Sex differences in upper respiratory symptoms prevalence and oral-respiratory mucosal immunity in endurance athletes

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ABSTRACT

The purpose of this study was to examine sex differences in oral-respiratory mucosal immunity and the incidence, severity and duration of upper respiratory symptoms (URS) episodes in endurance athletes during a 16-week winter training period. Blood was collected from 210 subjects (147 men and 63 women) at the start and end of the study for determination of differential leukocyte counts. Timed collections of unstimulated saliva were obtained at the start and at 4-week intervals during the study period. Saliva samples were analysed for salivary antimicrobial peptides and proteins (AMPs). Weekly training and daily illness logs were kept using validated questionnaires. Training loads averaged 11 h/week of moderate-vigorous physical activity and were not different for males and females. The salivary concentration of lysozyme and lactoferrin (both $P<0.04$) but not salivary immunoglobulin A (SIgA) or amylase were higher in males than females. Saliva flow rates were significantly higher in males than females ($P < 0.03$) and consequently so were the salivary secretion rates of lysozyme, lactoferrin and amylase (all $P<0.01$) but not SIgA ($P = 0.097$). Total blood leukocyte, monocyte and lymphocyte counts were not different between the sexes but females had higher numbers of circulating neutrophils ($P = 0.040$). The average number of URS episodes was 0.6 ± 0.8 (mean ± SD) in males and 0.8 ± 1.0 in females ($P = 0.103$) and the number of URS days was higher in females (4.7 vs 6.8 days, $P < 0.02$). The duration of URS episodes was longer in females (11.6 vs 15.5 days, $P < 0.03$). The findings of this study concur with recent reports of illness incidence at major competitive games indicating that female athletes may be more susceptible than their male counterparts to URS and that lower oral-respiratory mucosal immunity may, in part, account for this.

Keywords: exercise training, leukocytes, immunoglobulins, antimicrobial proteins, illness

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INTRODUCTION

Resistance to infection is strongly influenced by the effectiveness of the immune system in protecting the host against pathogenic micro-organisms. Within the general healthy human population there is a range of immuno-competency due to genetic differences, age, nutritional deficiencies and lifestyle habits. The sex of the individual also affects immune function. In females, oestrogens and progesterone modulate immune function (41) and thus immunity is influenced by the menstrual cycle and pregnancy (29). Consequently, sex-based differences in responses to infection, trauma and sepsis are evident (6). Within the general population women are generally more resistant to viral infections and tend to have more autoimmune diseases than men (6). In a review of the literature on respiratory tract infections (RTIs) (20) in which data from 84 studies was extracted it was concluded that males are more susceptible than females to most types of RTIs in all age groups (children, adolescents, adults and the elderly). Anatomic, lifestyle, behavioural and socioeconomic differences between males and females may explain the observed findings and the involvement of sex hormones in the regulation of immune function may also contribute to the reported sex differences in the incidence and severity of the various types of RTIs, especially in adults and adolescents (20). Oestrogens are generally immune enhancing, whereas androgens, including testosterone, exert suppressive effects on both humoral and cellular immune responses. Females have higher levels of plasma immunoglobulin M (IgM) than men and exhibit more vigorous responses to exogenous antigens, indicating a higher level of humoral immunity in females than in males (8). In females, there is increased expression of some cytokines in peripheral blood and vaginal fluids during the follicular phase of the menstrual cycle and with use of hormonal contraceptives (9). In the luteal phase of the menstrual cycle, blood leukocyte counts are higher than in the follicular phase (18), mononuclear cell expression of the heterodimeric transcription factor 1 (a key regulator of the innate immune response) is lower (47), and the immune response is shifted towards a T helper (Th) 2-type response (18). Thus, in the general population, there are differences in some aspects of immune function between men and women that appear to result in women getting fewer viral infections, including those affecting the respiratory tract.

In addition to these sex differences in resting conditions, several studies have documented sex differences in some aspects of the immunological response to exercise (22, 49, 50) including larger post-exercise increases in circulating lymphocytes and natural killer cells in females. The expression of pro-inflammatory and anti-inflammatory genes in response to exercise is also influenced by the menstrual cycle and there are distinct differences in gene expression between women in the luteal phase and men (40). Prolonged strenuous exercise has been associated with a transient depression of immune function (23, 24, 53) and a heavy schedule of training and competition can lead to immune impairment in both male and female athletes (53). This is associated with an increased susceptibility to upper respiratory symptoms (URS) (7, 19, 27, 30, 39, 43, 53) and several studies suggest that reduced secretion of salivary immunoglobulin A (SIgA) and possibly other mucosal antimicrobial proteins may be an important causal factor

(19, 24, 26, 27, 37, 53). However, it is not clear whether any substantial sex differences exist in any aspect of oral-respiratory mucosal immune function in an athletic population or whether any such differences affect URS risk. In contrast to what has been reported for the general population, some recent reports of illness rates among athletes attending large competitive events (e.g. winter and summer Olympic games, athletic and aquatic sport world championships) suggest that URS episodes may actually be more prevalent in the women than the men (4, 5, 14, 16, 17, 36, 46).

The aims of the present study were to determine if sex differences exist in resting immune variables including saliva antimicrobial proteins (AMPs) including SIgA, lysozyme, lactoferrin and amylase secretion and the numbers of circulating leukocyte numbers in an athletic population. We also wished to determine if the prevalence of URS episodes was different in male and female athletes during a period of winter training and competition. Our hypothesis was that saliva AMP secretion rates would be lower in females and that this might be associated with a higher prevalence of URS episodes.

METHODS

Subjects

Two hundred and sixty seven subjects (83 females, 184 males) aged 21 ± 3 years who were engaged in regular sports training (predominantly endurance-based activities such as running, cycling, swimming, triathlon, team games and racquet sports) from Loughborough University, UK volunteered to participate in the study during November 2011. Since our study population was a group of university athletes on a single campus site it is likely that environment and pathogen exposure were similar for all subjects. Subjects ranged from recreationally active to Olympic triathletes and their self-reported training loads (determined by a prescreening questionnaire) averaged 10 ± 3 h/week (mean ± SD). Two hundred and ten subjects (63 females, 147 males) completed the study and provided sufficient blood for routine haematology on 2 occasions and sufficient saliva for analysis of AMPs on all 5 occasions. Their baseline characteristics as shown in Table 1. Among the females 96% reported having regular periods and 40% were taking oral contraceptives. Reasons for dropout were given as foreign travel, injury or persistent non-respiratory illness (preventing subjects from performing training) or due to undisclosed reasons.

Subjects were required to complete a comprehensive health-screening questionnaire prior to starting the study and had not taken any regular medication or antibiotics in the 3 months prior to the study. All subjects were fully informed about the rationale for the study and of all experimental procedures to be undertaken. Subjects provided written consent to participate in the study, which had earlier received the approval of Loughborough University ethical advisory committee. Subjects were enrolled after having fulfilled all inclusion criteria, and presenting none of the exclusion criteria (determined by both questionnaire and interview). Subjects could be included if they were currently healthy, had been

involved in endurance training for at least 2 years, engaged in at least 3 sessions and at least 3 h of total moderate/high-intensity training time per week and were between 18-40 years of age. Subjects representing one or more of the following criteria were excluded from participation: smoking or use of any medication, suffering from or had a history of cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, haematological or psychiatric illness.

Study protocol

For the first visit to the laboratory, subjects arrived in the morning at 08:30-10:30 following an overnight fast of approximately 12 h and no strenuous exercise in the previous 24 h and their body mass and height were recorded. Information about the study was given to them and they then signed an informed consent form. Subjects then sat quietly for 10 min and completed a health-screening questionnaire and inclusion/exclusion criteria questionnaire before being asked to swallow to empty their mouth of any residual saliva before providing an unstimulated saliva sample by passive dribble into a pre-weighed sterile collection tube for a timed period (usually 2 min; longer was allowed if the volume of saliva collected after 2 min was insufficient). After centrifugation for 2 min at 5000 g to remove cells and insoluble matter, saliva samples were stored frozen at -80ºC prior to analysis. Subsequently, a resting venous blood sample (5 ml) was obtained by venepuncture from an antecubital forearm vein into a vacutainer tube (Becton Dickinson, Oxford, UK) containing K_3EDTA for immediate haematological analysis (including haemoglobin, haematocrit and total and differential leukocyte counts) using an automated cell-counter (A^c.T™5diff haematology analyser, Beckman Coulter, High Wycombe, UK). The intra-assay coefficient of variation for all measured blood variables was less than 3.0%. Subjects had to have all haematological values within the normal healthy range to be included in the study.

During the 4-month study period subjects were requested to continue with their normal training programs. Subjects completed a validated self-report health (URS) questionnaire (29) on a daily basis. Subjects were not required to abstain from medication when they were suffering from illness symptoms but they were required, on a weekly basis, to report any unprescribed medications taken, visits to the doctor or any prescribed medications. The illness symptoms listed on the questionnaire were: sneezing, headache, malaise, nasal discharge, nasal obstruction, sore throat, cough, ear ache, hoarseness, fever, chilliness and joint aches and pains. The non-numerical severity ratings of mild, moderate and severe of severity of symptoms were scored as 1, 2 or 3, respectively to provide a quantitative means of data analysis and the total symptom score for every subject each day was calculated as a sum of multiplied numbers of symptoms experienced by the numerical severity ratings. A URS was deemed present when (i) total symptom score was ≥15 on any two consecutive days and (ii) when a subject positively indicated suffering a common cold on ≥ 3 days according to Jackson et al. (31). Subjects were also asked to rate the impact of illness symptoms on their ability to train (above normal, at the same level, below normal or training stopped). The total number of URS days was also determined as the number of days with a symptom score of ≥5 according to Predy et al. (44).

Subjects were also asked to fill in a standard short form of the International Physical Activity Questionnaire (IPAQ; http://www.ipaq.ki.se/downloads.htm) at weekly intervals, thus providing a quantitative information on training loads in metabolic equivalents (MET)-h/week (13). Subjects attended the laboratory every 4 weeks following an overnight fast. Subjects were required to abstain from any strenuous physical activity for 24 h before coming to the laboratory. During these visits body mass was recorded and an unstimulated saliva sample was collected. Venous blood samples were collected only at the start and end of the study period and the mean values for these haematological values are reported in the Results.

Sample size estimation (21) of 41 subjects per gender group was based on an expected rate of 2.0 ± 1.0 URS episodes (mean ± SD) during the winter months (37), a target difference of 30% in number of episodes (effect size 0.6), statistical power of 80% and a type I error of 5%.

Saliva analysis

The saliva volume collected was estimated by weighing and the saliva flow rate was calculated. Saliva samples were analysed for secretory immunoglobulin A (SIgA) using an ELISA kit (Salimetrics, Philadelphia, USA) and α-amylase activity was measured as previously described (35). Salivary lactoferrin and lysozyme were analysed using commercially available ELISA kits (Calbiochem, USA and Biomedical Technologies, USA, respectively). Secretion rates for each of the salivary AMPs were calculated as the multiple of the saliva flow rate and the AMP concentration. Values obtained from the 5 visits at 4-week intervals were averaged for each subject. All saliva assays were carried out in duplicate. Coefficients of variation (CVs) for the assays were <5% for all salivary AMPs.

Statistical Analysis

The Shapiro-Wilk test was used to determine if data sets were normally distributed. The difference in proportion of subjects who presented with symptoms of infection during the trial between the males and females was assessed by a Chi-squared test. Self-reported training load (h/week), average IPAQ scores (MET-h/week), anthropometric and haematological variables (including blood leukocyte, neutrophil, monocyte and lymphocyte counts) were compared between males and females using unpaired t tests for normally distributed data. Changes in training load over time for both sexes were evaluated by 2-way ANOVA with post hoc Bonferroni t tests to locate differences from week 1. The salivary AMP concentrations and secretion rates were compared between males and females using nonparametric Mann-Whitney tests for data that were not normally distributed. The changes in the secretion rates of salivary AMPs over the 16 weeks of the study in males and females were assessed by non-parametric Friedman tests with post hoc Dunn's tests to compare values at weeks 4, 8, 12 and 16 with baseline within sex. Differences between sexes at specific sampling timepoints were examined using Mann Whitney tests. Statistical significance was accepted at $P < 0.05$. Data are expressed as mean ± SD or median and interquartile range as appropriate.

RESULTS

Anthropometric and haematological variables

There was no significant difference in age between males and females (Table 1) but males were taller, heavier and had higher BMI than females (all $P < 0.01$). Males had higher RBC count, haematocrit and haemoglobin concentration than females (all $P < 0.001$). Total blood leukocyte, monocyte and lymphocyte counts were not different between the sexes but females had higher circulating numbers of neutrophils than males ($P = 0.040$).

Table 1. Anthropometric, training and haematological variables in male and female athletes

	Males (n=147)	Females (n=63)	P
Age (years)	20.4 ± 1.9	20.5 ± 3.1	0.943
Height (cm)	1.80 ± 0.06	1.66 ± 0.06	<0.001
Body mass (kg)	77.7 ± 10.1	63.3 ± 7.6	<0.001
BMI (kg/m^2)	23.8 ± 2.3	22.9 ± 2.3	0.007
Previous training load (h/week)	10 ± 3	10 ± 3	0.857
IPAQ (MET-h/week)	65.2 ± 28.2	66.7 ± 31.4	0.746
RBC count (x10^{12}/L)	4.86 ± 0.55	4.33 ± 0.50	<0.001
Haematocrit (%)	46.8 ± 4.9	41.6 ± 4.6	<0.001
Haemoglobin (g/L)	148 ± 16	130 ± 15	<0.001
Leukocyte count (x10^9/L)	5.85 ± 1.30	6.16 ± 1.51	0.128
Neutrophil count (x10^9/L)	2.96 ± 0.97	3.28 ± 1.15	0.040
Lymphocyte count (x10^9/L)	2.06 ± 0.52	2.05 ± 0.50	0.931
Monocyte count (x10^9/L)	0.58 ± 0.15	0.59 ± 0.22	0.774

Values are expressed as mean ± SD.

Training loads

Self-reported weekly training loads (mean ± SD) based on information gathered in the pre-screening questionnaire were similar in males and females (both 10 ± 3 h/week, $P = 0.857$).Analysis of the IPAQ questionnaires indicated that the weekly training loads were relatively stable within both sexes over the 16 weeks of the study (Figure 1) although there was a significant main effect of time ($P<0.001$) with training load falling below week 1 values in weeks 6-11. There was no significant effect of sex and no significant sex x time interaction. Training loads were, on average, about 66 MET-h/week which is equivalent to about 11 h of moderate-vigorous activity per week. The training loads averaged over the whole

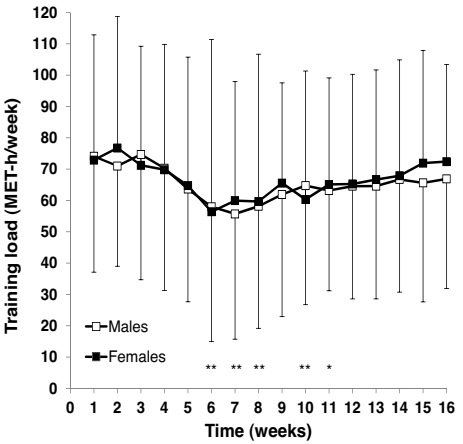

Figure 1. Training loads in MET-h/week over the 16-week study period for men (n=147) and women (n=63) who completed the study. Data are mean ± SD. There was a main effect of time (P<0.001) and the location of significant differences from week 1 are indicated as follows: * P<0.05, ** P<0.01. There was no significant effect of sex and no significant sex x time interaction.

16-week study period were not significantly different between males and females (Table 1).

Salivary variables

When averaged over the 5 sampling occasions, saliva flow rates ($P < 0.03$) and the secretion rates of lactoferrin, lysozyme and amylase (Table 2) were significantly higher in males than females (all $P < 0.01$). Concentrations of SIgA and amylase were not different between the sexes whereas lactoferrin ($P = 0.021$) and lysozyme ($P = 0.033$) concentrations were significantly higher in males. While there were significant effects of time (Friedman, $P < 0.05$) for the secretion rates of lactoferrin, lysozyme, amylase and SIgA in males, there were significant effects of time only for amylase and SIgA secretion rates in females (Figure 2). The changes over time followed the same pattern for both sexes.

Table 2. Salivary variables in male and female athletes

	Males (n=147)	Females (n=63)	P
Saliva flow rate (μL/min)	340 (263-446)	308 (220-404)	0.025
SIgA concentration (mg/L)	68.5 (49.3-97.8)	70.6 (44.8-107.9)	0.775
SIgA secretion rate (μg/min)	23.1 (13.9-34.4)	19.5 (12.2-28.8)	0.097
Lysozyme concentration (μg/L)	2000 (1112-3452)	1426 (886-2649)	0.033
Lysozyme secretion rate (ng/min)	629 (384-1033)	373 (229-685)	0.001
Lactoferrin concentration (μg/L)	2438 (1819-3596)	1930 (1183-3365)	0.021
Lactoferrin secretion rate (ng/min)	805 (561-1238)	554 (329-862)	0.001
Amylase activity (U/mL)	142 (76-243)	134 (75-173)	0.126
Amylase secretion rate (U/min)	51.6 (24.0-85.3)	37.8 (25.5-50.6)	0.009

Values are expressed as median and interquartile range. P value is from Mann-Whitney U test.

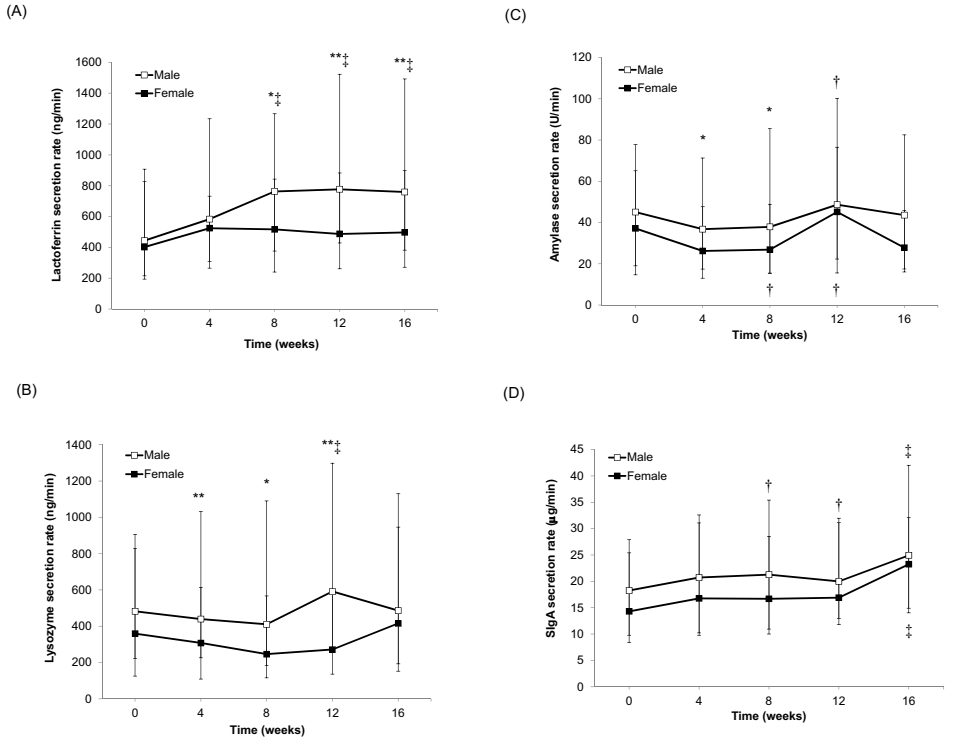

Figure 2. Changes in salivary secretion rates over time for (A) Lactoferrin, (B) Lysozyme, (C) Amylase and (D) SIgA. Data are median and interquartile range. Significantly different from baseline sample within sex: † P<0.05, ‡ P<0.01 (Dunn's post hoc test applied when Friedman test P<0.05). Significant difference between males and females at specific timepoint: * P<0.05, ** P<0.01 (Mann Whitney test).

URS incidence and the severity and duration of URS

Females tended to be more susceptible to URS than males: The proportion of males and females who experienced one or more URS episodes during the study period was 40 % of all males and 52 % of all females (P = 0.083, chi-squared test) and the average number of URS episodes was 0.6 ± 0.8 in males and 0.8 ± 1.0 in females (P = 0.103). The number of URS days was significantly higher in females (males: 4.7 ± 5.0 days vs females: 6.8 ± 7.1 days, P = 0.016). When an URS episode was present, the mean total symptom severity score was not significantly different between sexes (males: 90 ± 67 vs females: 106 ± 77, P = 0.312) but the mean duration of symptoms was significantly longer in females (males: 11.6 ± 6.8 days vs females: 15.5 ± 9.3 days, P = 0.024).

Only 17% of subjects reported that they took some medication when suffering from an URS episode and only 4% reported that they visited their doctor and none were given prescription drugs. The study results were not corrected for this (i.e. all URS episodes were included in the analysis).

Table 3. Illness incidence among athletes at major competitive events lasting 2-3 weeks.

Games (reference)	Season	Athletes (n)	Males (n)	Females (n)	Illness in all athletes (%)	Illness in males (%)	Illness in females (%)	Respiratory (% of total)
Olympics 2012 (16)	Summer	10568	5892	4676	7.2	5.3	8.6	41
Youth Olympics 2012 (46)	Winter	1021	562	459	8.4	6.0	11.0	61
IAAF 2011 (4)	Summer	1851	971	880	6.8	7.1	7.7	39
Olympics 2010 (17)	Winter	2567	1522	1045	7.2	5.2	8.7	63
IAAF 2009 (5)	Summer	1979	1082	897	6.8	5.6	8.4	36
FINA 2009 (36)	Summer	2318	1306	1012	6.6	5.1	7.9	50
All		20304	11335	8969	7.2 ± 0.6	5.7 ± 0.8	8.7 ± 1.2*	48 ± 12

IAAF: International Association of Athletics Federations; FINA: Federation Internationale de Natation; n = number of registered athletes.
* Significant difference in mean illness rates between male and female athletes ($P < 0.05$).

DISCUSSION

The main findings of the present study were that although URS incidence was not significantly different between male and female athletes, the women had more URS days and their URS episodes lasted several days longer than the men. Salivary SIgA concentration and amylase activity were not significantly affected by

sex but both lactoferrin and lysozyme concentrations were found to be lower in the females. Saliva flow rate was ~17% lower in females and the secretion rates of all the AMPS apart from SIgA were significantly lower in females. In both sexes saliva AMP secretion rates increased over time which could be due to the significant fall in the training loads of the athletes that was observed in the middle part of the study period.

Low SIgA concentration or secretion rate has been identified as a risk factor for development of URS in physically active individuals (19, 26-28, 37). In the present study, we found that female athletes tended to have lower SIgA secretion rates than male athletes during a 16-week winter training period although this difference was not statistically significant. It has been suggested that SIgA levels are a surrogate marker of host protection and the suppression of SIgA after prolonged exercise or heavy training is itself a probable consequence of altered T lymphocyte function (12). Females generally have lower unstimulated saliva flow rates than males (42), whereas SIgA concentration in unstimulated saliva has been reported to be unaffected by sex among relatively large cohorts of healthy young adults (33, 51, 52). A previous smaller scale study reported lower SIgA concentration and secretion rate in females (n=34) than in males (n=46) among a cohort of student athletes (25). Other small scale studies on elite swimmers have also reported lower SIgA concentrations in females compared with males (n= 11 females, n = 15 males (26); n = 5 females, n= 7 males (1)), as has a small scale study of recreational cyclists (n= 8 females, n = 8 males (2)); but, to our knowledge, our investigation is the first large scale study to report a sex difference in salivary AMP secretion rates in athletes from a range of endurance-based sports.

In the present study, it was observed that the female athletes had lower saliva amylase secretion rate than male athletes. Amylase, an enzyme that breaks down starch into maltose, is important to host defence in oral-respiratory mucosal immunity by inhibiting the adherence and growth of certain bacteria (3). The lower amylase secretion rate in the saliva of females could be due to lower circulating adrenaline levels that are observed both at rest (54) and after exercise (45) in females when oestrogen levels are high due to exogenous ovarian hormone administration. Both increased sympathetic nervous activity (48), and elevated plasma adrenaline and noradrenaline (11) are known to increase salivary amylase secretion. In addition, we also found that the secretion rates of lysozyme and lactoferrin were significantly lower in female athletes than male athletes. Lysozyme and lactoferrin play important roles in oral-respiratory mucosal immunity against pathogen infection: Lactoferrin possesses the ability to sequester iron, bind to bacteria, and has antimicrobial activities that act in synergy with SIgA and lysozyme (15, 34). Therefore, it is possible that the lower secretion rates of amylase, lysozyme and lactoferrin might leave female athletes at greater risk of contracting RTIs during winter training periods.

Of course, other factors could also account for differences in infection risk between the sexes. For example, in the general population, women have been reported to have fewer blood monocytes and NK cells, but more CD4+ cells and more neutrophils than men (8, 55) and women appear to suffer from fewer viral

infections including RTIs than men (6). The present study also found athletic females to have higher blood neutrophil counts than their male counterparts but it was the females who appeared to be more susceptible to URS than men. It is possible that the same training load could have a greater depressive effect on humoral and systemic immunity (e.g. lower secretion rates of mucosal AMPs and fewer numbers of circulating B cells and NK cells) for women (25) than for men (that is not evident in the normal, more sedentary population) but this possibility needs to be resolved by future research. Such an effect may be responsible for the reversal of the usual situation of more effective immune function in females into the opposite situation in athletes. Our data support the notion that URS are more prevalent in female athletes than their male counterparts when they engage in similarly high training loads. In recent years medical and sport science support personnel have collected data on rates of injuries and illnesses in large cohorts of athletes attending (and intending to compete in) large competitive events lasting 2-3 weeks (e.g. winter and summer Olympic games, athletic and aquatic sport world championships). The findings from these studies are summarised in Table 3 and suggest that illness episodes actually are more prevalent in the women than the men (4, 5, 14, 16, 17, 36, 46). About half of the illnesses reported at these events were URS episodes. Other epidemiological studies on physically active (38) and athletic (30, 32) men and women also suggest that URS are more prevalent in the females.

A limitation of the present study is that the phase of the menstrual cycle (when blood and saliva samples were taken) was not determined but we did establish that 40% of the females were taking oral contraceptives. It is possible that the high training loads of some of the female endurance athletes in our study could have caused them to be amenorrhoeic and one would expect that this would make their immune variables more similar to that of men. However, according to the health screen questionnaire used at the start of the study 96% of the females reported that they had regular periods so it seems likely that during the study period very few of the females were amenorrhoeic. This aside, menstrual cycle phase was not found to affect resting saliva SIgA responses in endurance trained female athletes (10). Another limitation is that we did not attempt to distinguish between symptoms of an infectious/illness nature vs inflammation throughout the 16 weeks of the study design. However, nearly all studies to date have used self-reported symptoms rather than pathogen identification in studies involving athletes and URS incidence. We used the validated Jackson score questionnaire which is a conservative instrument requiring a substantial symptom score criterion threshold to define a RTI episode (31). Given that the average duration of URS episodes in our study was 13 days, it is very likely that the vast majority of episodes were caused by infections as typically inflammation/allergy symptom episodes generally only last 1-3 days according to Walsh et al. (53).

The major strengths of our study are that we used a validated questionnaire (31) to determine URS episodes and measured saliva AMPs on 5 occasions at monthly intervals to better establish the average values for each individual. The average training loads of the athlete cohort were generally high and were not different between males and females. Our study population was a group of university athletes on a single campus site so that environment and pathogen exposure were likely to have been similar for all subjects.

In conclusion, the findings of this study concur with recent reports of illness incidence at major competitive games indicating that female athletes may be more susceptible than their male counterparts to URS and that lower oral-respiratory mucosal immunity (i.e. lower secretion rates of mucosal AMPs), may account for this in part.

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