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Sex differences in asthma in swimmers and tennis players

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1 Introduction

2

3 Asthma and allergic diseases are common and have increased during the last four decades
4 even if prevalence seems to have stabilized during the most recent years. The rise in asthma
5 and allergies has been especially prominent among children and adolescents⁽¹⁾. The cause of
6 the increasing prevalence might to some extent be improved diagnostics, but a multifactorial
7 explanation has been suggested where allergen exposure, environmental factors and lifestyle
8 changes each plays a role.

9

10 Before puberty, the prevalence of asthma is higher in boys than in girls. A gender switch in
11 the prevalence of asthma occurs in adolescence, with adult females having a higher
12 prevalence than males^(2, 3). The use of asthma-related health care is higher in males from two
13 to 13 years and greater in female subjects older than 23 years⁽⁴⁾. Since this change in asthma
14 prevalence seems to occur during puberty, hormonal changes have been discussed as one
15 potential underlying factor. The prevalence of asthma seen in each sex could be related to
16 hormonal differences through influence on airway size, inflammatory conditions, and smooth
17 muscle and vascular functions^(2, 5, 6).

18

19 There have been major changes in society, with changes in both lifestyle factors and physical
20 activity. It is common knowledge that physical activity is a health-promoting factor, and
21 physical activity in adolescence leads to a higher level of physical activity in adults⁽⁷⁾. Regular
22 physical activity reduces the risk of premature mortality and the frequency of many common
23 diseases and is also recommended as a part of treatment for several chronic diseases⁽⁷⁾.
24 Physical activity increases tolerance to exercise and thereby decreases the sensitivity to
25 exercise-induced symptoms among asthmatic children⁽⁸⁾. It is also suggested that physical

26 activity in adolescence promotes a healthy adult lifestyle and is positively associated with
27 mental health characteristics such as higher self-esteem, quality of life^(7, 9), fewer
28 psychosomatic symptoms⁽¹⁰⁾ as well as improved academic performance⁽¹¹⁾. Exercising on the
29 elite level may at the same time be a risk factor for allergic sensitization and the development
30 of both asthma and rhinitis⁽¹²⁾. However, the type of exercise and the surrounding
31 environment connected to the sporting activity is closely connected to this risk.

32

33 We have previously reported an increased prevalence of asthma among elite-aspiring
34 swimmers, compared to healthy controls⁽¹³⁾. The increased prevalence was not related to
35 atopy or evident allergic sensitization and seems to be related to duration and intensity of
36 training in the sport-specific environment. The increased prevalence of asthma symptoms
37 found is objectively supported by an increased number of subjects positive to mannitol, either
38 direct or measured as increased reversibility (defined as improvement of FEV₁ by $\geq 15\%$ after
39 terbutaline compared to the maximum fall in FEV₁)⁽¹⁴⁾. There was also an increased
40 prevalence of exercise-induced asthmatic responses.

41

42 The aim of the present study was to explore gender-related differences in asthma-related
43 outcomes in elite-aspiring swimmers, tennis players and a reference group, matched by age
44 and sex, i.e. if the asthma prevalence and the expression of airway disease differed between
45 males and females. A second aim was to investigate and compare gender differences in life
46 style, psychosomatic symptoms and wellbeing in the different groups.

47

48 **Methods**

49 **Subjects**

50 In the year 2007 all students at the age of 13-20 years in the community of Vellinge (n=1773)
51 were invited to the study, and 1628 (92%) were included. In 2007-2012 adolescent elite and
52 elite-aspiring swimmers and tennis players were recruited from three elite swimming clubs
53 and six elite tennis clubs in the south-western part of Sweden to participate in studies of
54 airway hyper-responsiveness. 105 swimmers were invited and 101 swimmers were included,
55 and 87 tennis players were invited and 86 were included.

56 **Questionnaire**

57 The questionnaire addressed presence of respiratory and allergic symptoms, life style factors,
58 psychosomatic symptoms and well-being⁽¹³⁾. The questions related to respiratory symptoms,
59 allergy and some of the lifestyle questions are validated and have previously been used in the
60 ISAAC⁽¹⁵⁾ and OLIN^(13, 16, 17). The other questions concerning lifestyle, psychosomatic
61 symptoms and quality of life have previous been used in different school studies in Sweden
62 and Europe^(13, 18). The remaining, mainly sport-related questions have been tested for
63 understanding and corrected by sample interview.

64

65 Three indices were created based on the questionnaire.

66 - *Psychosomatic symptoms* was based on self-reported frequency of symptoms of
67 headache, stomach ache, dizziness, irritability, nervousness, depression and sleep
68 disorders. Each symptom (seven in total) was scored (0= as not at all, 1=monthly,
69 2=weekly and 3=every day) with a total maximum score of 21.

70 - *Quality of life index* was done as a mean (VAS scale 1-10) of responses to questions
71 involving general well-being with regard to both well-being in school and at leisure as
72 well as questions about friends, loneliness, meaning in life, stress and anxiety.

73 - *Self-esteem index* was done as a mean (VAS scale 1-10) of responses to the questions
74 concerning school performance, how healthy and how physically fit they consider
75 themselves to be.

76

77 The reference group completed the questionnaire in their classrooms and the swimmers
78 completed the questionnaire in their training centre. Completion of the questionnaire was the
79 first study-related event for the athletes. The questionnaire was self-filled in. Both the
80 reference group and the swimmers had the opportunity to ask questions and the staffs were
81 the same for both groups.

82 The reference group was divided into three subgroups depending on the level of physical
83 activity reported in the questionnaire, sedentary controls (no physical activity outside school,
84 n=436), recreational controls (physical activity outside school of up to <10 h/week (median
85 4h, IQR 3-6h), n=942) and elite training controls (physical activity outside school \geq 10 h/week
86 (median 12h, IQR 10-15h), n=231).

87

88 **Allergy testing**

89 All subjects were skin prick-tested with a panel of airborne allergens, i.e pollen (birch,
90 timothy-grass and mugwort), pets (cat, dog and horse), mould (*Claudosporium* and
91 *Alternaria*) and house dust mite (*D. pteronyssinus* and *D. Farinae*).

92

93 **Exhaled Nitric Oxide**

94 A handheld device (NIOX Mino, Aerocrine, Sweden) was used and the testing procedure was
95 according to the ATS and ERS recommendations with a exhaled flow rate of 50 ml/s⁽¹⁹⁾.

96

97 **Mannitol challenge test**

98 All the swimmers (n=101) and most of the tennis players (n=79) performed the test at site for
99 the sport activities. Mannitol (Aridol™, Pharmaxis®) was inhaled in incremental doses until a
100 maximal cumulative dose of 635 mg was reached or a drop in FEV₁ of 15% occurred. A flow
101 volume spirometry was performed at baseline and 60 s after each dose. Post challenge FEV₁
102 was measured after 30 minutes. Thereafter all the athletes were given inhaled terbutaline (1
103 mg) followed by a new spirometry after another 30 minutes. A positive test was defined either
104 as positive *ordinary criteria* (a drop in FEV₁ of $\geq 15\%$ of baseline or a 10% fall between two
105 provocation steps) or as positive *extended criteria* (ordinary criteria and/or positive
106 reversibility $\geq 15\%$ compared to FEV₁ past provocation).

107

108 **Exercise challenge test**

109 Most swimmers (n=97) and tennis-players (n=67) performed an exercise challenge test. In the
110 *sport-specific exercise test for the swimmers* both males and females swam 600 m in 6-8
111 minutes. During the first 2 minutes the target pulse rate was 150. Thereafter they finished the
112 lap during the next 4-6 minutes, aiming to achieve a pulse rate $\geq 90\%$ of maximal capacity. In
113 the *sport-specific exercise test for the tennis players* all participants ran for six minutes on the
114 tennis court mimicking the movements in tennis. The target pulse for the first two minutes
115 was 150, while during the last four minutes they were aiming for $\geq 90\%$ of maximal capacity.
116 For both the swimmers and the tennis players the pulse rate was checked during the race by a
117 Polar waterproof pulse watch (Polar RS 400) and checked manually, the swimmers every 100

118 meters and the tennis players each minute. Flow-volume spirometry was performed before the
119 start, immediately after finishing the lap (about two minutes after the exercise) and then 5, 10,
120 15, and 30 minutes after the race. The subjects then inhaled 1 mg terbutaline and a new
121 spirometry was performed after another 30 minutes. A positive test was defined either as
122 positive ordinary criteria (a drop in FEV₁ of $\geq 10\%$ from baseline) or as positive extended
123 criteria (ordinary criteria and/or positive reversibility $\geq 15\%$ compared to the lowest FEV₁
124 value past provocation).

125

126 **Statistics**

127 SPSS version 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data is
128 given as median (IQR), unless otherwise stated. Pearson's Chi-square test, Fishers exact test
129 and Mann-Whitney's U-test were used for group comparisons. A p-value of < 0.05 (two
130 tailed) was considered significant. In calculation of prevalence of symptoms and diseases,
131 missing answers to individual questions (0.9-1.2%) were treated as missing answers and
132 excluded from the analyses.

133

134 The study was approved by the Regional Ethics review board in Lund, 87/2007 and 357/2008
135 and all the participants and/or parents gave written informed consent.

136 **Results**

137 **Study population**

138 In the reference group nobody refused to participate. Those who did not participate were not
139 in school during the school days the study took place (mostly the highest classes) or (15 years
140 old or younger) and had no written approval from their parents.

141

142 There was no significant difference in age or sex between the reference group, the swimmers
143 and the tennis players. For the training groups there were no significant differences in the time
144 they had been active in their sport but the swimmers trained significantly more hours per
145 week than the tennis players ($p \leq 0.0001$) and the tennis players trained significantly more than
146 the reference group ($p \leq 0.0001$)(Table 1). There was a clear tendency for the males in the
147 tennis group to have been training for a significantly longer period than the females
148 ($p=0.053$).

149

150 **Respiratory symptoms and doctor-diagnosed asthma**

151 *Reference group*

152 Exercise-induced symptoms (EIS), asthma in the past and asthmatic symptoms last year
153 (independent of whether the symptoms were triggered by allergens, exercise or irritants), were
154 significantly higher in females. There were also more respiratory symptoms reported earlier in
155 life ($p=0.055$) among the females. However there was no significant difference in physician-
156 diagnosed asthma or being on treatment with inhaled corticosteroids. There was no difference
157 in the frequency of asthma exacerbations or in rhinitis with impact on daily living. (Table 2a)

158

159 *Athletes*

160 Asthma symptoms during the last twelve months was significantly more frequent among the
161 female athletes ($p=0.029$). The difference between males and females was more pronounced
162 when looking at asthmatic symptoms in relation to exercise ($p=0.001$) but only a tendency for
163 more exercise-induced symptoms in females ($p=0.092$). (Table2b).

164 The female athletes had a significantly higher frequency of exacerbations than the females in
165 the reference group regarding all exacerbations including self-managed ($p=0.001$). There was
166 a tendency for more exacerbations among the male athletes compared to the reference group

167 (p=0.072). When looking at each sport separately, the swimming females had significantly
168 more asthma symptoms (p=0.005) than the males and the symptoms were not only exercise
169 related. This was in contrast to the tennis players where no similar difference could be found.
170 (Figure 1)

171

172 *Atopy*

173 There was no gender difference in the frequency of sensitization to airborne allergens. The
174 males had a significantly higher FeNO values (p=0.021) and there was a tendency for a higher
175 number of FeNO >20 ppb (p=0.063) among the males.

176

177 *Airway hyper-reactivity tests*

178 When investigating swimmers and tennis players as a group (=athletes), the females athletes
179 were more often reversible after provocation in both mannitol provocation test (p=0.032) and
180 exercise challenge test (p=0.024.) The females had a significantly higher frequency of
181 positive mannitol provocation test than the males, both using ordinary criteria (p=0.042) and
182 extended criteria (p=0.046). In the exercise challenge test there was a tendency for more
183 positive exercise tests with extended criteria (p=0.054) among the females. (Table 3)

184 When comparing the swimming females with their male peers there were significantly more
185 positive exercise challenge tests both with ordinary (p=0.042) and extended criteria (p=0.022)
186 not seen in the mannitol provocation test (data not shown).

187

188 *Health behaviour*

189 In the reference group the males had breakfast every day (70%) more often than the females
190 (63%)(p=0.004). The males were more prone to drink alcohol every week (24% of males and
191 18% of females, p=0.003) while the females more often were regular smokers (20% of

192 females and 15% of males, $p=0.005$). In the athlete group (swimmers and tennis players) there
193 were no differences between genders. However, the tennis playing males drank significantly
194 more alcohol than the swimming males ($p=0.036$); 22 of the tennis-playing males and 12 of
195 the swimming males drank alcohol every month, and four of the tennis-playing males and
196 none of the swimming males drank alcohol every week.

197

198 *Self-esteem and well-being*

199 The females in the reference group had significantly more psychosomatic symptoms (median
200 score: females 8.47 and males 5.18, $p\leq 0.0001$), while the males had higher self-esteem score
201 (median: males 7.44 and females 6.89, $p\leq 0.0001$) and felt more well-being than the females
202 (median score: males 8.0 and females 7.59, $p\leq 0.0001$).

203 Among the athletes, the same differences between genders were seen regarding psychosomatic
204 symptom scores (males 5.18 and females 7.14, $p=0.005$) and self-esteem score (males 8.45 and
205 females 8.11, $p=0.048$) though there was no difference regarding well-being (males 8.33 and
206 females 8.08). (Figure 2)

207 The male swimmers and tennis players had higher self-esteem ($p\leq 0.0001$) than the reference
208 males, but well-being and psychosomatic symptoms were the same. The swimming and tennis
209 playing females had significantly higher self-esteem ($p\leq 0.0001$), fewer psychosomatic
210 symptoms ($p=0.004$) and a tendency for more well-being ($p=0.069$) than the females in the
211 reference group. (Figure 2)

212 The males in both groups reported anxiety and stress adjacent to school matters and love
213 relationships. Their sport activities generated stress, especially for swimmers and tennis
214 players, but also for the elite training reference group. This pattern was also seen among the
215 girls in both groups, but family matters were also an important cause for concern among the
216 females. (Figure 3)

217

218 Motivation for training

219 In the reference group the most frequent motives for physical activity in both males and
220 females were related to fitness, well-being, appearance and weight control, but to have fun
221 was also important. There were no gender differences except weight control more often
222 reported by the females ($p \leq 0.00010$).

223 To have fun, to meet friends and to feel better were important to the swimmers and tennis
224 players but also to get better in their respective sport. One of the most reported motives for
225 training among the swimmers was to meet friends. No significant gender differences were
226 noted in the groups. (Figure 4)

227

228 Discussion

229

230 The females in both the reference group and the athlete group reported more asthma
231 symptoms than the males. The female swimmers and tennis players as a group were more
232 often positive in the mannitol provocation test than the males independent of if ordinary or
233 extended criteria were used. The female swimmers were also more often positive in the
234 exercise challenge test than their male colleagues. In contrast, there were no differences in
235 physician-diagnosed asthma or in the treatment with inhaled corticosteroids.

236

237 Respiratory symptoms

238 There was a high frequency of respiratory symptoms in all groups, unexpectedly high in the
239 reference group. A possible explanation could be the high percentage of physically active
240 adolescents in the reference group, both elite training (12.7%), but also recreational training

241 (27.7%). The respiratory symptoms reported were not only in relation to exercise but also
242 outside the training situation in all groups (reference group 25.5%, swimmers 56.4%, and
243 tennis players 34.5%).

244 In both in the reference group and among the swimmers there was a clear difference in
245 respiratory symptoms between genders, most pronounced in the reference group probably due
246 to the larger number in this group. The tennis playing females had been active in their sport
247 for a shorter period than their male peers and this could explain why there was no apparent
248 gender difference in this group.

249 The increased frequency of self-filled in respiratory symptoms was supported by the results in
250 the provocation tests where there were more positive tests among the females. In contrast to
251 these findings there was an absence of difference in physician-diagnosed asthma or regular
252 treatment with inhaled corticosteroids. A differences in the propensity to set an asthma
253 diagnosis depending on gender, more common in males, have been described previously⁽²⁰⁾.
254 Our study supports these findings; the male swimmers were given a proper asthma diagnosis
255 with proper treatment more often than the females. The interviews in relation to the study
256 revealed that health care professionals and coaches as well as the female athletes themselves
257 have difficulty in interpreting their respiratory symptoms. Although the female athletes had
258 obvious obstructive symptoms during the exercise challenge test, they explained their
259 symptoms in terms of poorer fitness than their peers, even though they were training more
260 than sixteen hours a week.

261
262 It is very important to be aware of the other diagnoses that can contribute to the high
263 frequency of respiratory symptoms reported, not only by the females. Obstructions in the
264 upper airways and dysfunctional breathing are common in this age group and have been
265 observed more frequently among female athletes⁽²¹⁻²⁴⁾. Vocal cord dysfunction was not tested

266 for in this study, and it is possible that there are some subjects with exercise-induced
267 symptoms that in fact have vocal cord dysfunction instead of asthma. This may have affected
268 the exercise-induced symptom outcome in this study. It is very important, in our opinion,
269 especially in this age group to take a thorough medical history and, if this does not provide
270 compelling evidence for an asthma diagnosis, to continue with further investigations such as
271 FeNO and appropriate provocations tests. It is essential to educate healthcare professionals,
272 but also coaches and athletes, both about asthma symptoms but also about other diagnoses
273 that may cause exercise-induced respiratory symptoms, so that they can give appropriate
274 training advice as well as proper medication to the athletes.

275

276 *Health behaviour and quality of life*

277 The males in the reference group had a more regular intake of breakfast than the females. The
278 females were more often regular smokers and the males drank more alcohol; this is in
279 agreement with earlier reports⁽²⁵⁾. The athletes as a group demonstrated healthier behaviour
280 earlier shown for the swimmers⁽²⁵⁾ and there were no gender differences regarding healthy
281 behaviour.

282 The gender differences seen in the reference group with females having more psychosomatic
283 symptoms, a lower self-esteem and a less well-being is in line with previous reports from
284 adolescents where gender was a strong predictor for more psychosomatic symptoms and more
285 nervous symptoms^(7, 26). The gender difference found in the reference group was less
286 pronounced among the athletes (swimmers and tennis players), where the females, even if
287 they had more psychosomatic symptoms, they were less pronounced and there were no
288 differences regarding self-esteem and well-being. This could be an indication of the
289 importance of regular physical activity when it comes to balancing gender differences
290 regarding quality of life.

291 Both the male and the female swimmers and tennis players had higher self-esteem compared
292 to the reference group. Unlike the male groups, showing no difference in psychosomatic
293 symptoms and well-being in relation to physical activity the females had significantly less
294 psychosomatic symptoms and a clear tendency towards more well-being. It might be that
295 physical activity may be more important for better life quality and healthy behaviour in the
296 female group. In agreement with this we found that the sedentary females had the lowest self-
297 esteem and experienced less well-being. They had the highest frequency of psychosomatic
298 symptoms, and were also the most frequent smokers.

299 The difference in terms of motivation for training did not differ so much between tennis
300 players and swimmers except “to meet friends” was ranked higher among swimmers. This
301 corresponds well with swimmers spending .a lot of time in the swimming pools outside
302 training sessions and socializing with other swimmers. The reference, however, was more
303 focused on appearance and the health benefits of the training.

304

305 Respiratory symptoms in relation to exercise were more frequent among females in both the
306 reference group and the athletes. The female athletes also had a higher prevalence of positive
307 mannitol and exercise challenge test. This may suggest that females may be more vulnerable
308 to the epithelial stress that is applied to the airways during long term exercise and sport. In
309 contrast to having more evident airway disease, fewer females were actually diagnosed
310 correctly, and thereby did not get the appropriate treatment. This indicates the need to have a
311 gender perspective when diagnosing sport-related asthma. There is also an indication that
312 physical activity is a stronger promoting factor for higher life quality in females.

313

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Table 1 Study population

	Reference group n=1626		Swimmers and Tennis players n=187		Swimmers n=101		Tennis players n=86	
	Male	Female	Male	Female	Male	Female	Male	Female
Gender n (%)	828 (50.9)	798 (49.1)	109 (58.5)	78 (41.5)	55 (54.5)	46 (45.5)	54 (62.8)	32 (38.6)
Age median (IQR)	16 (15-17)	16 (15-17)	16 (15-18)	16 (14-18)	16 (14-17)	16 (14-18)	17 (15-18)	16 (14-18)
Training more than 6 years n (%)	268 (32.4)	246 (30.8)	95 (87.1)	70 (89.7)	44 (80.0)	44 (97.5)	51 (94.4)	26 (81.3)
Weekly training. hours Median (IQR)	4 (0-8)	3 (0-6)	15 (12-18)	15 (12-18)	18 (16-20)	18 (14-20)	13 (11-15)	12 (10-15)

Table 2a Respiratory symptoms and Doctor-diagnosed asthma in the reference group

Reference group n=1626	Males n=828		Females n=798		p
	n	%	n	%	
Exercise induced symptoms	201	24.5	292	36,6	0.000
Asthma ever	227	28.8	266	33.3	0.050
Current asthma symptoms	183	22.3	322	29.1	0.002
Current asthma symptoms in relation to airborne allergens	52	6.3	72	9.0	0.041
Current asthma symptoms in relation to exercise	102	12.4	155	19.4	0.000
Current asthma symptoms in relation to irritants	75	9.1	130	16.3	0.000
Asthma exacerbations last year	44	5.3	52	6.5	0.069
Rhinitis with impact on daily living	165	20.1	190	23.8	NS
Doctors diagnosed asthma	146	17.8	129	16.2	NS
Inhaled corticosteroids regularly	43	5.2	36	4.5	NS

Table 2b Respiratory symptoms and Doctor-diagnosed asthma in Athletes

Swimmers and tennis players n=187	Males N=109		Females N=78		p
	n	%	n	%	
Exercise induced symptoms	64	59.8	56	71.8	0.092
Asthma ever	52	48.6	49	62.8	0.055
Current asthma symptoms	43	40.2	44	56.4	0.029
Current asthma symptom in relation to airborne allergens	13	12.1	13	16.7	NS
Current asthma in relation to exercise	34	31.8	40	51.3	0.007
Current asthma with hyperreactive symptoms	26	24.3	21	26.9	NS
Asthma exacerbations last year	10	9.3	13	16.7	NS
Rhinitis with impact on daily living	35	32.7	26	33.3	NS
Doctors diagnosed asthma	29	27.1	29	37.2	NS
Inhaled corticosteroid regularly	12	11.2	10	12.8	NS
Positive skin prick test	54	51.4	38	49.4	NS

Table 3 Bronchial hyper-reactivity to mannitol and exercise in swimmers and tennis players

Swimmers and tennis players n=187	Males n=109		Females n=78		p
	n	%	n	%	
Direct positive mannitol provocation test	13	12.4	17	22.7	0.042
Reversibility mannitol provocation test	25	23.8	29	38.7	0.032
Positive mannitol provocation test extended variables	26	24.8	29	28.7	0.046
Direct positive exercise test	14	15.1	16	22.5	0.219
Reversibility Exercise provocation test	11	11.8	18	25.4	0.024
Positive exercise provocation test extended variables	19	20.4	24	33.8	0.054
Any positive provocation test ordinary criteria	28	25.7	25	32.1	0.341
Reversibility any test	31	29.0	37	47.4	0.010
Any positive provocation test extended criteria	39	35.8	38	48.7	0.076

Figure legends

Figure 1 Respiratory symptoms, Doctor-diagnosed asthma and history of asthma exacerbations among reference group, swimmers and tennis players divided according to gender. EIS=exercise induced symptoms, AS=asthma symptoms, DDA=Doctor-diagnosed asthma.

Figure 2 Psychosomatic symptoms, well-being and self-esteem in relation to physical activity, sport and gender. The Y-axis shows the total score of the subject regarding headache, stomach ache, dizziness, irritability, nervousness, depression and sleep disorders. N.S=non significant, *= $p<0.05$, **= $p<0.01$ and ***= $p<0.001$.

Figure 3 Reasons for anxiety and stress in relation to gender and elite training.

Figure 4 Motive for exercise in relation to gender and physical activity.







