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Original article

No gender differences in growth patterns in a cohort of children with cystic fibrosis born between 1986 and 1995

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SUMMARY

Background & aims: A higher mortality rate at young ages has been reported in cystic fibrosis (CF) girls compared to boys. The reasons of this gap remain unclear but may be related to a different evolution of the disease, in terms of growth and lung function throughout childhood and adolescence. This study aimed at investigating gender differences in growth patterns in a cohort of children with CF through a longitudinal study, and as secondary objectives, to evaluate gender differences in forced expiratory volume in one second (FEV_1) trend and transplant-free survival.

Methods: We performed an historical cohort study of 203 CF patients born between 1986 and 1995. Weight and height were recorded from the time of CF diagnosis to the age of 18 years. Generalized estimated equations were used to evaluate the effect of gender on changes in z-score of BMI-for-age and z-score of height-for-age and FEV_1. Transplant-free survival to age 18 was computed by the Kaplan–Meier estimator.

Results: Girls did not show a worse growth pattern as compared to boys. The odds of being underweight [Odds Ratio (OR) for girls: 0.85, 95% CI: 0.51; 1.39] or stunted [OR for girls: 0.79, 95% CI: 0.42; 1.49] were not significantly different between genders. FEV1 trend was also similar in boys and girls, as well as the probability of surviving to age 18 without receiving lung transplantation (boys: 0.88, 95% CI: 0.82–0.95, girls: 0.92, 0.87–0.98, $P = 0.26$).

Conclusions: In a cohort of children with CF born between 1986 and 1995, no gender differences in growth patterns were observed. This finding suggests that CF girls and boys have benefited equally from the advances in treatments that have occurred over the last three decades.

1. Background & aims

Cystic fibrosis (CF) is the most frequent inherited disease in Caucasians. It is caused by mutations in the CF Transmembrane Conductance Regulator gene (CFTR) which is expressed in a variety of organs and tissues. CF is a multi-organ disease which significantly reduces the life expectancy and involves a heavy therapeutic burden over the entire life of the affected patients. The major cause of death in CF is a progressive lung disease resulting from recurrent pulmonary infections [1]. Patients are also at high risk of undernutrition and impaired growth due to increased energy requirement and fat malabsorption.

Over the last decades, survival has remarkably increased due to early diagnosis, improvement in nutritional management and more aggressive treatment of CF lung disease [1,2]. However, impaired growth and nutritional status are still present, and a female disadvantage in life expectancy is still reported [3]. A few studies suggested that with the improvement of CF care this survival disadvantage may have disappeared [4–6], however this issue still remains an area of controversy [7]. In fact, also in the modern era of aggressive treatment of CF lung disease, increased mortality in young and adolescent girls with CF has been still reported [8,9].

Abbreviations: BMIZ, BMI-for-age z-score; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in one second; GEE, generalized estimated equations; HTZ, height-for-age z-score.

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The reasons for the female disadvantage have not been yet understood, however current evidence suggests that estrogens could negatively affect mucociliary clearance and host immune response to P. *aeruginosa* [10] and probably to other pathogens including *Methicillin-resistant Staphylococcus aureus* (MRSA), *Achromobacter xylosoxidans*, *Aspergillus* species and nontuberculous mycobacteria, leading to a worse prognosis in CF females [3].

In this study, we aimed to verify gender differences in growth pattern in a cohort of CF children through a longitudinal study. As secondary outcomes, we evaluated the trend in forced expiratory volume in one second (FEV1) and the lung transplantation-free survival to age 18.

2. Materials and methods

2.1. Study design and data collection

In this historical cohort study, we retrospectively collected anthropometric and respiratory function data of a cohort of CF children followed at the CF center of Milan. We examined annual data starting from the first visit at the CF center until the patients reached 18 years of age or were transferred to CF centers outside the Lombardia region. Patients born between January 1, 1986 and December 31, 1995 were included in the study. Data of patients who moved from the CF center of Milan to the CF center of Brescia (established as a support Center within the Lombardia Region in 2003) were also collected.

From medical records, we retrieved CFTR mutations, CF diagnosis modalities and annual data on forced expiratory volume in one second (FEV_1), weight, stature and the results of nasopharyngeal aspirate or sputum cultures. CFTR genotype was considered severe for patients carrying mutations of class I–III in two CFTR alleles and mild for patients carrying CFTR mutation of class IV–VI in one or two alleles [11]. Pancreatic insufficiency was determined according to fecal elastase-1 concentration and values below 200 μg/g of stool were considered abnormal.

FEV_1 was expressed as percentage of the predicted values ($ppFEV_1$) [12] and only the best $ppFEV_1$ of the year of observation was included in the analysis.

National reference data were used to obtain the z-scores of BMI-for-age and height-for-age [13]. Patients were considered infected by P. *aeruginosa* if they had at least one positive culture during the year of observation. Patients were considered chronically infected by P. *aeruginosa* if they were infected for at least 3 consecutive years.

2.2. Statistical analysis

Primary outcome variables were: z-score of BMI-for-age (BMIZ) and z-score of height-for-age (HTZ). Secondary outcome variables were: $ppFEV_1$ and lung transplantation-free survival to age 18. Anthropometric variables and $ppFEV_1$ were also dichotomized to model the probability of being underweight (BMI-for-age below the 10th percentile), the probability of being stunted (Height-for-age below the 5th percentile) and the probability of moderate lung disease ($ppFEV_1 < 70\%$).

BMI analysis was limited to ages 2–18 years as length was not available for a considerable proportion of children below the age of 2 years. FEV_1 analysis was restricted to ages greater than 9 as a considerable proportion of subjects was not able to perform pulmonary function tests before that age.

We fitted generalized estimating equation (GEE) models [14] to evaluate the effect of gender on growth pattern and respiratory function trend in a longitudinal design. This approach allowed to address the correlation between repeated measurements on the same subject using a pre-defined correlation structure. A first-order autoregressive correlation structure was used for the analysis presented in this study. We used an identity link function for continuous response variables (BMIZ, HTZ and $ppFEV_1$) and a logit link function for binomially distributed response variables (underweight, stunting and moderate lung disease).

We evaluated the effect of gender on changes in response variables over time by examining the main effect and its interaction with age at observation. Two models for each response variable were selected: a basic model including only gender and age and a fully adjusted model including other covariates. Exocrine pancreatic function and age at diagnosis were included among predictors in all fully adjusted models, while chronic infection by P. *aeruginosa* was included as time varying covariate only in the model evaluating respiratory function.

We evaluated alternative methods for treating age in the GEE models such as first order fractional polynomial and natural splines (see online Supplemental materials Table S1-S6). These techniques allowed to evaluate curvilinear trend in the response variables. We used the quasi information criterion (QIC) to select the model which provided the best fit [15]. Wald's test was used to verify the statistical significance of the predictors.

Lung transplantation-free survival was computed by the Kaplan–Meier estimator and survival curves were compared by using the Log-rank test.

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Boards of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico approved the study. All living participants provided written informed consent to use their data, whereas the local Institutional Review Board allowed us to use data of the deceased persons after making them not identifiable.

3. Results

The study included 203 CF patients with 2541 anthropometric evaluations and 1262 pulmonary function tests. The severity of CFTR genotype was similar between genders ($P = 0.28$). A higher proportion of girls had CF diagnosis within 3 months compared to boys ($P = 0.025$). The likelihood of P. *aeruginosa* acquisition during the follow-up was greater in girls than in boys ($P = 0.015$), while the proportion of chronic infected patients was not significantly different between boys and girls ($P = 0.74$). Chronic P. *aeruginosa* infection tended to occur at younger ages in girls than in boys ($P = 0.059$) (Table 1).

During the observation period 17 patients died (10 boys and 7 girls) and 37 (20 boys and 17 girls) moved to others CF centers (outside the Lombardia Region) before the end of the follow-up. Two girls and one boy underwent lung transplantation during the follow-up. The probability of survival to age 18 without receiving lung transplantation was not significant different between genders (boys: 0.88, 95% CI: 0.82–0.95, girls: 0.92, 0.87–0.98, $P = 0.26$) (Online Supplementary Figure S1).

Figure 1 shows the average trajectories of BMIZ and prevalence of underweight estimated by GEE models. During prepubertal ages, BMIZ steeply declined while the proportion of underweight patients increased, however, during adolescence BMIZ increased and the proportion of underweight patients decreased. As indicated by the estimated parameter for the interaction between age and gender (Online Supplementary Table S7), the trajectories of BMIZ significantly differed between genders, with a steeper increase of BMIZ in girls during adolescence. Girls did not show an increased risk of being underweight (OR for girls estimated from the fully adjusted model was 0.85, 95% CI: 0.51; 1.39). The estimated prevalence of underweight at age 18 was 23.4% (95% CI: 15.6; 33.5%) in boys and 20.9% (95% CI: 14.4; 29.4%) in girls.

Table 1
Patients' characteristics.

	Males	Females	Tot	*P* value[a]
Number of patients	101	102	203	
CFTR Genotype				
Severe, n (%)	58 (57.4%)	65 (63.7%)	123 (60.6%)	0.28[b]
Mild, n (%)	15 (14.9%)	10 (9.8%)	25 (12.3%)	
Not determined, n (%)	28 (27.7%)	27 (26.5%)	55 (27.1%)	
Exocrine pancreatic function				
Pancreatic insufficiency, n (%)	57 (56.5%)	67 (65.7%)	124 (61.1%)	0.38[c]
Pancreatic sufficiency, n (%)	38 (37.6%)	34 (33.3%)	72 (35.5%)	
Unknown, n (%)	6 (5.9%)	1 (1.0%)	7 (3.4%)	
Meconium ileus, n (%)	6 (5.9%)	14 (13.7%)	20 (9.9%)	0.097
Age at diagnosis				
months, median (IQR)	4.1 (2.0; 21.7)	2.5 (1.3; 15.3)	3.1 (1.6; 17.1)	0.081
within 3 months, n (%)	42 (41.6%)	59 (57.8%)	101 (49.8%)	0.025
Main modality of diagnosis				
Symptoms, n (%)	61 (60.4%)	45 (44.1%)	106 (52.2%)	0.086[d]
Screening, n (%)	40 (39.6%)	49 (48.1%)	89 (43.9%)	
Familiarity, n (%)	0	8 (7.8%)	8 (3.9%)	
P. *aeruginosa* infection				
over the follow-up, n (%)	52 (51.5%)	70 (68.6%)	122 (60.1%)	0.015
Age at first infection (years), median (IQR)	10.5 (5–15)	9 (5–14)	9 (5–14)	0.35
Chronic infection, n (%)	23 (22.8%)	21 (20.6%)	44 (21.7%)	0.74
Age at chronic infection, (years), median (IQR)	14 (13–15)	12 (11–14)	13 (11–15)	0.059
B. *cepacia* complex infection				
over the follow-up, n (%)	6 (5.9%)	9 (8.8%)	15 (7.4%)	0.59
Age at first infection (years), median (IQR)	13.5 (10–16)	7 (3–11)	10 (5–15)	0.086

[a] Categorical variables were compared between genders by using the Fisher's exact test. Continuous variables were compared between genders using the Wilcoxon rank-sum test.
[b] Severe *vs*. mild.
[c] Insufficiency *vs*. sufficiency.
[d] Symptoms *vs*. screening.

Figure 2 shows the average trajectories for HTZ and the prevalence of stunting estimated by GEE models. HTZ decreased after age 14 in boys, whereas remained quite stable until adult age in girls. Prevalence of stunting slightly increased with age without significant differences between genders (OR for girls obtained by the fully adjusted model: 0.79, 95% CI: 0.42; 1.49) (Online Supplementary Table S8). The estimated prevalence of stunting at age 18 was 26.3% (95% CI: 18.1; 36.7%) in boys and 23.6% (95% CI: 16.5; 32.5%) in girls.

Figure 3 shows the average trajectories of $ppFEV_1$ values and prevalence of moderate lung disease by gender estimated by GEE models. $ppFEV_1$ slightly declined with increasing age while the proportion of patients showing moderate/severe lung disease increased. However, the parameter estimate for female gender indicates that being female was not associated with either lower $ppFEV_1$ values or with increased risk of moderate lung disease (Online Supplementary Table S9). These results were confirmed after adjusting for pancreatic insufficiency, P. *aeruginosa* infection and age at CF diagnosis. The prevalence of moderate lung disease over the age span considered in the study did not differ significantly between genders (the OR for girls estimated from the fully adjusted model was 1.31, 95% CI: 0.70; 2.46). There was no evidence of a different trend between genders for both $ppFEV_1$ and prevalence of moderate lung disease as indicated by the non-significant effect of the interaction term. The estimated prevalence of moderate lung disease at age 18 was 21.3% in boys (95% CI: 13.7; 31.5%) and 24.4% in girls (95% CI: 17.3%; 33.3%).

4. Discussion

Our study shows that a cohort of girls with CF born between 1986 and 1995 and regularly followed-up in a specialized center of Northern Italy, did not have a worse growth pattern or a more rapid decline in lung function until adult age compared to boys from the same center.

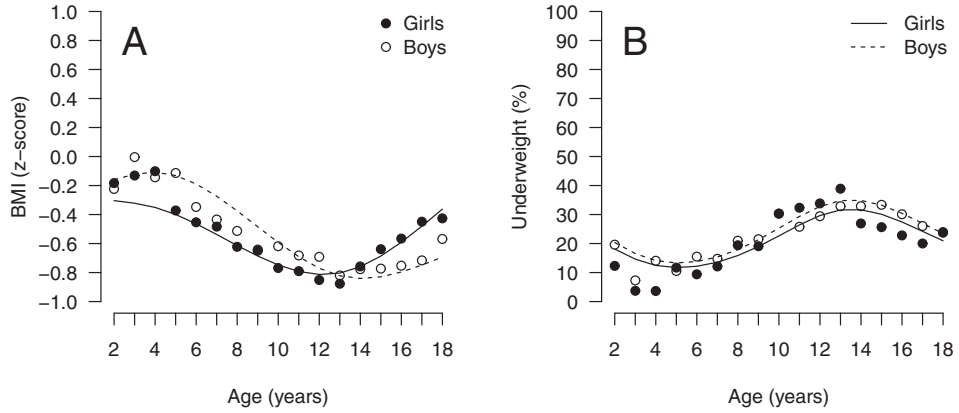

Fig. 1. Average population trajectories estimated for z-score of BMI-for-age (Panel A) and prevalence of underweight (Panel B) by gender. The figure shows the observed mean values of BMI (z-score) and the observed proportion of underweight (dots) for boys and girls at each age along with the values (lines) estimated by the GEE models (Model #1) shown in the online supplementary material Table S7. Underweight has been defined as z-score of BMI < −1.28 (10th centile).

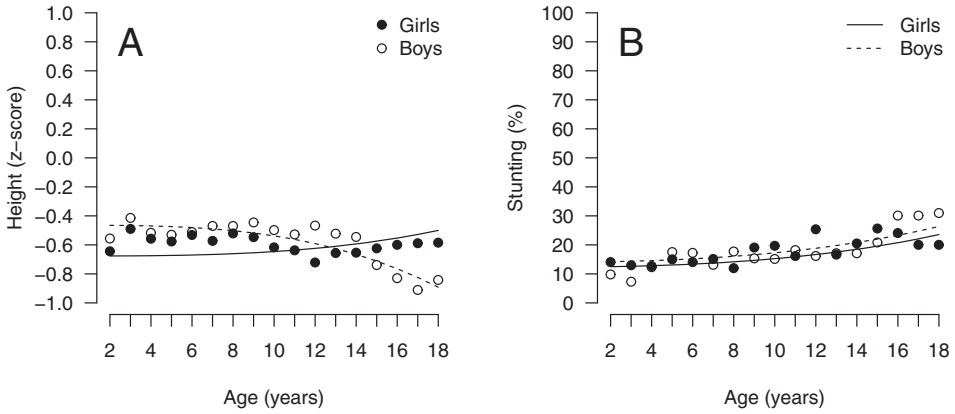

Fig. 2. Average population trajectories estimated for z-score of height-for-age (Panel A) and percentage of patients with stunting (Panel B) by gender. The figure shows the observed mean values of height-for-age z-score and the observed proportion of stunting (dots) for boys and girls at each age along with the values (lines) estimated by the GEE models (Model #1) shown in the online supplementary material Table S8. Stunting has been defined as z-score of height < −1.64 (5th percentile).

In our CF cohort, BMI was close to the normal values for healthy children in early childhood, then it declined remarkably until adolescence when some catch-up was observed. Linear growth had a sex-specific trend with height keeping constantly below 0.5 standard deviation for girls, while a further reduction until adult age was observed in boys. These trends are in agreement with registry data and partially with other studies carried out in single CF centers. Reduced weight and linear growth have been reported in the first years of life along with a subsequent catch-up toward normal values for healthy children during childhood [16–18]. During adolescence, results are heterogeneous with a cross-sectional study from Italy reporting the highest prevalence of malnutrition [19], whereas a study from Denmark [17] reported a BMI similar to the national reference during childhood and adolescence, that declined to 90% of the normal value in adult men and to 83% in adult women. In the same study, all the patients had normal height, although the final height was achieved a little later than in healthy controls. In a study from the USA on 107 CF children born in the period 1985–1994, age- and sex-specific z-scores of height were almost constant between the age of 2 and 18 years, with better values in patients diagnosed by neonatal screening as compared to those diagnosed by symptoms [20].

Previous studies from the USA, Canada, Australia and Sweden, aiming at investigating gender difference in lung function decline, achieved also conflicting results [21–25].

These results may have raised from differences in the CF population analyzed in terms of birth cohorts, availability of treatments, severity of the disease and different therapeutic regimen adopted in those countries. Moreover, most of the studies on growth patterns in CF have a cross-sectional design and include different birth cohorts, thus interpretation of the results is quite challenging as any changes of the growth parameters during childhood, adolescence and adult age may indeed be attributable to both a true age effect or to a cohort effect. Indeed, better growth during childhood could reflect the availability of more effective treatments of the disease for the recent cohorts, which have benefited from early treatment of malabsorption and nutritional support that has remarkably improved the growth pattern. In the same way, FEV_1 data have strongly improved in the last decades, and children of recent birth cohort have significantly better lung function compared to those born before [26,27].

Moreover, the absence of any gender differences in FEV_1 decline observed in this study, is in contrast with previous CF mortality data in Italy in the period 1970–2011 [8] showing increased mortality rates in females in the age range 1–19 years. The significant advances in the treatment of CF lung disease, introduced since the '90s, has remarkably changed the FEV_1 trend in most of the patients, although some of them may still experience an early and fatal decline. Thus, the percentage of patients with a very compromised lung disease may be higher in females, while the

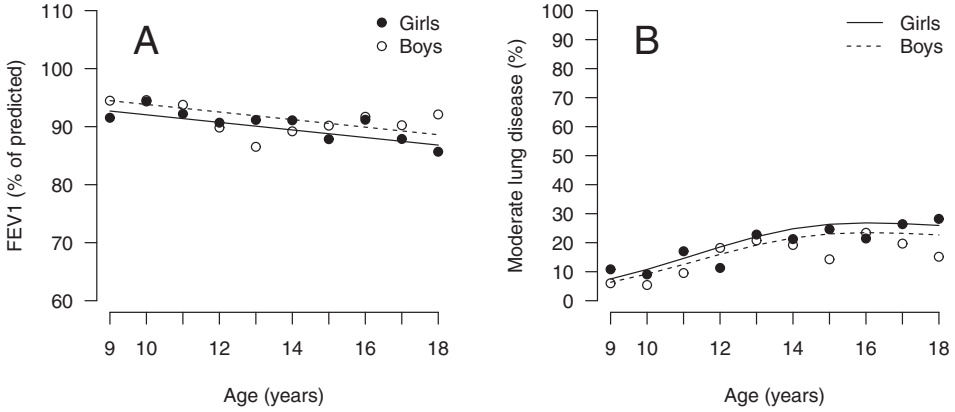

Fig. 3. Average population trajectories estimated for FEV_1 (Panel A) and prevalence of moderate lung disease (Panel B) by gender. The figure shows the observed mean values of FEV_1 (% of predicted) and the observed proportion of moderate lung disease (dots) for boys and girls at each age along with the values (lines) estimated by the GEE models (Model #1) shown in the online supplementary material Table S9. Moderate lung disease has been defined as FEV_1 < 70% of predicted.

average FEV_1 trend is not different. Our study, being carried out in a single center, cannot test this hypothesis due to the limited number of patients with very low FEV_1.

The main strength of the present study relies on the fact we provide, for the first time, growth trajectories for the whole pediatric age that can better characterize the growth pattern of the more recent cohorts of CF children.

The study has a main weakness related to the retrospective design. This did not allow to systematically collect data on pubertal status that may have affected the evaluation of the anthropometric indices, especially during adolescence, when a delay in puberty can be at least partially responsible for the differences between CF adolescents and healthy peers. A longitudinal study [28] from the USA carried out on 1862 CF children born in the period 1984–87 found peak height velocity delayed in 9%, attenuated in 21% and both delayed and attenuated in 5% of the children, with the attenuated group being shorter than those who had normal or delayed peak height velocity, while the delayed group reached a similar adult height than those showing normal peak height velocity.

In the last few years, new biomarkers of early lung function deterioration have become available, such as the Lung Clearance Index (LCI) and clinical scores derived from computed tomography [29,30]. These biomarkers are more accurate than FEV_1 in detecting early lung function abnormalities and seems to be particularly useful in children where spirometry fails to detect lung abnormalities at their very early stage. Therefore, we cannot exclude that a more accurate assessment of early lung abnormalities would have provided different results.

Moreover, our results come from a single CF center, however, their generalizability seems plausible since our center is a specialized center which is compliant with the European Standard of Care that promotes aggressive treatment of airway infection, early treatment of fat malabsorption and prompt nutritional support [31].

In conclusion, our data suggest that recent cohorts of girls and boys with CF have benefited equally from effective nutritional interventions and advances in treatments that have occurred in the last three decades.

Authorship

GA conceived the study. GA and CC drafted the manuscript. GA and MR analyzed the data. All authors participated in the interpretation of the results and approved the manuscript.

Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.025.

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