Journal Pre-proof

Efficacy of a digitally supported intervention for children and adolescents with difficult-to-control asthma (INSPIRINGKIDS): results from a multicentre randomized controlled trial

Eva Maroto PT MSc Maria del Mar Esteban Lombarte PT MSc Teresa Garriga-Baraut MD PhD Gemma Garcia del Cerro MD M. Araceli Caballero-Rabasco MD Gimena Hernández MD PhD Laura Valdesoiro Shane Fitch MSc Raquel Sebio-Garcia PT PhD Ines de Mir Messa MD PhD

PII: S0300-2896(25)00140-1

DOI: https://doi.org/doi:10.1016/j.arbres.2025.04.004

Reference: ARBRES 3785

To appear in: *Archivos de Bronconeumologia*

Received Date: 25 November 2024

Accepted Date: 15 April 2025

Please cite this article as: Maroto E, Lombarte MdME, Garriga-Baraut T, Cerro GGd, Araceli Caballero-Rabasco M, Hernández G, Valdesoiro L, Fitch S, Sebio-Garcia R, de Mir Messa I, Efficacy of a digitally supported intervention for children and adolescents with difficult-to-control asthma (INSPIRINGKIDS): results from a multicentre randomized controlled trial, *Archivos de Bronconeumología* (2025), doi: https://doi.org/10.1016/j.arbres.2025.04.004

TITLE: Efficacy of a digitally supported intervention for children and adolescents with difficult-to-control asthma (INSPIRINGKIDS): results from a multicentre randomized controlled trial

AUTHORS

- Eva Maroto PT, MSc. Lovexair Foundation. Physiotherapy Department. Universidad CEU San Pablo Madrid. Madrid, Spain.
- Maria del Mar Esteban Lombarte PT, MSc. Lovexair Foundation. Centro Neumovital. Madrid, Spain.
- Teresa Garriga-Baraut MD, PhD. Paediatric Pulmonology and Cystic Fibrosis Unit. Vall d'Hebron University Hospital. Barcelona, Spain.
- Gemma Garcia del Cerro. MD. Pulmonology and Allergology Unit. Hospital Santa Creu I Sant Pau. Department of Paediatrics, Obstetrics and Gyneacology and Preventive Medicine and Public Health. Universitat Autonoma de Barcelona. Barcelona, Spain.
- M. Araceli Caballero-Rabasco. MD. Pulmonology and Allergology Unit. Paediatric Pulmonology and Allergy Unit. Hospital del Mar. Department of Medicine and Life Sciencies. Universitat Pompeu Fabra.
- Gimena Hernández. MD. PhD. Pulmonology and Allergy Unit. Hospital del Mar.
- Laura Valdesoiro. Barcelona, Spain. MD. PhD. Pulmonology and Allergology Unit. Corporacio Sanitaria Parc Tauli.
- Shane Fitch MSc. Lovexair Foundation. Madrid, Spain
- Raquel Sebio-Garcia PT, PhD. Department of Physical Medicine & Rehabilitation. Hospital Clinic de Barcelona. Fundacio Clinic per a la Recerca Biomèdica (FRCB-IDIBAPS). Hospital Clinic de Barcelona.
- Ines de Mir Messa MD, PhD. Paediatric Pulmonology and Cystic Fibrosis Unit. Hospital Universitari Vall d'Hebron.

CORRESPONDING AUTHOR

Raquel Sebio-Garcia PT, PhD. Department of Physical Medicine & Rehabilitation. Hospital Clínic de Barcelona. Fundació Clinic per a la Recerca Biomèdica (FRCB-IDIBAPS). Hospital Clinic de Barcelona. Casanova 160 bis 08036 Barcelona.

Email: sebio@clinic.cat

TRIAL REGISTRARION NUMBER: NCT04166344

WORD COUNT: 1550

Difficult-to-control asthma (DA) represents a small percentage of all the patients diagnosed with asthma (up to 12 or 15%) (1), but accounts for a disproportionate amount of the healthcare expenditure (2). Fortunately, patients with DA exhibit potentially modifiable causes influencing asthma control such as errors in inhaler technique, unmanaged comorbidities or sub-optimal adherence (3), that can be improved through the use of specific digital tools such as mobile apps, wearables or platform webs (4). However, many of these lack behavioral strategies or interaction with healthcare professionals, which could provide additional benefits, particularly for long-term maintenance.

Therefore, the main objective of this study was to evaluate the feasibility and preliminary effectiveness of a web-based interactive platform (HappyAir®) with behavioural change support provided by a respiratory physiotherapist to increase self-reported asthma control in children and adolescents with DA compared to the standard care. Secondary objectives included: i) to explore feasibility (recruitment rates, adherence with the platform) and safety and ii) to assess the effectiveness of the platform to improve lung function, peak expiratory flow and reducing the frequency of exacerbations at six months and one year after inclusion. We hypothesized that patients and families with access to the HappyAir® platform who are supported by a respiratory physiotherapist will improve their symptom control according to the ACT compared to the standard care (no intervention).

This open-label, randomized, multicentre controlled trial was conducted at four tertiary hospitals in Spain. and registered in Clinicaltrials.gov (NCT04166344). Approval by the Ethics Committee of each participating centre was obtained and informed consent was provided from the parents of participants or legal guardians. The CONSORT Guidelines were followed to report the results of this trial (5). Consecutive patients who met the following inclusion criteria were invited to participate: a) children and adolescents between 6 and 18 years old; b) moderate to severe persistent asthma according to the GEMA guidelines (6); c) non-controlled asthma according to a score of $\leq$19 points in the Asthma Control Test (ACT) (7); d) access to internet and a smartphone, tablet or computer; e) ability to understand and use the web-based platform (in children <12 years the ability of the tutor or

legal guardian). Exclusion criteria were: a) patients who have had an exacerbation in the previous two weeks to recruitment; b) patients with intermittent asthma or well-controlled asthma according to an ACT score >20; c) inability to speak or understand Spanish/Catalan; d) any neurological or psychiatric condition that prevents patients to use adequately the platform or the devices used during the trial. The sample size was calculated to detect a minimally clinical significant difference (MCID) of 2 points in the ACT or C-ACT(8). Assuming a common standard deviation of 2.5 units, a sample size of 54 (26 per arm) was needed for the study. As we estimated a dropout rate of 15%, we increased the sample size to a total of 60 participants.

Participants were randomly allocated to either the intervention group (GI) or the control group (CG) in a 1:1 ratio (Granmo® v7.12 IMIM, Barcelona). Participants in the IG were given access to the HappyAir® platform (https://happyair.org/- Vídeo app) during six months and were encouraged to register daily in the platform information regarding their day (https://happyair.org/tu-diario-2). In addition to the online features of the platform, patients were assigned a respiratory coach (physiotherapist) who was responsible to monitor their progress and provide support to increase adherence to the intervention. A detailed description of the intervention is depicted in the Supplemental File no.1. Subjects in the CG received standard care according to their respective hospitals.

The main outcome was change in asthma control according to the ACT (9) at 6 months between both study groups. The test was self-administered by the patients or caregivers. Secondary outcomes included: i) feasibility of the intervention (recruitment and retention rates) as well as adherence and safety; and ii) pulmonary function (FEV1 and PEF) (10); and iii) number of exacerbations in the previous six months based on current literature (11). Patients were assessed three times during the study period: 1) at baseline (T0); 2) post-intervention (6 months, T1) and 3) at follow-up (12 months, T2).

The statistical analysis was conducted under the intention-to-treat principle with missing data replaced using the expectation-maximization method. A per-protocol analysis including only those who completed the intervention and those adherent (at least >10 interactions with the platform). Repeated measures ANOVA were conducted for each variable of interest using time as the between-subject factor and randomization arm as the condition. All analyses were conducted using SPSS v.26® (IBM Corporation) for Windows© and a P value of <.05 was considered as statistically significant.

Between June 2021 and May 2023, a total of 77 patients were screened for eligibility and 60 met inclusion criteria and gave consent, resulting in a recruitment rate of 77.9% (Figure 1 Supplemental File no.2). Patients in both groups were similar at baseline in terms of age, gender, sociodemographic

background and clinical features (Table 1, Supplemental File no.2). In the intention-to-treat analysis, the repeated measured ANOVA showed a significant effect of time on ACT ($F_{2,116}$=81.451, p<.0001) but no effect of group or the interaction between group and time ($F_{2,116}$=.119, p=.888) (Figure 1). Similar results were obtained in the per-protocol analysis including patients with full data available. Adherence to the intervention was low with only 43% of patients providing weekly data on symptoms, PEF and physical activity patterns. The number of interactions ranged from 3 to 186 (median 65, IQR 26, 118). Regarding safety, one minor adverse event was reported in the IG (minor asthma crisis after repeated measures of peak flow) which was resolved with the use of rescue medication with no further medical assistance. Secondary outcomes are displayed in Table 2. In terms of lung function, a significant effect of time was observed on FEV1 ($F_{2,116}$=11.627 p<.0001) as well as PEF ($F_{2,114}$= 10.775, p<.0001), but again no effect of the interaction between group and time. However, a tendency was observed for a group effect on PEF ($F_{2,116}$=2.939, p=.057). Pairwise comparisons performed at T1 and T2 showed that the IG significantly improved both parameters at six months while the CG did not. Finally, no significant differences were observed for asthma-related exacerbations at T2.

Strengths of this study including its novelty in using a web-based platform with the support of a respiratory coach as well as its multicentric nature. Unfortunately, adherence to the intervention was low resulting in no significant differences between groups at any follow-up for the main outcome (asthma control), although improvements in lung function (PEF) at six months were observed for the IG.

Asthma control can be substantially influenced by patients' self-efficacy and self-management, thus interventions based on digital tools such as ours are increasingly popular (12,13). In a previous study (14), a mobile app intervention combining tracking of lung function with personalised recommendations was found to increase ACT scores (mean difference 0.70 95% CI 0.06, 1.34) but was not effective in increasing adherence to medication. In another more recent study, Fedele et al. (15) reported a significant and clinically meaningful improvement in asthma control among adolescents who participated in a behavioural change and goal-setting digital intervention for four months, but no difference compared to controls. Our findings show that our intervention was not appealing enough for the patients, considering the low engagement, leading to the negative findings observed. Potential factors such as low socioeconomic background, burden of reporting symptoms and activity daily as well as low motivation might have contributed to this low adherence. Despite this, a positive change in lung function (PEF) was reported in the IG (Cohen's d=0.7), indicating that regular monitoring of PEF could have led to better maintenance of pulmonary function. Unfortunately, this improvement was not associated with a decrease in exacerbations, as seen in previous studies (16,17). Despite the

growing interest in digital interventions to improve asthma control, there is still much heterogeneity in the population included, as well as the type of intervention (web-based, mobile app, etc.) (18,19). Based on the results of a systematic review (19), more interactive features are generally associated with better outcomes; yet, in our study, we found no differences in the number of exacerbations between groups. The low adherence to the intervention as well as the lack of objective measures to track medication adherence (such as Electronic Monitoring Devices or EMDs) could be at fault for the lack of change in this parameter.

Some limitations in our trials need to be acknowledged. First, due to restrictions in funding, we couldn't include EMDs to monitor adherence to medication. Second, we have used a self-reported outcome to monitor asthma control (ACT). As observed in previous studies (20), patients tend to overestimate their asthma control, which may have biased our results. Last, although adequately powered for the main outcome, our sample size was probably too small to observe significant changes in other clinical variables such as exacerbations.

Based on our findings, the use of an interactive, online platform with self-monitoring of lung function, symptoms and activity did not result in an improvement in asthma control in children and adolescents with DA. However, the intervention was effective to increase PEF, suggesting a positive effect on lung function. Further studies need to be undertaken to ascertain if this improvement in lung function could be associated with greater medication adherence or improvement in other clinical outcomes.

FUNDING

This study was conducted thanks to the Lovexair Foundation® and supported through a research grant by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Reference number: 942/2019.

DECLARATION OF INTEREST

Dr. Raquel Sebio-Garcia has received royalties from AstraZeneca and Pfizer in the past 12 months.
Dr. Inés de Mir Messa has received fees for conferences and advisor boards from Sanofi, Gebro, GSK and Novartis in the past 12 months.
Dr. Teresa Garriga-Baraut has received fees for conferences and advisor boards from Sanofi, Leti, Allergopharma, AstraZeneca and Gebro in the past 12 months.

ACKNOWLEDGMENTS

The author of this study would like to thank the patients and their families for their participation in this research. We would also like to acknowledge the support from the Lovexair® Foundation as well as the clinical staff at each participating centre who collaborated in the data acquisition.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

Yes

If yes; please provide name of the ethical committee approving these experiments and the registration number. :

Hospital Universitari Vall d'hebron PR(AG)286/2019 Hospital Santa Creu i Sant Pau: 20/018 Hospital del Mar-Parc Salut Mar: 2019/888/I Coorporación Sanitaria Parc Tauli de Sabadell: 2019/310

If yes; please confirm authors compliance with all relevant ethical regulations. :

Yes

If yes; please confirm that written consent has been obtained from all patients. :

Yes

3. Does your study include a clinical trial?:

Yes

If yes; please confirm that experiments have been conducted according to the CONSORT guidelines. :

Yes

Please provide name of the ethical committee approving these experiments and the registration number:

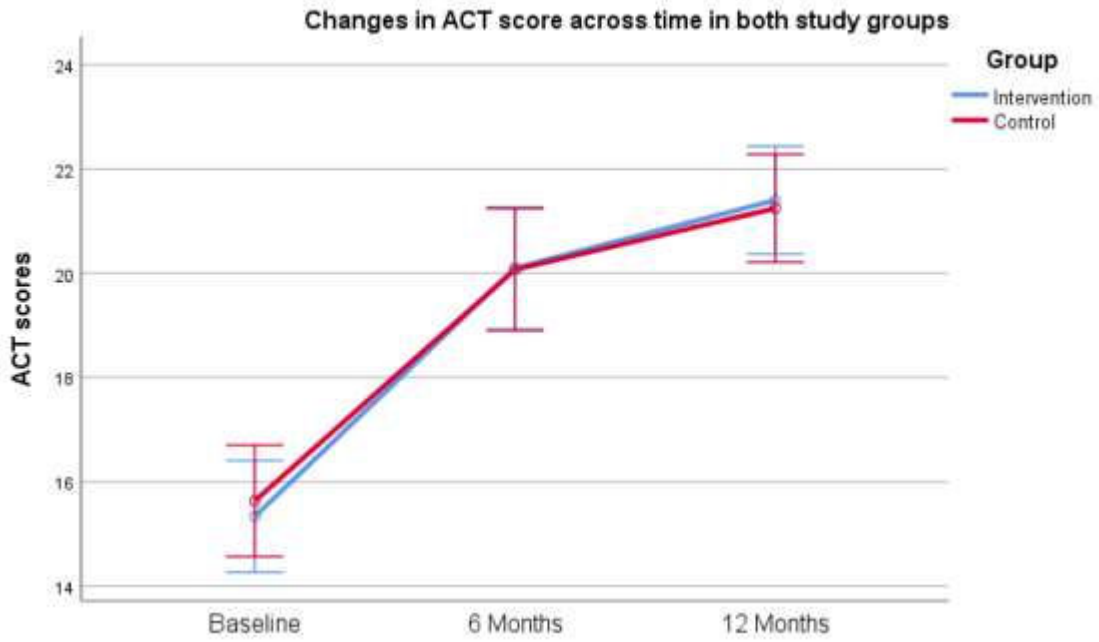
Hospital Universitari Vall d'hebron PR(AG)286/2019 Hospital Santa Creu i Sant Pau: 20/018 Hospital del Mar-Parc Salut Mar: 2019/888/I Coorporación Sanitaria Parc Tauli de Sabadell: 2019/310

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

FIGURE LEGENDS

Figure 1. Changes in ACT score across time in both study groups.



REFERENCES

1. Bush A, Fitzpatrick AM, Saglani S, Anderson WC, Szefler SJ. Difficult-to-Treat Asthma Management in School-Age Children. J Allergy Clin Immunol Pract. 2022 Feb;10(2):359–75.

2. Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, et al. Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting. J Allergy Clin Immunol Pract. 2016;4(1):120-129.e3.

3. von Bülow A, Backer V, Bodtger U, Søes-Petersen NU, Vest S, Steffensen I, et al. Differentiation of adult severe asthma from difficult-to-treat asthma - Outcomes of a systematic assessment protocol. Respir Med. 2018 Dec;145:41–7.

4. Ferrante G, Licari A, Marseglia GL, La Grutta S. Digital health interventions in children with asthma. Clin Exp Allergy J Br Soc Allergy Clin Immunol. 2021 Feb;51(2):212–20.

5. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 24;340:869.

6. Plaza Moral V. GEMA4.0. Guía española para el manejo del asma. Arch Bronconeumol. 2015;51:2–54.

7. Ko FWS, Hui DSC, Leung TF, Chu JHY, Wong GWK, Ng SSS, et al. Asthma control test: Cut off values of control according to GINA guideline and its ability to predict exacerbations and treatment decisions. Eur Respir J. 2011;38(Suppl 55).

8. Bonini M, Paolo MD, Bagnasco D, Baiardini I, Braido F, Caminati M, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev [Internet]. 2020 Jun 3 [cited 2024 Oct 30];29(156). Available from: https://publications.ersnet.org/content/errev/29/156/190137

9. Pérez-Yarza EG, Castro-Rodriguez JA, Villa Asensi JR, Garde Garde J, Hidalgo Bermejo FJ. Validation of a Spanish version of the childhood asthma control test (SC-ACT) for use in Spain. An Pediatría Engl Ed. 2015 Aug 1;83(2):94–103.

10. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70–88.

11. Picado C, Badiola C, Perulero N, Sastre J, Olaguíbel JM, Viña AL, et al. Validation of the spanish version of the asthma control questionnaire. Clin Ther. 2008 Oct 1;30(10):1918–31.

12. Alquran A, Lambert KA, Farouque A, Holland A, Davies J, Lampugnani ER, et al. Smartphone Applications for Encouraging Asthma Self-Management in Adolescents: A Systematic Review. Int J Environ Res Public Health. 2018 Oct 29;15(11):2403.

13. Huckvale K, Car M, Morrison C, Car J. Apps for asthma self-management: a systematic assessment of content and tools. BMC Med. 2012 Nov 22;10(1):144.

14. Ljungberg H, Carleborg A, Gerber H, Öfverström C, Wolodarski J, Menshi F, et al. Clinical effect on uncontrolled asthma using a novel digital automated self-management solution: a physician-blinded randomised controlled crossover trial. Eur Respir J. 2019 Nov;54(5):1900983.

15. Fedele DA, Thomas JG, McConville A, McQuaid EL, Voorhees S, Janicke DM, et al. Using Mobile Health to Improve Asthma Self-Management in Early Adolescence: A Pilot Randomized Controlled Trial. J Adolesc Health. 2021 Dec 1;69(6):1032–40.

16. Bender BG, Cvietusa PJ, Goodrich GK, Lowe R, Nuanes HA, Rand C, et al. Pragmatic Trial of Health Care Technologies to Improve Adherence to Pediatric Asthma Treatment: A Randomized Clinical Trial. JAMA Pediatr. 2015 Apr 1;169(4):317–23.

17. Britto MT, Rohan JM, Dodds CM, Byczkowski TL. A Randomized Trial of User-Controlled Text Messaging to Improve Asthma Outcomes: A Pilot Study. Clin Pediatr (Phila). 2017 Dec;56(14):1336–44.

18. Milne-Ives M, Lam C, Meinert E. Digital Technologies for Monitoring and Improving Treatment Adherence in Children and Adolescents With Asthma: Scoping Review of Randomized Controlled Trials. JMIR Pediatr Parent. 2021 Sep 17;4(3):e27999.

19. Unni E, Gabriel S, Ariely R. A review of the use and effectiveness of digital health technologies in patients with asthma. Ann Allergy Asthma Immunol. 2018 Dec;121(6):680-691.e1.

20. Vennera M del C, Picado C, Herráez L, Galera J, Casafont J, Study Group CONTROL. Factors associated with severe uncontrolled asthma and the perception of control by physicians and patients. Arch Bronconeumol. 2014 Sep;50(9):384–91.

Table 1: Summary of the secondary outcomes in both groups after the intervention

VARIABLE	**INTERVENTION GROUP**					**CONTROL GROUP**				
	T0	T1	Mean Change (T0-T1)	T2	Mean Change (T0-T2)	T0	T1	Mean Change (T0-T1)	T2	Mean Change (T0-T2)
ACT/C-ACT	15.3 (2.9)	20.1 (2.6)*	4.8 (3.8)*	21.4 (2.9)*	6.1 (4.3)	15.6 (2.9)	20.1 (3.7)*	4.4 (3.6)*	21.2 (2.8)*	5.6 (3.9)*
PEF (l/min)	405.2 (144)	504.75 (159.1)*	99.6 (125.9)*#	479.3 (190.6)	74.1 (122.1)	385.6 (122.8)	514.5 (141.2)	29.9 (89.9)#	422.1 (163.7)*	36.6 (95.7)
FEV1 (l/s)	2.3 (0.8)	2.6 (0.9)*	0.2 (0.4)*	2.6 (0.9)*	0.3 (0.4)	2.2 (0.8)	2.3 (0.8)	0.09 (0.6)	2.5 (0.7)*	0.3 (0.5)

Numbers are expressed as mean and (Standard Deviation)

*P<.05 intra-group compared to baseline; #P<.05 inter-group

ACT: Asthma Control Test; C-ACT: Children Asthma Control Test; PEF: Peak Expiratory Flow; FEV1: Forced Expiratory Volume 1 second