	1	
Extrathoracic DB	0.8	0.4 - 1.5
Thoracic DB	0.7	0.3 - 1.5
Asthma + DB	1.1	0.6 - 2.2
Cough + other	0.2	0.1 - 0.4
Cough		
Asthma (base)	1	
Extrathoracic DB	0.6	0.3 - 1.2
Thoracic DB	0.3	0.2 - 0.7
Asthma + DB	0.3	0.2 - 0.6
Cough + other	0.8	0.5 - 1.5
Dyspnea		
Asthma (base)	1	
Extrathoracic DB	1.7	0.7 - 4.4
Thoracic DB	5.4	1.3 - 23.1
Asthma + DB	4.9	1.5 - 16.2
Cough + other	0.6	0.3 - 0.9
Tingling feeling		
Asthma (base)	1	
Extrathoracic DB	1.2	0.5 - 3.2
Thoracic DB	3.0	1.2 - 7.3
Asthma + DB	2.3	1.1 - 5.0
Cough + other	1.6	0.8 - 3.4
Other	*Too few observations to perform multinomial regression analysis	



The graphs represent relative risk ratios from multinomial regression analysis with diagnosis categories as outcome (asthma as base variable) and types of symptom (wheeze, cough, dyspnea, tingling sensation in fingertips/lips, other symptoms) adjusted for age and sex. RRR, relative risk ratio; 95%CI, 95% confidence interval; DB, dysfunctional breathing

Figure 3 Comparison of activities triggering exercise-induced between diagnosis groups using multinomial regression models adjusted for age and sex

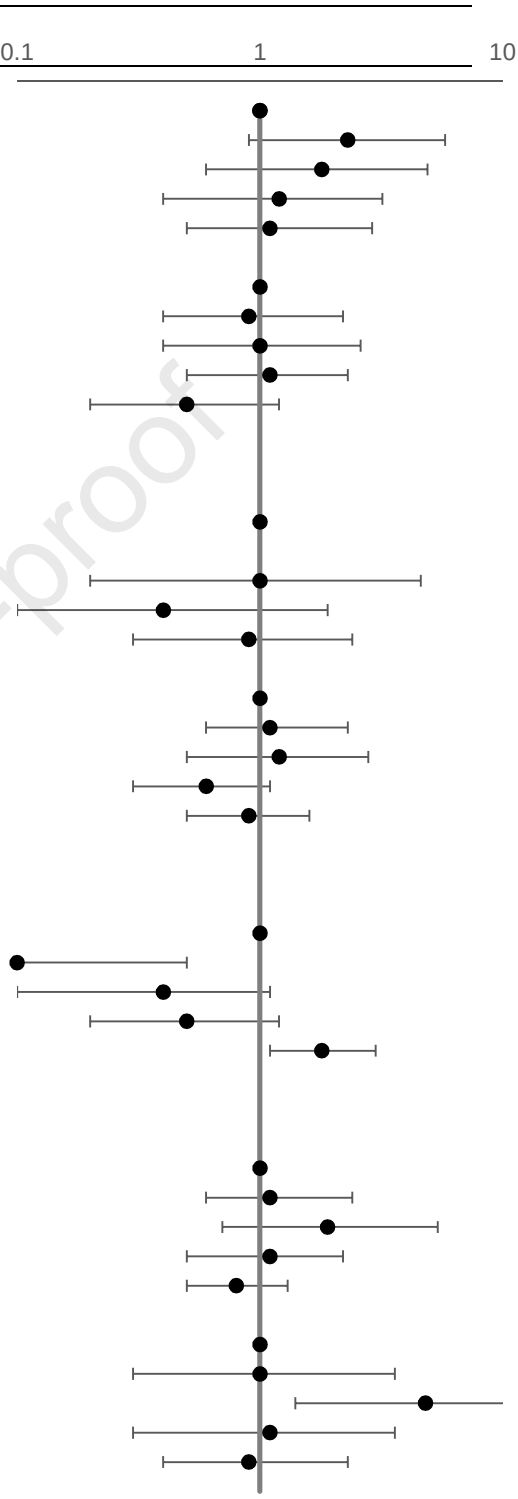
	RRR	95%CI
Run short distance (50-100 m)		
Asthma (base)	1	
Extrathoracic DB	1.7	0.8 - 3.6
Thoracic DB	1.2	0.6 - 2.8
Asthma + DB	1.5	0.8 - 3.0
Cough + other	1.3	0.8 - 2.3
Run long distance (>1 km)		
Asthma (base)	1	
Extrathoracic DB	0.9	0.3 - 2.3
Thoracic DB	0.7	0.3 - 1.7
Asthma + DB	0.9	0.4 - 2.4
Cough + other	0.8	0.4 - 1.5
Bicycle riding		
Asthma (base)	1	
Extrathoracic DB	2.0	1.0 - 4.2
Thoracic DB	2.0	0.9 - 4.4
Asthma + DB	1.2	0.6 - 2.3
Cough + other	1.1	0.6 - 1.8
Intensive sport games		
Asthma (base)	1	
Extrathoracic DB	0.9	0.4 - 2.0
Thoracic DB	1.2	0.5 - 3.0
Asthma + DB	2.4	1.0 - 5.8
Cough + other	0.8	0.5 - 1.4
Swimming		
Asthma (base)	1	
Extrathoracic DB	1.0	0.5 - 2.0
Thoracic DB	2.9	1.3 - 6.2
Asthma + DB	1.8	0.9 - 3.4
Cough + other	2.1	1.2 - 3.4



The graphs represent relative risk ratios from multinomial regression analysis with diagnosis categories as outcome (asthma as base variable) and trigger activities (run, cycle, intensive sport games, swim) adjusted for age and sex. RRR, relative risk ratio; 95%CI, 95% confidence interval; m, meter; km, kilometer; DB, dysfunctional breathing

Figure 4: Comparison of exercise-induced symptom characteristics (localization of dyspnea, respiratory phase, onset, and duration of symptoms) between diagnosis groups using multinomial regression models adjusted for age and sex

	RRR	95% CI		
Localization: Throat vs. Chest				
Asthma (base)	1			
Extrathoracic DB	2.3	0.9	-	5.8
Thoracic DB	1.8	0.6	-	4.9
Asthma + DB	1.2	0.4	-	3.2
Cough + other	1.1	0.5	-	2.9
Localization: Throat and chest vs. chest				
Asthma (base)	1			
Extrathoracic DB	0.9	0.4	-	2.2
Thoracic DB	1.0	0.4	-	2.6
Asthma + DB	1.1	0.5	-	2.3
Cough + other	0.5	0.2	-	1.2
Respiration phase (reference category: inspiration)				
Expiration				
Asthma (base)	1			
Extrathoracic DB	-			
Thoracic DB	1.0	0.2	-	4.6
Asthma + DB	0.4	0.1	-	1.9
Cough + other	0.9	0.3	-	2.4
Expiration and inspiration				
Asthma (base)	1			
Extrathoracic DB	1.1	0.6	-	2.3
Thoracic DB	1.2	0.5	-	2.8
Asthma + DB	0.6	0.3	-	1.1
Cough + other	0.9	0.5	-	1.6
Onset of symptoms				
After exercise vs. during exercise				
Asthma (base)	1			
Extrathoracic DB	0.1	0.03	-	0.5
Thoracic DB	0.4	0.1	-	1.1
Asthma + DB	0.5	0.2	-	1.2
Cough + other	1.8	1.1	-	3.0
Duration of symptoms				
5-10 min vs 1-2 min				
Asthma (base)	1			
Extrathoracic DB	1.1	0.6	-	2.4
Thoracic DB	1.9	0.7	-	5.4
Asthma + DB	1.1	0.5	-	2.2
Cough + other	0.8	0.5	-	1.3
>10 min vs 1-2 min				
Asthma (base)	1			
Extrathoracic DB	1.0	0.3	-	3.6
Thoracic DB	4.8	1.4	-	16.8
Asthma + DB	1.1	0.3	-	3.6
Cough + other	0.9	0.4	-	2.3
Effect of asthma medication	*			



The graphs represent relative risk ratios from multinomial regression analysis with diagnosis categories as outcome (asthma as base variable) and characterizations of exercise-induced symptoms (localization of dyspnea, respiration phase, and duration) as explanatory variables. RRR, relative risk ratio; 95%CI, 95% confidence interval; DB, dysfunctional breathing
*Too few observations to perform multinomial regression analysis