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Targeting quality of life in asthmatic children: The MyTEP pilot randomized trial

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ABSTRACT

Background: Quality of life (QoL) is an important outcome in the management of children with asthma. Mobile Health (m-Health) and Therapeutic Education Programs (TEPs) are increasingly recognized as essential components of pediatric asthma management to improve disease outcomes.
Objective: To evaluate the effect of an education program (MyTherapeutic Education Program, MyTEP) that couples multidisciplinary TEP intervention with an m-Health Program (mHP) in improving QoL in asthmatic children.
Methods: This single-center study employed a nonblinded randomized clinical trial design. Italian-speaking children (6–11 years) with mild-moderate asthma were eligible for participation. Participants were randomly paired 1:1 with a control group that received mHP (smartphone app) or an intervention group that received MyTEP (TEP plus a smartphone app). Patients were followed up for 3 months. Descriptive statistics, Least Square (LS) mean change and Generalized Linear Mixed model were used for analysis.
Results: Fifty patients were enrolled. The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) score improved in both MyTEP ($p = 0.014$) and mHP ($p = 0.046$) with the minimally clinically significant difference of $\geqslant 0.5$ points reached in 23% of MyTEP and in 16% of mHP. Changes in PAQLQ scores were significantly greater in MyTEP than in mHP (LS mean difference: 0.269 $p = 0.05$). PAQLQ score was: positively associated with MyTEP ($p = 0.023$) and study time ($p = 0.002$); and inversely associated with current passive smoke exposure ($p = 0.003$).
Conclusion: Despite the small sample size and short observation period, this study demonstrated that implementing a multidisciplinary TEP with an m-Health program results in gains in QoL of children with asthma.

1. Introduction

Asthma-related Quality of life (QoL) refers to the perceived impact of the disease on the patient's QoL. The latter generally includes multiple domains characterizing the burden of disease as perceived by the patient and is considered an important outcome of asthma management [1]. The availability of validated tools for assessing QoL makes it possible to consider this issue as a primary outcome in clinical trials [2]. Since QoL also represents a measure of the asthma burden at pediatric age, measuring this outcome contributes to evaluating of the effectiveness of clinical interventions in children with asthma [3,4].

Mobile communication and Internet access have become widespread among children. In Italy 45% of children own a smartphone and 42% use it daily [5]. Growing evidence supports mobile-health (m-Health) as a valuable tool for promoting patient's empowerment and self-management, as well as quality of care [6] and QoL [7,8] in patients with asthma, who can benefit from specifically tailored and accurate interventions [9]. Smartphone apps represent a powerful m-

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Health solution, recently used in several interventional studies on asthma self-management, especially in adolescents [10,11]. Studies implementing the use of a smartphone app investigating QoL in asthmatic children have not been performed so far.

Therapeutic Education Programs (TEPs) are widely recognized as an essential component of pediatric asthma management to improve disease outcomes [12]. TEPs are delivered to children and their parents in order to provide knowledge and training to acquire competency in understanding the disease and its treatments as well as in achieving greater individual autonomy [13]. TEPs have been described in different settings [14,15] demonstrating their efficiency on clinical outcome changes as well as on QoL improvement [16,17]. A previous 3-month TEP study in outpatient asthmatic children did not show a significant improvement in QoL [18]. Studies that combine TEP and m-Health with the aim of improving QoL in asthmatic children have not been performed so far.

This study was designed to evaluate whether educational sessions offered in the context of a m-Health program improved QoL within a randomized control trial. Conducting this pilot study allowed us to collect preliminary results in order to determine whether a larger trial would be feasible and useful. We hypothesized that an education program (MyTherapeutic Education Program, MyTEP) that couples multidisciplinary TEP intervention with a m-Health Program (mHP) could improve QoL in children with mild-moderate asthma. This change was predicted to be maintained at the 3-month follow-up for the intervention group. Secondary objectives of the present study were to assess the effects on asthma control, adherence to treatment, and spirometry parameters. Lastly, we investigated risk factors associated with QoL.

2. Methods

2.1. Study population and design

This single-center study employed a nonblinded randomized clinical trial design. Children were recruited from the Clinical and Environmental Epidemiology Department of Pulmonary and Allergic Pediatric Diseases (CEEPAPD), an outpatient clinic of IBIM CNR, Palermo, Italy, between March and May 2017. Inclusion criteria were age 6–11 years and persistent mild-moderate asthma according to GINA [19]. Exclusion criteria were the following : 1) enrollment in previous asthma educational programs; 2) no access to the Internet; 3) poor understanding of written or spoken Italian; 4) upper or lower respiratory tract infections in the last 2 weeks; 5) severe asthma exacerbations and/or emergency visits for asthma in the last year; 6) use of oral systemic antibiotics in the last 4 weeks; 7) active smoking.

Sixty children attended at screening (-7 days). According to a computer-generated randomization sequence, the fifty eligible patients and their parents/caregivers were assigned to an intervention group that received MyTEP (no. = 25) or mHP (no. = 25). After randomization (T1, day 0), enrolled children attended follow-up examinations at T2 (day 30), T3 (day 60) and T4 (day 90) (Fig. 1). All participants received an Espace spacer (Air Liquide Medical System, S.p.A., Italy) to optimize the metered dose inhaler technique.

The study was approved by the local Institutional Ethics Committee (02/2017), and informed consent was obtained from all parents before study entry. The study was registered on ClinicalTrials.gov (NCT02636920).

2.2. Study assessments

Baseline characteristics were recorded through standardized questionnaires administered to parents/caregivers [20]. The PACQoL nomogram [21] was used for estimating QoL starting from the Childhood Asthma Control Test (C-ACT) [22]; adherence to treatment was assessed through the Medication Adherence Report Scale (MARS-9) [23]. Spirometry parameters were assessed by Lab (Pony FX portable spirometer, Cosmed, Rome, Italy) spirometry before and after the bronchodilator (BD) test performed in accordance with ATS/ERS guidelines [24] as well as by the Smart One® (MIR Medical International Research, Rome, Italy), a portable spirometer connected to a Bluetooth-enabled smartphone (for a detailed description see Supplementary Material). Atopy was defined as at least one positive (wheal ≥ 3 mm) skin prick tests (SPT) to a panel of common aeroallergens [Dermatophagoides mix, cat, dog, pellitory, olive, cupressus, mixed grasses, alternaria] [25]. Emergency visits and severe exacerbations were defined respectively as non-scheduled health care accesses and as ≥ 3 days of oral prednisone prescription [26].

2.3. MyTEP intervention description

DragONE is an innovative mobile application, available in Italian for both iOS and Android systems, developed in collaboration with the Istituto di Tecnologie Didattiche (ITD) of the National Research Council of Palermo, Italy (Fig. S1). The app featured Smart One® (MIR Medical International Research, Rome, Italy), a portable spirometer connected to a Bluetooth-enabled smartphone. For a detailed description see Supplementary Material.

The multidisciplinary MyTEP team included a pediatrician (VM), a pediatric pulmonologist (SLG), a pediatric psychologist (LM) and two experts in the field of Information and Communication Technologies-based tools for innovative learning and teaching processes (M Arrigo, DLG). During the first examination, families understood the goals of MyTEP and saw the program as easy to follow. The MyTEP was performed at T1 examination and was divided into three phases. The first phase, educational diagnosis, a collective session (10 parents/caregivers and children), aimed at investigating patients' skills, including delivery of a written action plan and agreement of a strategy between the medical team and patients with their parents/caregivers (estimated time: 45 min). The second phase led by a pediatric psychologist, a collective session (10 parents/caregivers and children), aimed at better understanding asthma and how to cope with it (estimated time: 1 h). The third phase conducted by the multidisciplinary MyTEP team, an interactive collective session (10 parents/caregivers and children), aimed at evaluating the skills acquired, by treatment demonstrations and interactive gaming (estimated time: 30 min). Families were assured the MyTEP team would be present along the study period to further establish rapport, encourage engagement, and provide assistance, if necessary.

3. Statistical analysis

The sample size of the present study was based on data from a previous study investigating the effect of TEP on QoL in adults [27]. The QoL increased from a baseline mean value of 59.7 ± 13.9 to 63.5 ± 15.33 at T1. To detect a similar change with an 85% statistical power and a 5% significance level a sample of 20 children for each treatment group was needed. Taking into account a 25% dropout rate, the sample size was therefore established at 25 patients per group. Mean values were compared using the *t*-test. Differences in categorical variables were evaluated using the X^2 test. A paired *t*-test was used for comparing changes in PAQLQ, C-ACT, and MARS-9 scores between examinations within the MyTEP and mHP groups. A Bonferroni adjustment was applied to p-values (p-adjust), dividing each p-value by the number of comparisons being made. Comparisons between PAQLQ and C-ACT scores in myTEP and mHP were performed in terms of Least Square mean change (using the R package lsmeans) adjusting for birth order, allergic rhinitis, parental education, current exposure to passive smoke and pet dander (selected using a stepwise procedure). A Generalized Linear Mixed model (GLMM) for assessing factors associated with PAQLQ score was developed. This model is recommended for longitudinal data with repeated measurements. GLMM was developed using a supervised stepwise selection procedure starting from a full

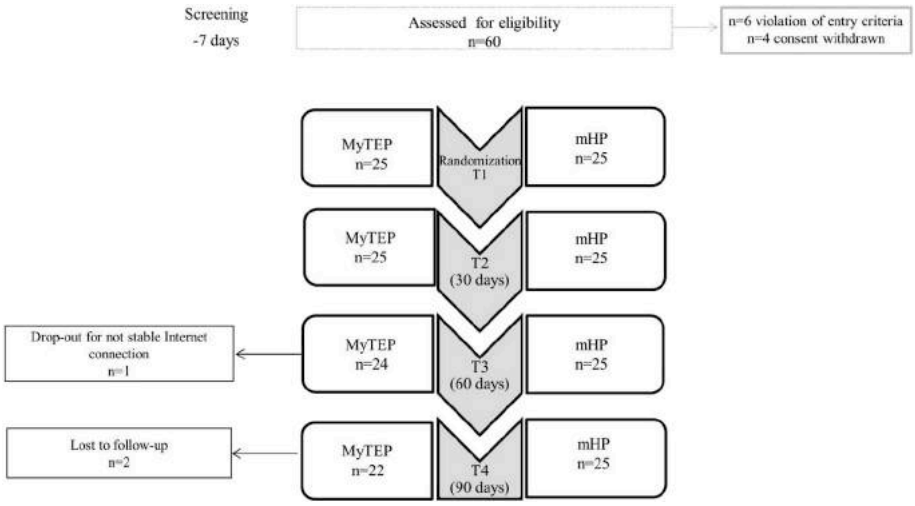

Fig. 1. Flow diagram showing patients' progress throughout the study.

model including gender, age, BMI, Smart One FEV_1, current exposure to passive smoke and pet dander, parental education, pet ownership, atopic status, allergic rhinitis, sinusitis, otitis, eczema, asthma onset, number of severe exacerbations, birth order, and emergency visits. If the Variance Inflation Factor (VIF) was higher than 4 -indicating collinearity-, the variable with the highest VIF was removed and the model re-evaluated. As final steps, variables with a p-value above 0.10 were removed from the model only if they didn't change the direction of effect of one of the other included variables. The final reduced model included Smart One FEV_1, allergic rhinitis, sinusitis, otitis, eczema, birth order, maternal education and current pet ownership. All estimates are presented with corresponding 95% confidence intervals (95%CI). Analyses were performed using R (3.4.0) software; a p-value < 0.05 was considered statistically significant.

4. Results

A total of 47 children completed the study (Fig. 1). The mean age at doctor diagnosed asthma was no different in the two groups. At the time of enrollment, there were no differences between participants in both the MyTEP and mHP groups in regards to level of controller therapy, frequency of asthma exacerbations and emergency visits during the last year (Table 1). 34.69% were females. Allergic rhinitis was the most common comorbidity (65.31%), and 90.91% were sensitized to at least one of the tested allergens, with no differences between indoor and outdoor allergens (data not shown).

4.1. Primary and secondary outcomes multiple comparisons in MyTEP and mHP

Fig. 2 illustrates the observed PAQLQ and C-ACT scores over time in myTEP and mHP without any adjustment. From T1 to T4, the PAQLQ score (Fig. 2, first row) significantly increased in both the MyTEP ($p = 0.014$, p-adjust = 0.042) and mHP ($p = 0.046$, p-adjust = 0.138) groups, whereas a significant increase in C-ACT score (Fig. 2, second row) was only found in MyTEP ($p = 0.009$, p-adjust = 0.027). No differences between groups were found in the MARS-9 score (data not shown).

At baseline, Lab spirometry and BD response (%) values were similar in MyTEP and mHP; the computed z-scores were in the normal range (Table 2). A significant improvement from T1 to T4 was found in both groups. The Smart One® FEV_1 z-score trend did not differ between MyTEP and mHP for AM and PM measurements, which were just below zero but in the normal range (Fig. S2). The Bland Altman analysis showed a random point distribution with no evidence of heteroscedasticity both for AM and PM Lab and Smart One® FEV_1 in the two study groups (Fig. S3). In MyTEP and mHP, no correlations were found between variation in FEV_1 in terms of the size of the day's range (amplitude) and the BD response (%) (data not shown) [28]. The mean FEV_1 variation (expressed as amplitude/mean) was −0.98 in MyTEP

Table 1
Children characteristics by group at T1.

n	All	MyTEP	mHP	p-value
	50	25	25	
Female	17 (34.69%)	10 (41.67%)	7 (28%)	0.481
Age, years	9.18 (1.56)	9.04 (1.6)	9.32 (1.55)	0.538
BMI $kg{\cdot}m^2$	16.99 (3.01)	16.99 (3.36)	17 (2.69)	0.990
Current passive smoke exposure	12 (25%)	6 (26.09%)	6 (24%)	1.000
Paternal education ≥8 years	40 (80.00)	21 (84.00)	19 (76.00)	0.724
Maternal education ≥8 years	38 (76.00)	20 (80.00)	18 (72.00)	0.741
Pet ownership	6 (12.00)	4 (16.00)	2 (8.00)	0.663
Atopic status	40 (90.91%)	20 (95.24%)	20 (86.96%)	0.667
Allergic rhinitis	32 (65.31%)	17 (70.83%)	15 (60%)	0.619
Asthma onset, years	4.18 (2.12)	4.56 (2.39)	3.83 (1.86)	0.325
Severe exacerbations (last year)	5.28 (3.8)	4.94 (3.8)	5.67 (3.9)	0.598
Emergency visits (last year)	8 (23.53%)	3 (18.75%)	5 (27.78%)	0.830
Median ICS dose (fluticasone propionate) $\mu g{\cdot}day^{-1}$	200 (100–500)	200 (100–500)	200 (100–500)	0.221

Data are presented as n (%) or median (IQR) and were computed based on the total number of non-missing cases; p-values were calculated using a *t*-test or a Chi-squared test; ICS: inhaled corticosteroids.

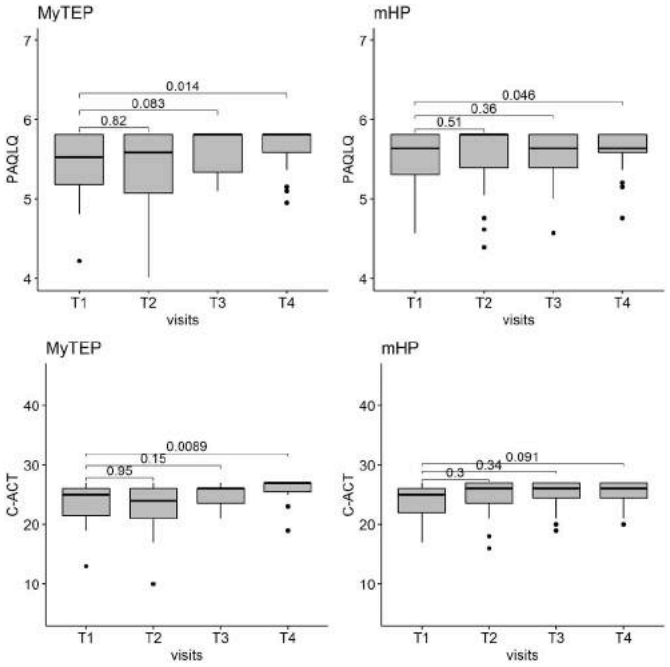

Fig. 2. PAQLQ and C-ACT scores over time in myTEP and mHP. p-values for paired comparisons from paired Wilcoxon test.

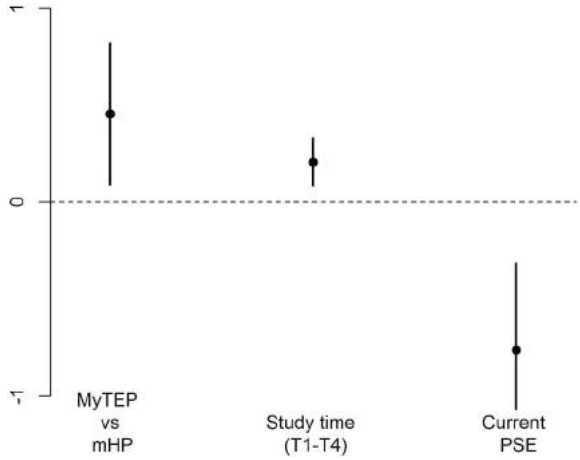

Fig. 3. Estimates and 95% Confidence Intervals for PAQLQ score.

and 0.58 in mHP [29]. FEV_1 variation did not show significant correlations with the patient's QoL (data not shown).

The minimally clinically significant differences (MCID) were the following: ≥0.5 points for the PAQLQ [30], reached in 23% of MyTEP and in 16% of mHP; 2 points for C-ACT, achieved in 36% of the MyTEP and 44% of the mHP group [31]; 10% change [considered relevant for adults [26]] for FEV_1, reached in 50% of the MyTEP and 36% of the mHP group.

When adjusting for confounders, changes in PAQLQ and in C-ACT scores were significantly greater in MyTEP than in mHP (LS mean difference: 0.269 p = 0.05 and 2.324 p = 0.03, respectively).

During the study period no differences were found between MyTEP and mHP in terms of % of patients free from symptoms for > 90% days per month (data not shown). No adverse events occurred in either study group.

4.2. Risk factors associated with QoL

Fig. 3 reports the associations between potential facets of asthma and PAQLQ score controlling for MyTEP and mHP. PAQLQ score was positively associated with MyTEP (regression coefficient 0.455, p = 0.023); significantly higher with study time (0.207, p = 0.002); inversely associated with current passive smoke exposure (−0.764, p = 0.003).

5. Discussion

Increasing evidence suggests that children with chronic illnesses

Table 2
Changes in Lab spirometry parameters (FEV_1, FVC, FEF_{25-75}) from T1 to T4, in the study population and by study groups.

n		All	MyTEP	mHP	p-value
		50	25	25	
Mean Lab FEV_1% predicted	T1	113.22 (22.81)	112.06 (25.2)	114.38 (20.62)	0.728
	T4[a]	126.93 (22.27)	131.55 (25.63)[a]	124.91 (18.88)	
	p-value	< 0.001	0.001	< 0.001	
Mean Lab FEV_1 z-score	T1	1.14 (1.97)	1.04 (2.16)	1.24 (1.8)	0.721
	T4[a]	2.34 (1.98)	2.74 (2.28)[a]	2.16 (1.67)	
	p-value	< 0.001	0.002	< 0.001	
BD responsiveness (%)	T1	0.04 (0.25)	0.04 (0.32)	0.05 (0.15)	0.892
	T4[a]	0.06 (0.14)	0.08 (0.11)[a]	0.08 (0.16)	
	p-value	0.533	0.07	0.092	
Mean Lab FVC% predicted	T1	116.99 (21.7)	117.19 (24.77)	116.8 (18.66)	0.950
	T4[a]	126.92 (23.44)	131.45 (28.59)[a]	126.06 (20.40)	
	p-value	< 0.001	0.003	< 0.001	
Mean Lab FVC, z-score	T1	1.38 (1.79)	1.38 (2.04)	1.38 (1.54)	0.992
	T4[a]	2.20 (1.90)	2.52 (2.29)[a]	2.15 (1.68)	
	p-value	< 0.001	0.003	< 0.001	
Mean Lab FEF_{25-75},% predicted	T1	98.31 (29.93)	97.13 (32.36)	99.48 (27.94)	0.788
	T4[a]	114.92 (26.31)	119.30 (19.01)[a]	111.40 (27.38)	
	p-value	< 0.001	0.020	0.016	
Mean Lab FEF_{25-75}, z-score	T1	−0.17 (1.35)	−0.24 (1.5)	−0.11 (1.21)	0.743
	T4[a]	0.56 (1.14)	0.80 (0.82)[a]	0.39 (1.18)	
	p-value	< 0.001	0.014	0.017	

Data are presented as mean (SD). The percentages and the means were computed based on the total number of non-missing cases; p-values were calculated using a *t*-test between groups and with a paired *t*-test within the groups.
FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow at 25–75% of the FVC.
[a] Three children in the MyTEP group dropped out due to technical problems (n = 1) or lost to follow-up (n = 2).

such asthma may benefit from TEPs in achieving competency in understanding the disease and its treatments as well as greater individual autonomy [13]. The current study showed that implementing an education program (MyTherapeutic Education Program, MyTEP) that couples multidisciplinary TEP with an m-Health Program (mHP) improves QoL in asthmatic children.

Uncertainties exist as to whether the use of m-Health interventions in childhood asthma can confer positive effects on different asthma outcomes. Indeed, such strategies resulted in non-significant differences with regard to symptoms control, self-efficacy [32] and health-care use [33], when compared to usual care. However, improved adherence and control among underserved minority adolescents were reported [34], suggesting that an intervention featuring an electronic medication monitor and companion smartphone asthma application can improve disease outcome in a low health literacy population. Interestingly, in this pilot study we found improvements in QoL, asthma control and spirometry parameters in all participants, regardless of their participation in the intervention, which points to a potential benefit of implementing m-Health strategies on both self-reported and objective outcomes over a short-term period in a population of outpatient asthmatic children.

Patient education is now recognized as a cornerstone of asthma management, as recommended by guidelines [12]. Hence, the development of TEPs raised increasing attention as an integral part of asthma care, especially at pediatric age. Long-term TEPs were found to reduce asthma morbidity and to improve knowledge of the disease in asthmatic children with different level of severity [35,36]. Uncertainties still remain on the impact of TEPs on QoL of children, since conflicting results have been reported in different settings (such as school or emergency department) when considering asthma control, self-management and QoL [18,37–39]. Our study shows the positive effect of a program combining multidisciplinary TEP with m-HP on asthmatic children, emphasizing that implementing such a strategy could be a promising model for achieving a better health status in asthmatic children, with a special focus on QoL. In this connection, the improvement of QoL was significantly more pronounced in children receiving MyTEP than in those exclusively experiencing m-HP. Conversely, the lack of significant differences in secondary outcomes (asthma control, adherence and spirometry parameters) could probably be due to a tailored pattern of care based on the use of the DragONE app, which allowed engagement of children and their caregivers in better managing the disease. Another factor that may have contributed to these findings is that there were no differences between participants in both the MyTEP and mHP groups in regards to level of controller therapy, frequency of asthma exacerbations and emergency examinations during the last year. The criteria for entry into the present study excluded children who had severe asthma exacerbations and/or emergency visits for asthma in the last year, suggesting that our sample of children had relatively few disease-related complications. Other children, including those with more severe disease or poorer disease management skills as well as minority underserved children may have benefited more from this type of intervention.

In addition, the lack of significant improvement in MARS-9 score in the present study may be related to the high levels of self-reported adherence in both MyTEP (mean MARS-9 score: 43.6 ± 1.75) and mHP (mean MARS-9 score: 42 ± 7.25) groups, since the T1 examination. This could probably be due to children's awareness of taking part in a trial evaluating asthma outcomes, including adherence, which might have enhanced their motivation in following the medication prescription.

With regard to spirometry parameters, although significant improvement was found in both MyTEP and mHP throughout the study period, a minimally clinically significant difference was more frequently reached in children receiving MyTEP. This last finding suggests that training and education led to a better performance of forced expiratory maneuvers, as well as to obtaining reliable measurements over a short-term period. Moreover, FEV_1 z-scores obtained by means of the Smart One® did not differ between the two groups for AM and PM measurements, since all participants were skilled in performing spirometry. Notably, unlike previous data [40], our findings demonstrate good agreement between Smart One® FEV_1 and Lab FEV_1, showing that this portable home spirometer provides reliable measurements in children with asthma.

Confirming the aforementioned results, we found that QoL was significantly associated with receiving the MyTEP and maintaining this intervention over time. However, exposure to environmental risk factors affects QoL in our study population. In particular, subjects currently exposed to passive smoking were those reporting a greater negative impact on their QoL, suggesting that avoiding exposure to this modifiable risk factor may reduce the subjective burden of asthma [20]. Moreover, this finding suggests that an improvement in QoL could be reached by performing multicomponent interventions aimed at contrasting one of the most detrimental triggers of asthma morbidity in children [41]. Therefore, we believe that smoking cessation actions for parents of children with asthma might be an issue to be considered when TEPs for childhood asthma care are delivered.

These results should be interpreted with caution as this is a pilot study with a small sample of participants. The main strength is the involvement of a multidisciplinary staff, which helped over time to reinforce the relationship between participants and staff in view of progressive empowerment in asthma self-management. However, the present study faced some potential limitations. First, blinding of staff and participants/caregivers was not possible. Anyway, we performed objective measurements, such as spirometry. Second, the high levels of self-reported adherence in both the study groups, since the T1 examination, may have led to a conservative bias. Third, the study was only performed on children with mild-moderate asthma, so the present findings cannot be generalized to children with different degrees of asthma severity. Lastly, the monitoring period was relatively short; longer studies are needed to confirm our findings.

In conclusion, this study demonstrated that implementing a multidisciplinary TEP with an m-Health program results in gains in QoL of children with asthma. The integration of MyTEP and DragONE app may be a powerful way to achieve the goals of asthma management, as recommended by current guidelines. Even though a single model of management cannot suit all children with asthma, we believe that performing objective monitoring is a fundamental benefit as well as building a strong relationship with patients and their caregivers. At last, incorporating smoking reduction strategies might help to increase children's QoL and potentially to decrease the burden of the disease.

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Conflicts of interest

All co-authors declare no conflicts of interest.

Author contribution

LM, GF, and SLG designed the study. GF and SLG wrote the initial draft and had final responsibility for the decision to submit for publication. GC conducted the statistical analyses. MG, M Arrigo, DLG, and M Allegra contributed to develop the DragONE app. LM, GF, SLG, VM, RPG contributed to the collection and/or provided the health and covariate data. MB performed a critical revision of the manuscript and offered precious technical advice on how the study might be improved. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all

aspects of the work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.05.008.

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