Sex differences in asthma in swimmers and tennis players

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Introduction

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

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

There have been major changes in society, with changes in both lifestyle factors and physical activity. It is common knowledge that physical activity is a health-promoting factor, and physical activity in adolescence leads to a higher level of physical activity in adults[7]. Regular physical activity reduces the risk of premature mortality and the frequency of many common diseases and is also recommended as a part of treatment for several chronic diseases[7]. Physical activity increases tolerance to exercise and thereby decreases the sensitivity to exercise-induced symptoms among asthmatic children[8]. It is also suggested that physical activity in adolescence promotes a healthy adult lifestyle and is positively associated with mental health characteristics such as higher self-esteem, quality of life[7, 9], fewer psychosomatic symptoms[10] as well as improved academic performance[11]. Exercising on the elite level may at the same time be a risk factor for allergic sensitization and the development of both asthma and rhinitis[12]. However, the type of exercise and the surrounding environment connected to the sporting activity is closely connected to this risk.

We have previously reported an increased prevalence of asthma among elite-aspiring swimmers, compared to healthy controls[13]. The increased prevalence was not related to atopy or evident allergic sensitization and seems to be related to duration and intensity of training in the sport-specific environment. The increased prevalence of asthma symptoms found is objectively supported by an increased number of subjects positive to mannitol, either direct or measured as increased reversibility (defined as improvement of FEV_1 by $\geq$15% after terbutaline compared to the maximum fall in FEV_1)[14]. There was also an increased prevalence of exercise-induced asthmatic responses.

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

Methods

Subjects

In the year 2007 all students at the age of 13-20 years in the community of Vellinge (n=1773) were invited to the study, and1628 (92%) were included. In 2007-2012 adolescent elite and elite-aspiring swimmers and tennis players were recruited from three elite swimming clubs and six elite tennis clubs in the south-western part of Sweden to participate in studies of airway hyper-responsiveness. 105 swimmers were invited and 101 swimmers were included, and 87 tennis players were invited and 86 were included.

Questionnaire

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

Three indices were created based on the questionnaire.

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

- *Quality of life index* was done as a mean (VAS scale 1-10) of responses to questions involving general well-being with regard to both well-being in school and at leisure as well as questions about friends, loneliness, meaning in life, stress and anxiety.
- *Self-esteem index* was done as a mean (VAS scale 1-10) of responses to the questions concerning school performance, how healthy and how physically fit they consider themselves to be.

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

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

Allergy testing

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

Exhaled Nitric Oxide

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

Mannitol challenge test

All the swimmers (n=101) and most of the tennis players (n=79) performed the test at site for the sport activities. 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% occurred. A flow volume spirometry was performed at baseline and 60 s after each dose. Post challenge FEV_1 was measured after 30 minutes. Thereafter all the athletes were given inhaled terbutaline (1 mg) followed by a new spirometry after another 30 minutes. A positive test was defined either as positive *ordinary criteria* (a drop in FEV_1 of ≥15% of baseline or a 10% fall between two provocation steps) or as positive *extended criteria* (ordinary criteria and/or positive reversibility ≥15 % compared to FEV_1 past provocation).

Exercise challenge test

Most swimmers (n=97) and tennis-players (n=67) performed an exercise challenge test. In the *sport-specific exercise test for the swimmers* both males and females swam 600 m in 6-8 minutes. During the first 2 minutes the target pulse rate was 150. Thereafter they finished the lap during the next 4-6 minutes, aiming to achieve a pulse rate ≥90% of maximal capacity. In the *sport-specific exercise test for the tennis players* all participants ran for six minutes on the tennis court mimicking the movements in tennis. The target pulse for the first two minutes was 150, while during the last four minutes they were aiming for ≥90% of maximal capacity. For both the swimmers and the tennis players the pulse rate was checked during the race by a Polar waterproof pulse watch (Polar RS 400) and checked manually, the swimmers every 100 meters and the tennis players each minute. Flow-volume spirometry was performed before the start, immediately after finishing the lap (about two minutes after the exercise) and then 5, 10, 15, and 30 minutes after the race. The subjects then inhaled 1 mg terbutaline and a new spirometry was performed after another 30 minutes. A positive test was defined either as positive ordinary criteria (a drop in FEV_1 of ≥10% from baseline) or as positive extended criteria (ordinary criteria and/or positive reversibility ≥15 % compared to the lowest FEV_1 value past provocation).

Statistics

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

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

Results

Study population

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

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

Respiratory symptoms and doctor-diagnosed asthma

Reference group

Exercise-induced symptoms (EIS), asthma in the past and asthmatic symptoms last year (independent of whether the symptoms were triggered by allergens, exercise or irritants), were significantly higher in females. There were also more respiratory symptoms reported earlier in life (0=0.055) among the females. However there was no significant difference in physician-diagnosed asthma or being on treatment with inhaled corticosteroids. There was no difference in the frequency of asthma exacerbations or in rhinitis with impact on daily living. (Table 2a)

Athletes

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

The female athletes had a significantly higher frequency of exacerbations than the females in the reference group regarding all exacerbations including self-managed (p=0.001). There was a tendency for more exacerbations among the male athletes compared to the reference group (p=0.072). When looking at each sport separately, the swimming females had significantly more asthma symptoms (p=0.005) than the males and the symptoms were not only exercise related. This was in contrast to the tennis players where no similar difference could be found. (Figure 1)

Atopy

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

Airway hyper-reactivity tests

When investigating swimmers and tennis players as a group (=athletes), the females athletes were more often reversible after provocation in both mannitol provocation test (p=0.032) and exercise challenge test (p=0.024.) The females had a significantly higher frequency of positive mannitol provocation test than the males, both using ordinary criteria (p=0.042) and extended criteria (p=0.046). In the exercise challenge test there was a tendency for more positive exercise tests with extended criteria (p=0.054) among the females. (Table 3)
When comparing the swimming females with their male peers there were significantly more positive exercise challenge tests both with ordinary (p=0.042) and extended criteria (p=0.022) not seen in the mannitol provocation test (data not shown).

Health behaviour

In the reference group the males had breakfast every day (70%) more often than the females (63%)(p=0.004). The males were more prone to drink alcohol every week (24% of males and 18% of females, p=0.003) while the females more often were regular smokers (20% of females and 15% of males, p=0.005). In the athlete group (swimmers and tennis players) there were no differences between genders. However, the tennis playing males drank significantly more alcohol than the swimming males (p=0.036); 22 of the tennis-playing males and 12 of the swimming males drank alcohol every month, and four of the tennis-playing males and none of the swimming males drank alcohol every week.

Self-esteem and well-being

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

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

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

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

Motivation for training

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

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

Discussion

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

Respiratory symptoms

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

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

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

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

It is very important to be aware of the other diagnoses that can contribute to the high frequency of respiratory symptoms reported, not only by the females. Obstructions in the upper airways and dysfunctional breathing are common in this age group and have been observed more frequently among female athletes[21-24]. Vocal cord dysfunction was not tested for in this study, and it is possible that there are some subjects with exercise-induced symptoms that in fact have vocal cord dysfunction instead of asthma. This may have affected the exercise-induced symptom outcome in this study. It is very important, in our opinion, especially in this age group to take a thorough medical history and, if this does not provide compelling evidence for an asthma diagnosis, to continue with further investigations such as FeNO and appropriate provocations tests. It is essential to educate healthcare professionals, but also coaches and athletes, both about asthma symptoms but also about other diagnoses that may cause exercise-induced respiratory symptoms, so that they can give appropriate training advice as well as proper medication to the athletes.

Health behaviour and quality of life

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

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

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

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

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

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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		
	n	%	n	%	p
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		
	n	%	n	%	p
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		
	n	%	n	%	p
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

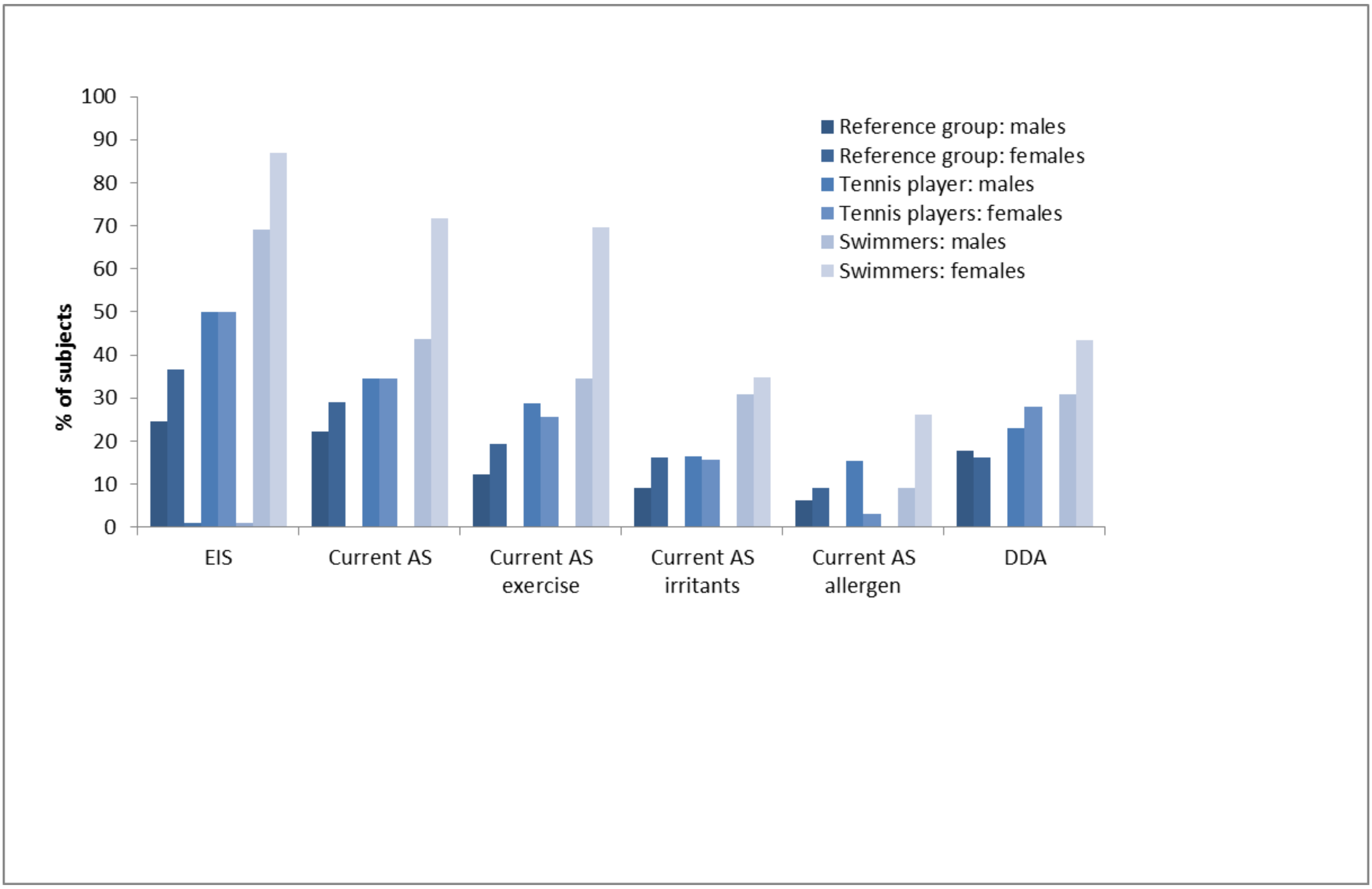
Figure legends

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.

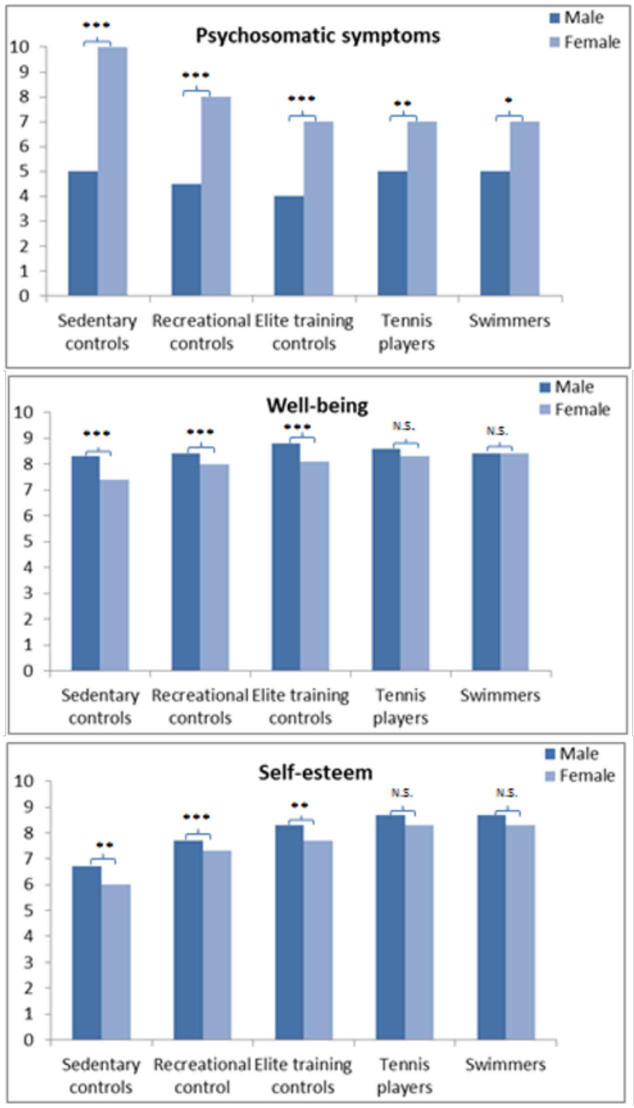
Figure 2 Psychosomatic symptoms, well-being and self-esteem in relation to physical activity, sport and gender. The Y-axis shows the total score of the subject regarding headache, stomach ache, dizziness, irritability, nervousness, depression and sleep disorders. N.S=non significant, *=$p<0.05$, **=$p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



100
90
80
70
60
50
40
30
20
10
0
% of subjects
Reference group: males
Reference group: females
Tennis player: males
Tennis players: females
Swimmers: males
Swimmers: females
EIS
Current AS
Current AS exercise
Current AS irritants
Current AS allergen
DDA



Psychosomatic symptoms
Male
Female
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4
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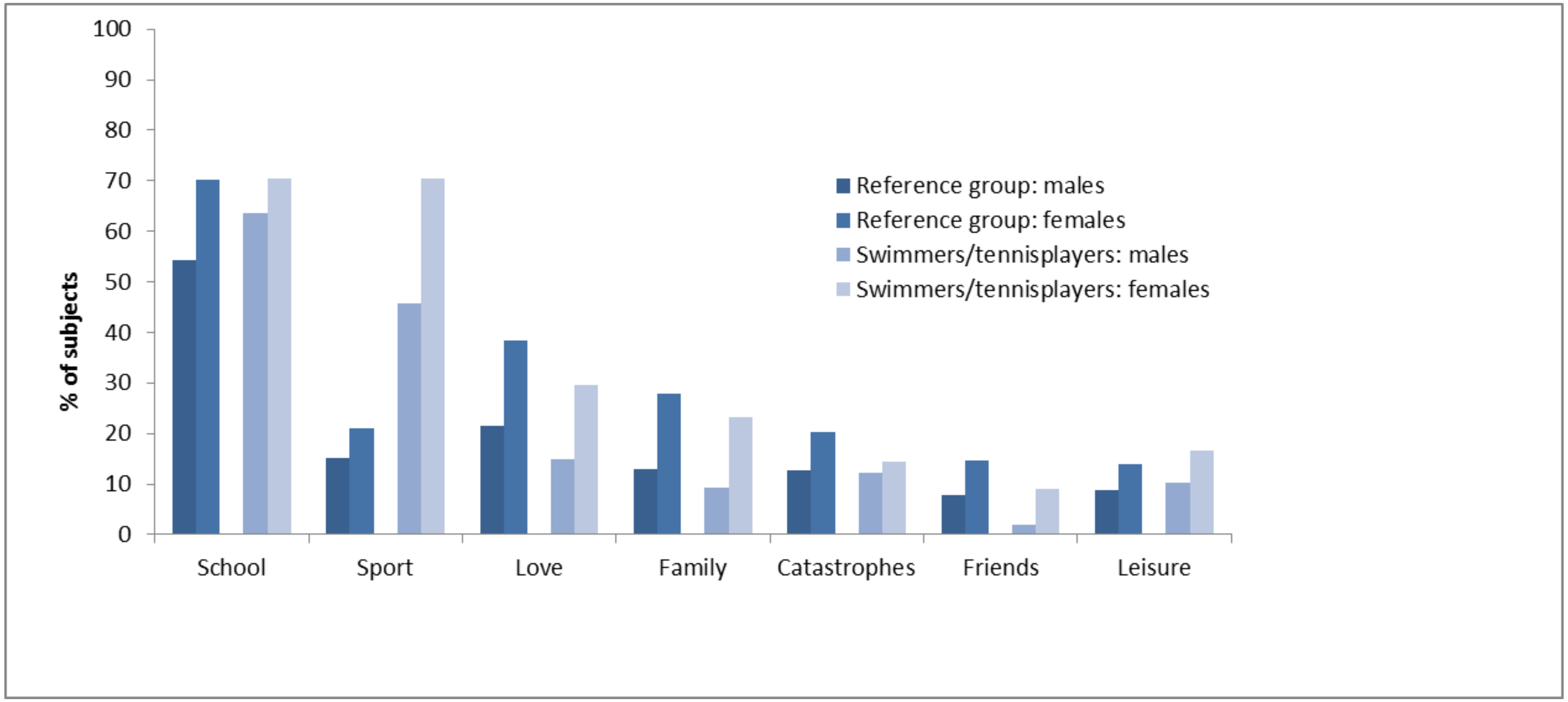
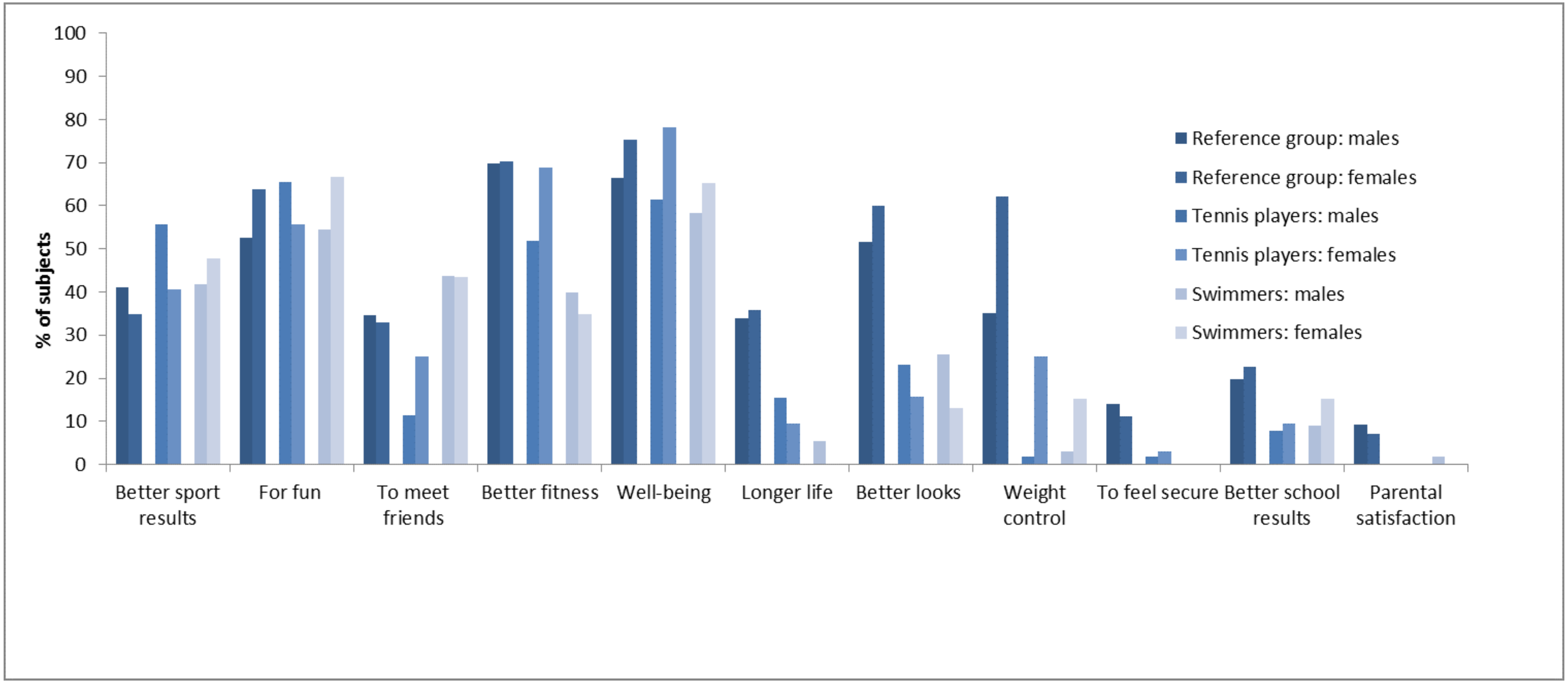
1
0
Sedentary controls
Recreational controls
Elite training controls
Tennis players
Swimmers
Well-being
Male
Female
***
***
***
N.S.
N.S.
Sedentary controls
Recreational controls
Elite training controls
Tennis players
Swimmers
Self-esteem
Male
Female
**
***
**
N.S.
N.S.
Sedentary controls
Recreational control
Elite training controls
Tennis players
Swimmers



100
90
80
70
60
50
40
30
20
10
0
% of subjects
Reference group: males
Reference group: females
Swimmers/tennisplayers: males
Swimmers/tennisplayers: females
School
Sport
Love
Family
Catastrophes
Friends
Leisure


100
90
80
70
60
50
40
30
20
10
0
% of subjects
Reference group: males
Reference group: females
Tennis players: males
Tennis players: females
Swimmers: males
Swimmers: females
Better sport results
For fun
To meet friends
Better fitness
Well-being
Longer life
Better looks
Weight control
To feel secure
Better school results
Parental satisfaction