Maria Angela Tosca[1], Irene Schiavetti[2], Gian Luigi Marseglia[3], Giorgio Ciprandi[4]

The gender effect in children and adolescents with asthma: practical outcomes from the "ControL'Asma" study

[1]Allergy Center, Department of Pediatrics, Istituto Giannina Gaslini, Genoa, Italy
[2]Department of Health Science, University of Genoa, Genoa, Italy
[3]Pediatrics Clinic, Department of Pediatrics, Policlinico San Matteo, University of Pavia, Pavia, Italy
[4]Allergy Clinic, Department of Outpatients, Casa di Cura Villa Montallegro, Genoa, Italy

Key words
Asthma; asthma control; children; adolescents; gender.

Corresponding author
Giorgio Ciprandi
Allergy Clinic
Department of Outpatients
Casa di Cura Villa Montallegro
via Montezovetto 27
16132 Genoa, Italy
ORCID: 0000-0001-7016-8421
E-mail: gio.cip@libero.it

Doi
10.23822/EurAnnACI.1764-1489.235

To the Editor,

gender medicine is attracting more and more attention also in clinical practice (1). Differences between genders exist in many diseases. The evaluation of the gender impact on asthma arouses current and outstanding interest and is an interesting research field, as recently pointed out (2). Currently, asthma control is the cornerstone strategy in the management of patients with asthma, as stated by the Global Initiative for Asthma (GINA) document (3). The asthma control evaluation should be based on a global assessment of symptoms, lung function, medications' use, limitations, and respiration perception. The asthma control perception may be assessed in a standardized way by the Asthma Control Test (ACT) questionnaire. In this regard, a recent study evaluated a large group of outpatients with asthma in a real-world setting (4). Interestingly, the asthma control, assessed by objective and subjective measures, was not influenced by gender. However, differences between female and male adults concerned only lung function and smoking. Asthmatic women had higher FVC and FEV1 values than men, but men smoked more than women. Otherwise, there were no significant differences between genders. Consistently, we reported no difference between female and male children with asthma concerning the lung function and the perception of breathlessness (5). However, some pediatric studies do not investigate the assessment of asthma control. In this regard, the Italian Society of Paediatric Allergy and Immunology recently established a prospective study ("ControL'Asma") to investigate the asthma control in children and adolescents managed in clinical practice. As asthma and allergy are dynamic events, the present study aimed to compare genders about asthma control and other clinical-functional characteristics in children and adolescents recruited in a real-world setting, such as Italian pediatric third-level allergy and asthma clinics.

This cross-sectional study included 471 children and adolescents consecutively visited across 10 Italian pediatric third-level allergy clinics. Asthma diagnosis was performed following the GINA document criteria. All patients were currently treated according to the GINA guidelines based on the asthma control level.

The Ethics Committee of the Istituto Giannina Gaslini of Genoa initially approved the procedure (code number: 22253/2017, in the Italian Project "ControL'Asma" promoted by the Italian Society of Paediatric Allergy and Immunology). All the other Review Ethics Committees further approved the study procedure and written informed consent was obtained from all parents. Clinical data were recorded by an electronic case report form designed expressly for this study. Due to the nature of this study, no sample size justification was needed as no formal *a priori* hypothesis was tested.

Descriptive data summary was expressed as frequency (percent); mean ± standard deviation; median and interquartile range (IQR). Two separate analyses were performed, independently considering children and adolescents. Any relationship between categorical variables was assessed by Chi-square test or Fisher's exact test, as appropriate. The independent samples t-test or Mann-Whitney U test was used to compare the continuous variables.

Table I reports the outcomes, considering children and adolescents separately. Male gender was prevalent both in children- and adolescents-group.

In children, there was no significant difference between females and males concerning BMI, rhinitis, type 2 high phenotype, ARIA classes, lung function, asthma control level, cACT, and perception of asthma symptoms by children's parents and doctors. Lung function differed between genders in adolescents: males had lower FVC and FEV1 values than females ($p = 0.006$ and 0.02, respectively).

These outcomes highlighted no significant difference between female and male children, mainly concerning the asthma control level, assessed both by GINA criteria and cACT. Other clinical variables, including the perception of breathlessness, comorbidities, and lung function, were similar in both genders. Substantially, the same findings were observed in adolescents, but lung function, although the higher values observed in females were without clinical relevance.

Curiously, there was an inversion between genders about the quote of subjects with uncontrolled asthma. Uncontrolled asthma was more prevalent in male children (14.8% *vs* 10%) and female adolescents 14.1% *vs* 8.1%), even though without statistical significance.

These results confirmed previous findings obtained in adulthood (4). Therefore, the impact of gender seems to be scarcely important in patients with asthma, if not for the different prevalence: higher in male children and adolescents, but higher in women. These outcomes could represent a risk of bias. However, these results were obtained in a real-life setting, as derived from ten Italian pediatric clinics. These data reflected what occurred in clinical practice and outlined the relevance of gender in affecting asthma prevalence.

The present outcomes were conflicting with a recent Chinese study showing that maternal sleep, physical activity, and screen time during pregnancy were significantly associated with the risk of childhood allergies, mainly in males (6). However, the setting was different and asthma control was not investigated.

Another study evaluated subjects (age range 10-18 years) from the Isle of Wight birth cohort (7). That study showed that there was a gender difference concerning the DNA methylation associated with the risk of asthma. However, also that study did not address the asthma control.

A Korean study demonstrated that there was a between gender difference concerning factors associated with bronchial hyperresponsiveness (8), but asthma control was not investigated.

On the other hand, the current real-world study had one main limitation because it was performed as a cross-sectional, so further longitudinal studies should be performed to confirm these findings. On the other hand, the real-world setting allowed to represent a third-level asthma clinic's daily practice, including a wide range of asthma severity. In addition, no sample size calculation was provided *a priori* due to the exploratory nature of this study.

In conclusion, the ControL'Asma study showed no clinically relevant differences between genders, about asthma control, symptom perception, lung function, and comorbidities, in Italian children and adolescents with asthma.

Fundings

None

Contributions

MAT: study design. IS: data analysis. GLM: discussion of results. GC: writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgements

We would thank the "ControL'Asma Study Group" members: Elisa Anastasio, Carlo Caffarelli, Federica Caricato, Loredana Chini, Elisabetta Del Duca, Valentina De Vittori, Maria Elisa Di Cicco, Ahmad Kantar, Maddalena Leone, Amelia Licari, Viviana Moschese, Roberta Olcese, Diego G Peroni, Valeria Talarico, and Martina Votto, who participated in the research.

Table I *- Comparison between gender and age classes in children and adolescents.*

	Children (n = 270)			Adolescents (n = 201)*		
	Female (n = 81)	**Male (n = 189)**	**p**	**Female (n = 64)**	**Male (n = 137)**	**p**
BMI	18.0 ± 3.29	18.6 ± 3.47	0.24	22.3 ± 4.94	21.1 ± 3.80	0.10
Rhinitis comorbidity	68 (84.0)	161 (85.2)	0.85	60 (93.8)	125 (91.2)	0.78
Type 2 high asthma	75 (92.6)	174 (93.0)	0.99	64 (100.0)	131 (97.0)	0.31
ARIA Category						
Mild intermittent allergic rhinitis (MIAR)	22 (32.4)	59 (36.9)	0.62	23 (38.3)	51 (40.8)	0.92
Moderate-severe intermittent allergic rhinitis (MSIAR)	8 (11.8)	12 (7.5)		7 (11.7)	11 (8.8)	
Mild persistent allergic rhinitis (MPAR)	33 (48.5)	81 (50.6)		27 (45.0)	58 (46.4)	
Moderate-severe persistent allergic rhinitis (MSPAR)	5 (7.4)	8 (5.0)		3 (5.0)	5 (4.0)	
FVC (% predicted)	98.2 ± 13.94	98.1 ± 13.44	0.68	104.4 ± 15.21	98.3 ± 12.78	**0.006***
FEV_1 (% predicted)	95.4 ± 13.59	94.7 ± 15.78	0.91	103.0 ± 17.69	96.4 ± 13.30	**0.020***
Bronchial obstruction (FEV_1 < 80%)	9 (12.7)	28 (17.1)	0.44	7 (11.1)	11 (8.7)	0.61
FEV_1/FVC	97.7 (9.72)	96.8 ± 11.24	0.64	98.8 ± 10.33	98.3 ± 9.40	0.72
$FEF_{25–75}$ (% pred.)	87.4 (26.58)	82.9 ± 27.06	0.42	89.3 ± 29.15	84.8 ± 22.38	0.13
Asthma control level (GINA)						
Well-controlled	41 (51.2)	99 (52.4)	0.46	35 (54.7)	86 (63.2)	0.34
Partly controlled	31 (38.8)	62 (32.8)		20 (31.3)	39 (28.7)	
Uncontrolled	8 (10.0)	28 (14.8)		9 (14.1)	11 (8.1)	
Childhood Asthma Control Test (adjusted age)	23.0 (19.0-25.0)	22.0 (19.0-24.0)	0.08	22.0 (17.0-25.0)	23.0 (19.0-24.0)	0.37
VAS (by patient)	8.3 (7.0-9.0)	8.0 (7.0-9.0)	0.94	8.5 (7.0-9.0)	8.0 (7.0-9.0)	0.32
VAS (by patient)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.82	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.45
VAS (by physician)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.57	8.3 (7.0-9.3)	8.0 (7.0-9.0)	0.54

Data are expressed as frequency (percent); mean ± standard deviation; median (IQR).

References

1. Lippi D, Bianucci R, Donell S. Gender medicine: its historical roots. Postgrad Med J. 2020;96(1138):480-6. doi: 10.1136/postgradmedj-2019-137452.
2. Raghavan D, Jain R. Increasing awareness of sex differences in airway diseases. Respirology. 2016;21(3):449-59. doi: 10.1111/resp.12702.
3. Global Initiative for Asthma. GINA guidelines. Global Strategy for Asthma Management and Prevention. Available at: htpp://www.ginasthma.org/. Last access date: 02/01/2021.
4. Ricciardolo FLM, Levra S, Sprio AE, Bertolini F, Carriero V, Gallo F, et al. Asthma in the Real-World: The Relevance of Gender. Int Arch Allergy Immunol. 2020;181(6):462-6. doi: 10.1159/000506808.
5. Ciprandi G, Tosca MA, Brambilla I, Arturo Rossi G, Marseglia G. Perception of dyspnea in prepubescent children with mild intermittent asthma: is there any gender difference? J Asthma. 2011;48(9):886-7. doi: 10.3109/02770903.2011.616617.
6. Chen Y, Lyu J, Xia Y, Zhu J, Tong S, Ying Y, et al. Effect of maternal sleep, physical activity and screen time during pregnancy on the risk of childhood respiratory allergies: a sex-specific study. Respir Res. 2020;21(1):230. doi: 10.1186/s12931-020-01497-8.
7. Patel R, Solatikia F, Zhang H, Wolde A, Kadalayil L, Karmaus W, et al. Sex-specific associations of asthma acquisition with changes in DNA methylation during adolescence. Clin Exp Allergy. 2021;51(2):318-28. doi: 10.1111/cea.13776.
8. Kim YH, Jang YY, Jeong J, Chung HL. Sex-based differences in factors associated with bronchial hyperresponsiveness in adolescents with childhood asthma. Clin Exp Pediatr. 2021;64(5):229-38. doi: 10.3345/cep.2020.01585.