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Transitioning adolescents and young adults with asthma: insights from a severe asthma series

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Abstract

Thanks to improvements in asthma care and availability of new biologic treatments, a relatively novel population of adolescents and young adults (AYA) with severe asthma (SA) is growing. Transition from pediatric to adult care represents a critical phase in the management of SA. We herein describe clinical outcomes, therapeutic adjustments and disease management in a group of SA patients transitioning from the pediatric to the adult care center. This is a retrospective study in which demographic and clinical (comorbidities, baseline treatment, number of asthma attacks, spirometry, airway inflammation [fractional exhaled nitric oxide (FeNO) measurements], patient's compliance) data of four SA patients during visits in the Pediatric center as well as after transition into the Adult Center, were retrospectively recollected. All patients transitioned at 18 years of age. Clinical parameters, spirometry and FeNO showed significant improvement following the addition of biologics to baseline asthma regimen during pediatric follow-up and the early transition phase. Several months after transition to the Adult Center, two males experienced SA exacerbations following voluntary discontinuation of the biologic treatment. Symptom control was gained after a phenotype driven re-introduction of a biologic drug in the regimen. Male patients were less compliant and independent than females in the adult setting. Transition from pediatric to adult care for patients with SA can be effectively managed with coordinated and structured transition processes. While some patients maintain stable clinical and respiratory outcomes, others risk to lose asthma control. A personalized approach supporting both patient's independence and adherence to treatment is requested for a successful long-term management.

Keywords

Transition, children, adolescents, severe asthma, biologic treatment, patient independence

Introduction

The prevalence of non-communicable chronic disorders including asthma and chronic obstructive pulmonary disease (COPD) is progressively increasing at all ages, with a significant impact on morbidity and mortality [1]. Approximately 10% of school-age children have asthma and some continue to have symptoms also later in the teenage years or adulthood [2]. Therefore, thanks to the improvement in asthma care and the availability of new effective medications, a relatively novel population of adolescents and young adults (AYA) with asthma, even those with the uncontrolled symptoms of severe asthma (SA), is growing significantly [3].

Transition is an active process that incorporates several changes from one stage of life, or physical or mental conditions, which can significantly affect the normal life of an individual [4]. In chronic diseases, transition involves an adjustment period to the new needs of the patients, which include the development of self-management skills and an increasing responsibility for their medical care [5]. Currently, both pediatric and adult pulmonologists and allergists are called upon to address the issues associated with a difficult moment in the lives of patients moving from child- to adult-centered asthma care, and this can largely influence the future course of the disease [6].

In this manuscript, we have critically examined retrospectively a small series of patients with SA who transitioned from our pediatric to adult asthma care. Our aims were to highlight the difficulties encountered in the transition process and to optimize the care for patients with high morbidity as occurs in SA.

At the Azienda Ospedaliera Universitaria Federico II, Naples, Italy, two specialized services providing separately care to children (Department of Mother and Child, Pediatric Pulmonology and Asthma center) and adults (Department of Medicine and Clinical Complexities, Allergy and Clinical Immunology) with asthma, respectively, have been instituted since 1993. In both units, the follow-up with visits scheduled at intervals of 3 to 6 months (based on the patients' needs) includes spirometry, airways inflammation measurement by fractional exhaled nitric oxide (FeNO), laboratory analysis (for evaluating atopy), and hospital admission for drug administration and/or treatment of medical/surgical complications. Local treatment protocols generally derive from major updated pediatric and adult asthma guidelines or published documents [7]. In the last 5 years, pediatric and adult specialists have jointly organized the transition from the Pediatric to the Adult Asthma Centers. First, the transition program includes an outpatient visit a few months before the patient's 18th birthday in the presence of both pediatric and adult specialists, as well as both parents or just one.

We herein report retrospectively about 4 transitioned patients with SA. For each patient, we described the clinical manifestations of SA, treatment at referral to the Pediatric Asthma unit and the course of the disease, which included the main laboratory findings at referral and one year after the addition of biologics. Similarly, we reported the characteristics of the same patients at transition to the Adult Asthma (division of internal medicine and clinical immunology) Center and during the follow-up. All patients provided written informed consent for the publication of their anonymized clinical and laboratory data.

Case report

The charts of 4 adolescents (2 males, 2 females) with SA, followed first at the Pediatric and then at the Adult Asthma Center were reviewed. They were all living in Campania (Southern Italy). We herein briefly describe the individual clinical course of the patients.

Case 1

Pre-transition

A 9-year-old boy was referred to the Pediatric Asthma Center for poorly controlled early-onset asthma. Recurrent-to-persistent wheezing started at 3 months of age after viral bronchiolitis. At age 5 years sensitization to multiple aeroallergens and high levels of total serum IgE (2,328 kIU/L) were found. At school age, recurrent asthma exacerbations—defined according to GINA 2024 as an acute or subacute deterioration in symptoms and lung function from the patient's usual status, necessitating a change in treatment [7]—were identified based on patient reports, physician evaluation (including by our team), and medical records. These events, along with exercise-induced dyspnea, required add-on therapy with high-dose inhaled fluticasone propionate/salmeterol (Flu/Sal; 1,000/100 mcg/d), the leukotriene receptor antagonist (LTRA) montelukast and repeated courses of oral corticosteroids (OCS). As spirometry progressively decreased despite maintenance antiasthma treatment, subcutaneous (SC) omalizumab started at age 13 years, which resulted in marked reduction in symptoms frequency and severity, as well as significant decrease in additional antiasthma medications. Spirometry improved significantly. The patient transitioned to the Adult Asthma Center at age 18.

Post-transition

During the first year of follow-up at the Adult Center, a prolonged episode of cough and dyspnea led to change asthma baseline medications, thus Flu/Sal was withdrawn and inhaled budesonide/formoterol (bud/form; 640/18 mcg/d) as maintenance and reliever therapy (MART) regimen started. Asthma control was gained for the subsequent 5 years, the patient reported sustained well-being and decided to discontinue omalizumab despite medical advice. Nevertheless, 3 exacerbations requiring OCS treatment occurred. Given the suboptimal asthma control, after 6 months of therapy interruption, the patient agreed to restart treatment with biologics and dupilumab 300 mg/14d SC was started, based on T2 patient's phenotype characterization. Soon after, the patient reported relevant clinical benefits in terms of improved asthma control, and current treatment now includes oral montelukast (10 mg/d) in addition to inhaled bud/form (640/18 mcg/d) and SC dupilumab (300 mg/14d). Interestingly, the patient, currently at age 24 years, is still accompanied by his mother to all the routine check-up visits as she represents his point of reference. The adult medical team asked the patient to come alone for the following visits to grow self-awareness and independence.

Case 2

Pre-transition

A 16-year-old girl with sensitization to multiple aeroallergens was referred to the Pediatric Asthma Center for the management of chronic rhinosinusitis with nasal polyps (CRSwNP) and monthly asthma exacerbations. Despite bilateral nasal polyps being excised, nasal obstruction persisted and nasal mometasone furoate (50 mcg twice per day) was introduced. Efforts to optimize asthma control included a step-up in maintenance therapy, which included inhaled bud/form and montelukast. Adherence to treatment was optimal. However, daily chest tightness and limited exercise capacity imposed frequent use of rescue asthma medications. As blood eosinophilia (1,470 cells/μL) was demonstrated, SC mepolizumab (100 mg monthly) was started. Asthma control progressively improved, and 8 months after starting treatment, chest tightness and cough had completely disappeared. Frequency and severity of asthma attacks also decreased, allowing for a step-down in the maintenance regimen. Inhaled bud/form as MART was confirmed and montelukast was discontinued. Transition at the Adult Asthma Center occurred at age 18.

Post-transition

Two years after transition to the Adult Center, the patient has reported clinical well-being. Asthma treatment previously initiated was confirmed and no asthma exacerbations were registered. CRSwNP and allergic rhinocongiuntivitis-related symptoms further improved following addition of anti-H1 treatment

(ebastine 10 mg/d) as needed to nasal mometasone spray. The patient is highly compliant with treatment and except for the first visit when she was accompanied by her mother, she comes to the scheduled appointments alone.

Case 3

Pre-transition

A 14-year-old girl was referred to the Pediatric Asthma Center for evaluation of poorly controlled asthma. Since the age of 3 years, she had been experiencing recurrent asthma attacks, primarily triggered by respiratory viruses and multiple aeroallergens which she was sensitized to. Despite consistent adherence to treatment with inhaled bud/form as MART started at age 12, asthma control was suboptimal and worsened by obesity (body mass index: 31.5 kg/m^2) and insulin resistance, which necessitated oral metformin (2 g/d) in addition to a calorie-restricted diet. In 2021, she developed interstitial pneumonia associated with SARS-CoV-2 infection, requiring hospitalization and oxygen support. The diagnosis of SARS-CoV-2 infection was confirmed via RT-PCR on a nasopharyngeal swab in a patient with typical symptoms during an epidemic period. Due to diffuse crackles on chest examination and the need for oxygen therapy, a high-resolution computed tomography (HRCT) was performed, revealing bilateral ground-glass opacities consistent with interstitial pneumonia. Oxygen therapy was required for 48 hours until stable saturation (93–94%) was achieved in ambient air. The patient received intravenous methylprednisolone (40 mg/day, reduced to 20 mg/d after two days, for a total duration of six days) alongside asthma maintenance therapy. Although she recovered fully, asthma symptoms persisted uncontrolled over the following year, with monthly exacerbations. Given the presence of blood eosinophilia (1,490 cells/μL), treatment with SC mepolizumab (100 mg monthly) was started. Symptoms control progressively improved. Frequency and severity of asthma exacerbations were significantly reduced, eliminating the need for hospitalizations or OCS use. At age 18 transition to Adult Asthma Center was accepted by the patient and her family.

Post-transition

Two years since transition to the Adult Asthma Center, asthma treatment previously prescribed has been confirmed and progressive improvement in symptom control has been reported. For the scheduled appointments, the patient is still accompanied by her mother as she does not feel confident enough to attend the visit alone in an adult clinical setting.

Case 4

Pre-transition

A 7-year-old boy was referred to the Pediatric Asthma Center for SA attacks and allergic rhinoconjunctivitis. At age 10 months he developed atopic dermatitis and recurrent-to-persistent wheezing. Sensitization to multiple inhalant allergens and significantly elevated total serum IgE levels (2,219 kIU/L) were demonstrated at age 6 years. Despite prolonged treatment with inhaled corticosteroids (ICS) plus montelukast, exercise-induced dyspnea and monthly asthma exacerbations necessitating OCS were reported, with progressive lung function deterioration. Omalizumab SC was initiated at age 9 years. After one year of treatment, we observed a marked reduction in the frequency of asthma exacerbations, as well as decreased need of rescue inhaled β_2 agonists and OCS, with progressively improving spirometry. At age 18 the transition towards an Adult Asthma Center was planned.

Post-transition

During the first year of transition, asthma treatment was confirmed as the patient was clinically stable and no asthma flairs occurred. Unfortunately, the patient decided to discontinue omalizumab treatment despite medical advice and a single severe exacerbation took place requiring OCS treatment. In addition, the patient reported persistent exercise induced dyspnea which prevented him from engaging in any physical activity. After 4 months interruption of omalizumab, following consultation for asthma treatment and T2 phenotype assessment SC dupilumab (300 mg/14d) was prescribed and inhaled bud/form as MART regiment was

confirmed. The re-introduction of biologic treatment resulted in asthma control and reinforced patient's compliance. At present, the patient claims to be able to manage his clinical condition on his own, however, both his parents are still present during hospital visits.

Clinical characteristics and summaries

Clinical characteristics of Cases 1 to 4 at referral to the Pediatric Asthma Center are shown in Table 1. Table 2 summarizes disease control, spirometry and airway inflammation before and 1 year after the start of biologics at the Pediatric Asthma Center of the same patients. In Table 3 we reported the clinical characteristics of the study patients at transition to the Adult Asthma Center. Summary of disease control, spirometry, airway inflammation and treatment at the time of the transition and during the subsequent follow-up at the Adult Asthma Center is shown in Table 4.

Table 1. Clinical characteristics of the study patients at referral to the Pediatric Asthma Center

Individual data	Case 1	Case 2	Case 3	Case 4
Age at asthma onset	3 months	12 years	3 years	10 months
Allergic sensitization	House dust mites, cat dander, *Olea Europaea*, *Alternaria alternata*	Grass pollen, Artemisia, *Olea europaea*, *Parietaria judaica*	House dust mites, cat dander, *Olea europaea*, *Parietaria judaica*	House dust mites, cat/dog dander, *Alternaria alternata, Grass pollen*
Symptoms burden	Cough, exercise-induced dyspnea, frequent asthma attacks	Daily chest tightness, cough, exercise-induced dyspnea	Weekly cough, dyspnea, and night awakenings	Daily cough, exercise-induced dyspnea, frequent asthma attacks
T2-related comorbidity	No	Nasal polyposis	No	Atopic dermatitis, allergic rhinitis
NonT2-related comorbidity	No	No	Obesity and insulin resistance	No
Treatment	Flu/Sal + LTRA	Bud/Form + LTRA	Bud/Form	Flu + LTRA
Age at start of biologic	13 years	16 years	14 years	9 years
Asthma attacks/year	7	5	6	7

Flu/Sal: fluticasone propionate/salmeterol; LTRA: leukotriene receptor antagonist; Bud/Form: budesonide/formoterol

Table 2. Summary of disease control, spirometry and airway inflammation before and 1 year after the start of biologics at the Pediatric Asthma Center

Disease control and instrumental data	Case 1		Case 2		Case 3		Case 4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
C-ACT	8	23	16	20	13	20	10	22
Asthma attacks/year	8	2	12	6	9	2	10	3
FEV_1 (%pred)	61	82	85	90	89	111	67	75
FVC (%pred)	88	100	104	104	111	132	117	97
FEV_1/FVC (%)	69	81	81	86	80	84	57	77
$FEF_{25–75}$ (%pred)	71	96	66	80	73	89	25	82
FeNO (ppb)	38	14	53	14	120	42	24	17

C-ACT: childhood asthma control test; FEV_1: forced expiratory volume during the first second; FVC: forced vital capacity; $FEF_{25–75}$: forced mid-expiratory flow; FeNO: fractional exhaled nitric oxide

Table 3. Clinical characteristics of the study patients in transition to the Adult Asthma Center

Individual data	Case 1	Case 2	Case 3	Case 4
Symptoms burden	Exercise-induced dyspnea	Nasal obstruction, hyposmia	Exercise-induced dyspnea, nasal obstruction	Cough, exercise-induced dyspnea
T2-related comorbidity	Allergic rhinoconjunctivitis, atopic dermatitis	Allergic rhinoconjunctivitis, CRSwNP	Allergic rhinoconjunctivitis	Allergic rhinoconjunctivitis, atopic dermatitis

Table 3. Clinical characteristics of the study patients in transition to the Adult Asthma Center (*continued*)

Individual data	Case 1	Case 2	Case 3	Case 4
NonT2-related comorbidity	No	No	Insulin resistance; obesity	No
Adolescents risk factors*	No	No	No	No
Self-management capacity§	1	1	1	1
Length of biologic treatment at transition	5 years	2 years	2 years	9 years

* Smoking, alcohol and illicit drugs, depression, sexuality and suicide risk. § (Based on clinical evaluation): 0—does not independently adhere to therapy and is accompanied by parents to medical appointments; 1—independently adheres to therapy and is accompanied by parents to medical appointments; 2—independently adheres to therapy and is not accompanied by parents to medical appointments. CRSwNP: chronic rhinosinusitis with nasal polyps

Table 4. Summary of disease control, spirometry, airway inflammation and treatment at the time of transition and during the follow-up at the Adult Center

Disease control, instrumental data and treatment	Case 1		Case 2		Case 3		Case 4	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
C-ACT	25	25	22	25	22	23	22	24
Asthma attacks*	0	3	0	0	0	0	0	1
FEV_1 (% pred)	68	59	88	89	98	112	75	81
FVC (% pred)	90	80	101	96	106	113	97	95
FEV_1/FVC (%)	66	62.9	84	81	82	87	77	73
FEF_{25-75} (% pred)	40	34	68	78	87	112	57	52
FeNO (ppb)	40	20	53	60	17	18	55	42
Treatment	Flu/Sal + LTRA + OMA	Bud/Form + LTRA +DUPI	Bud/Form + LTRA +MEPO	Bud/Form + LTRA +MEPO	Bud/Form + MEPO	Bud/Form + MEPO	Bud/Form + OMA	Bud/Form + DUPI

* Cumulative number of asthma attacks during the years after transition. C-ACT: childhood asthma control test; FEV_1: forced expiratory volume during the first second; FVC: forced vital capacity; $FEF_{25–75}$: forced mid-expiratory flow; FeNO: fractional exhaled nitric oxide; Flu/Sal: fluticasone propionate/salmeterol; LTRA: Leukotriene receptor antagonist; OMA: omalizumab; Bud/Form: budesonide/formoterol; DUPI: dupilumab; MEPO: mepolizumab

Discussion

It is well known that while most asthmatic children achieve optimal control with low-to-medium ICS, some have persistent difficult-to-treat asthma symptoms despite higher doses of ICS plus a second controller drug and/or OCS [8]. Once ruled out or modified some factors such as poor pulmonadherence, incorrect inhaler technique or comorbidities, children unable to achieve symptom control despite high doses of medications have likely developed SA [9]. A recent systematic review and meta-analysis of 9 studies from Europe indicated a 3% prevalence of SA in children and adolescents with asthma [10], yet the condition has an unacceptably high personal and economic burden because of frequent asthma attacks, continuous need for reliever and additional maintenance asthma medications, impaired lung function and poor quality of life (QoL) [11]. Pediatric SA prevalence has been most evaluated in studies investigating a mixed population of children and adolescents, while studies conducted exclusively in adolescents are lacking. Adolescents affected by chronic diseases are indeed under-studied, probably also because at this age there is a risk of misperception of one's own health status, with over- or under-reporting symptoms. Teenagers with asthma, especially those with SA, face unique challenges. Due to their concerns about self-image, self-identity creation, and peer acceptance, they are at risk of behaviors resulting in poor adherence to relievers and maintenance treatment and/or refusal of scheduled visits, and this eventually compromises asthma control [12].

In the life of a teenager with SA, transition from the pediatric patients to adult-oriented care is a critical moment that can add further elements of complexity to the management of their asthma, especially SA [5].

The transition of SA teenagers requires specialized care tailored to their age-specific needs not only to guarantee the continuity of their care but also to face and address patients' troubles [13]. On the other hand, developing a transition program including pediatric and adult asthma specialists can uncover the challenges of managing AYA with SA, which, once identified and addressed, help improve patients care and outcome.

Starting from these considerations, we retrospectively evaluated a small series of patients followed for a long time at a Pediatric Asthma Center, who transitioned to an Adult Asthma Center. The description of the cases highlights the most relevant aspects of transition of patients with a chronic disruptive disorder such as SA. Cases 1 and 4 from the series had asthma exacerbations during the transition follow-up period, likely due to patient-driven interruption of the biologic treatment. The lack of adherence to treatment during transition may be attributed to the complex psychological mechanisms occurring in adolescents [14, 15]. Probably, a prolonged period of absence of asthma exacerbations during the transition period and a long-lasting SA history from childhood to adolescence led patients to consider the possibility of clinical remission. The choice of interruption of the biologic was not shared by the adult specialist as criteria of complete clinical remission (need for OCS, symptoms, exacerbations or attacks, and pulmonary function stability) were not completely met [16, 17]. In fact, the disease inflammatory process was still present, and asthma exacerbations re-occurred. Thus, a phenotype-based reintroduction of biologic treatment took place. As both patients showed a Type 2 phenotype with elevated T2 biomarkers (IgE, FeNO and blood eosinophil count), dupilumab, which blocks signaling by interleukin-4 and interleukin-13, key and central drivers of Type 2 inflammation, was prescribed [18]. This choice led to better compliance due to self-administration with a pre-filled pen rather than the prefilled omalizumab syringe that requires monitoring by healthcare personnel during administration.

Similar to the pediatric setting, also in the adult outpatient clinic it is extremely important to guarantee to the young patients a careful follow-up, with tempestive and closely spaced schedule that offers the possibility of immediate therapeutic adjustments to reestablish clinical well-being. Notably, both female patients (cases 2 and 3) did not undergo significant changes of their therapeutic program, nor had asthma attacks or experienced significant clinical deterioration. All patients, despite of age, were accompanied by one or both parents. Case 2 was indeed fully independent from parental help and control, while case 3 still relied on her mother although she was convinced of the need to take care of her health on her own. Cases 1 and 4 reported being completely independent about treatment and have expressed willingness to implement future encounters independently. Our considerations were based on clinical observation, ability to discuss with the patient about pathology and treatment. Both male patients (cases 1 and 4) experienced exacerbations following an interruption of their biological therapy and appear still dependent on their parents for any needs related to the illness. Children typically attend pediatric clinics with their parents until they are teenagers or young adults, and parents take on the responsibility of managing the illness also to reduce the burden on their children. This can result, at least in some individuals, in less understanding of the illness and its management even once followed in the adult clinic [19]. Our observations are indeed based on a small case series report and a much larger number of transitioned patients with SA should be observed and monitored at our center to achieve definitive conclusion remarks. However, we observed a different gender approach of transition with males being less compliant and probably less independent than females. This needs more confirmation on larger study population.

In various personal interviews, all our patients have repeatedly requested the intervention of a psychologist addressing the critical aspects of the transition from the Pediatric to the Adult care. By providing support, the psychologist could also promote more effective communication among patients, families and specialists and prepare the patients for the new journey.

Although limited by small sample, this case series leads us to confirm that transitioning from child-centric to adult-oriented care is crucial for young adolescents with chronic inflammatory diseases such as SA [20]. It appears mandatory to schedule and program the transition from early adolescence (13–14 years) in accordance with the patient's developmental stage, in consideration of the individual's

changes that can complicate the process if not adequately managed. In this context, risk factors such as smoking, drug abuse and emerging mental health problems should not be neglected. On the other hand, poor compliance related to adult independence status and therapy self-management may lead to uncontrolled disease and further reduced QoL. On the basis of what has just been said, it appears necessary for multidisciplinary approaches, integrating pulmonologists, allergists, psychologists, and social workers, to support both clinical and psychosocial transition challenges.

Pediatricians should inform the adolescent and the family about the upcoming transition in advance. The first scheduled visit would take place in the pediatric setting with both pediatric and adult specialists being present. During the first transition visit, the adult specialist will be introduced to the young patient and a detailed letter of the patient's medical records including current diagnosis and treatment will be delivered. In this context, all our patients had the opportunity to meet the adult specialists in the pediatric clinic. They reported to be satisfied with the relationship established with their "new" doctors and the adult clinical setting.

Our study, which is a retrospective case series, is subject to several limitations, the main ones being the small sample size, which limits the generalizability of the findings, potential selection bias, the absence of a control group, and reliance on retrospective records, which may vary in accuracy and detail. Furthermore, we didn't use standardized tests for assessing caregiver independence and self-management capacity. What is described is the result of our clinical evaluation and direct communication with the patient. However, this study may be useful for planning a national study that complements international research efforts on the transition of SA patients from pediatric to adult care as longitudinal studies that evaluate transition outcomes in larger populations of SA over extended periods of time.

Abbreviations

AYA: adolescents and young adults

Bud/Form: budesonide/formoterol

CRSwNP: chronic rhinosinusitis with nasal polyps

FeNO: fractional exhaled nitric oxide

Flu/Sal: fluticasone propionate/salmeterol

ICS: inhaled corticosteroids

MART: maintenance and reliever therapy

OCS: oral corticosteroids

QoL: quality of life

SA: severe asthma

SC: subcutaneous

Declarations

Author contributions

A Dorato: Conceptualization, Methodology, Writing—review & editing. RB: Methodology, Resources, Writing—review & editing. MB: Data curation, Writing—original draft. AdP: Data curation, Supervision. CF: Data curation, Resources. AC: Data curation. FS and A Detoraki: Conceptualization, Writing—original draft, Writing—review & editing, Supervision. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. According to the regulatory content of the Institutional Review Board of the "Federico II" Medical School, ethical review and approval were not required, as case series are considered exempt from Institutional Review Board oversight.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Informed consent to publication was obtained from relevant participants.

Availability of data and materials

The data of this manuscript could be available from the corresponding authors upon reasonable request.

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