Physical activity and body mass related to catch-up lung function growth in childhood: a population-based accelerated cohort study

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ABSTRACT

Objective: The existence of catch-up lung function growth and its predictors is uncertain. We aimed to identify lung function trajectories and their predictors in a population-based birth cohort.

Methods: We applied group-based trajectory modelling to z-scores of FEV_1 and FVC from 1151 children assessed at around 4, 7, 9, 10, 11, 14, and 18 years. Multinomial logistic regression models were used to test whether potential pre- and postnatal predictors were associated with lung function trajectories.

Results: We identified four lung function trajectories: a low (19% and 19% of the sample for $zFEV_1$ and zFVC, respectively), normal (62% and 63%), and high trajectory (16% and 13%) running in parallel, and a catch-up trajectory (2% and 5%) with catch-up occurring between 4 and 10 years. Fewer child allergic diseases and higher body mass index z-score (zBMI) at 4 years were associated with the high and normal compared to the low trajectories, both for $zFEV_1$ and zFVC. Increased children's physical activity during early childhood and higher zBMI at 4 years were associated with the catch-up compared to the low $zFEV_1$ trajectory (relative risk ratios: 1.59 per physical activity category (1.03 – 2.46) and 1.47 per z-score of BMI (0.97-2.23), respectively). No predictors were identified for zFVC catch-up growth.

Conclusion: We found three parallel-running and one catch-up $zFEV_1$ and zFVC trajectories, and identified physical activity and body mass at 4 years as predictors of $zFEV_1$ but not zFVC catch-up growth.

KEY MESSAGES

What is already known on this topic:

The existence of accelerated lung function growth, also referred to as catch-up growth, has previously been suggested but not yet replicated in multiple birth cohorts from different countries. Furthermore, little is known about its predictors.

What this study adds:

Using an accelerated longitudinal cohort design with data from the Infancia y Medio Ambiente (INMA) birth cohorts with repeated lung function measures from 4 to 18 years, our study supports the existence of catch-up lung function growth trajectories for z-scores of forced expiratory volume in 1 second ($zFEV_1$), vital capacity (zFVC) and their ratio ($zFEV_1$/FVC), as well as percent predicted values of FEV_1 and FVC. We identified that higher levels of physical activity between the ages of 4 and 7 years and greater z-scores of body mass index (zBMI) at 4 years are independently related to higher likelihood of belonging to the catch-up compared to the low $zFEV_1$ trajectory. Our study did not identify statistically significant predictors of the catch-up zFVC trajectory.

How this study might affect research, practice or policy:

The replication of the existence of catch-up lung function growth for both $zFEV_1$ and zFVC, and the identification of physical activity and body mass at 4 years as its predictors for $zFEV_1$ demand future research to investigate underlying mechanisms and the identification of further predictors. Public health policies that support and promote healthy diet and increases in children's physical activity levels are needed. In terms of clinical management, parents of children with low initial lung function values, suboptimal environmental settings, or early-life allergies should encourage their children to engage

in physical activity and adhere to a healthy diet to overcome lung function growth limitations at or after birth.

Introduction

Lung function predicts mortality independently of cardiovascular health and inflammatory status,[1] and is a hallmark risk factor for chronic respiratory diseases.[2] Typically, lung function increases during childhood and declines with age after a plateau period [3,4]. Understanding the predictors of lung function growth and decline is of importance to prevent chronic respiratory disease. Initially, research focused on predictors of lung function decline in adulthood. However, as evidence emerged that chronic respiratory disease can originate also in below-average lung function growth during childhood, research on lung function growth patterns was reinforced.[3,4]

To date, between two and six distinct, parallel-running lung function growth and decline trajectories have been identified and confirmed in the Tucson,[5] the Manchester Asthma and Allergy Study (MAAS),[6] the Avon Longitudinal Study of Parents and Children (ALSPAC),[6] the Tasmanian Longitudinal Health Study (TAHS),[2] the Australian Raine Study[7], the Swedish BAMSE [8], and the Dutch PIAMA[8] cohorts. “Catch-up” lung function growth, referring to the recovery of early-life deficits through accelerated growth, was initially identified in the TAHS [2,9], and recently also in the BAMSE, and PIAMA cohorts [8]. Its replication in other birth cohorts from different countries, characterized by different lifestyles, environmental exposures, and cultural specifics, together with the identification of its predictors, would open avenues for the prevention of health issues derived from low lung function in early childhood. Early-life risk factors such as maternal asthma, lower respiratory illnesses and allergic sensitisation, and tobacco smoke exposure, alone or in combination, have been consistently identified as predictors of below-average lung function growth and/or predictors of catch-up growth.[5,6,10] However, with the exception of tobacco smoke exposure, there is a lack

of knowledge about potentially modifiable risk factors that could facilitate lung function growth.

Therefore, we aimed to identify lung function growth trajectories and their predictors using data from the Spanish population-based Infancia y Medio Ambiente (INMA) birth cohort [11]. We overcome limitations of previous studies by including an earlier age period, more repeated measurements of lung function, some of them in early childhood, as well as a wide range of potentially relevant pre- and postnatal predictors.

METHODS

See complete Methods in the supplemental material.

Study design, setting, and participants

We used an accelerated longitudinal cohort design combining data of four birth cohorts from the Spanish INMA network including 1151 children who had ≥ 2 repeated lung function measures between 4 to 18 years of age (Figure S1).[11,12]. Accelerated longitudinal designs allow the investigation of age-related changes in a shorter period of time than would be possible with a single cohort, by pooling multiple cohorts, each one starting and ending at different ages.[12]

This study was approved by appropriate ethical committees and conducted according to the Declaration of Helsinki. Written informed consent was obtained from parents, legal guardians, or children once they reached the age of 18 years.

Measures

Lung function assessment

We assessed lung function (forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)) by forced spirometry, calculated the FEV_1/FVC ratio, and generated z-

scores ($zFEV_1$, zFVC, and $zFEV_1$/FVC) at each visit using the Global Lung Function Initiative (GLI) 2012 reference equations.[13,14] Upon collection, all spirometry maneuvers underwent quality control to ensure acceptability and reproducibility criteria were met. Additional spirometry quality checks were performed prior to the current analyses for all curves in a one-by-one review resulting in the removal of 211 (6.5%) FEV_1, and 134 (4.3%) FVC values. Spirometry maneuvers were considered acceptable if the back extrapolated volume (BEV) was below 0.1L, forced expiratory time (FET) was between 1 and 10 seconds, and the shape of the curve adequate. Criteria used to evaluate the shape of the flow-volume curves were (i) a sharp rise with no signs of hesitation or cough within the first second; (ii) no signs indicative of cough, inhalation, or early termination during the exhalation phase; and (iii) existence of a volume-time plateau shape. All children included in the analysis had a minimum of one acceptable and reproducible spirometry maneuver at every single assessment timepoint.

Predictors of lung function growth

We collected information on: (i) demographic and birth characteristics: sex, child's ethnicity, season of birth, type of birth, parity, children's day care attendance before the age of 1 year, maternal age at birth, parental education, gestational age and weight, and breastfeeding duration; (ii) allergic diseases: ever asthma, rhinitis and eczema in mothers, fathers, and in children at the ages of 4 and 7 years; a cumulative score referred to as "number of allergic diseases" for mothers, fathers, and children; and remittent asthma, rhinitis or eczema in children between the ages of 4 and 7 years; (iii) smoking and other environmental exposures: smoking status of the mother and father during pregnancy, and at children's age of 4 years, maternal smoking in packyears from pregnancy to children's age of 4 years, pets in the household during pregnancy and childhood, and gas stove and heating at home during pregnancy; and (iv) physical activity and body mass: children's

physical activity levels at ages 4 and 7 (low, moderate, and high, using an internally validated questionnaire), and physical activity levels between ages 4 and 7 years (low, moderate, high), z-scores of measured body mass index (zBMI) at ages 4 and 7, and body growth (change in zBMI per year between 4 and 7 years –Table S1 and Figure S2).

Statistical analyses

Before modelling lung function trajectories, we visually examined the spirometry values of each cohort for possible differences in lung function growth (for absolute and z-scores at comparable age ranges (Figures S3A and S3B). In our primary analyses, we built $zFEV_1$ and zFVC trajectories with group-based trajectory modelling, [15] starting with two all the way up to six trajectories. The optimal number of trajectories was determined using statistical criteria (BIC value, posterior probability, number of subjects/trajectory group with a lower limit set to 3% in at least one respiratory parameter), and knowledge of the scientific literature. Furthermore, we evaluated agreement between trajectory assignment for $zFEV_1$ and zFVC. In a secondary analysis, we built lung function growth trajectories for the z-scores of the ratio of FEV_1/FVC.

To identify predictors of lung function trajectories, we built multinomial multivariable logistic regression models (one per lung function parameter) with the low trajectory as reference, following a directed acyclic graph (DAG) built a priori from the literature (Figure S2) and standardised model building strategies. [16] In an exploratory analysis, we built trajectories separately for boys and girls and identified predictors of the obtained sex-specific trajectory groups.

Our sensitivity analyses included: (i) restricting to children with ≥2 acceptable and reproducible spirometry maneuvers at every assessment (n=740); (ii) restricting to children with no wheeze or asthma (n=656); (iii) using percent predicted FEV_1 and FVC

as outcome, and (iv) using BMI groups [17] instead of zBMI as continuous variable to investigate the role of overweight and obesity on lung function trajectories.

All analyses were completed in Stata 17.0 (Stata Corp, College Station, TX, USA) using 20 imputed datasets. The dataset of 1151 children had a total of 12% missing observations in potential predictors, which we assumed were missing either at random or completely at random after reviewing their missing patterns (for more information, please see "handling of missing data" section in the supplemental material and Table S2, which shows variables' distribution in the observed and imputed datasets).

RESULTS

Participants characteristics

We included 1124 and 1151 participants to build $zFEV_1$ and zFVC trajectories, respectively. Excluded study participants (n = 1601) include children with no spirometry assessment and those with less than 2 maneuvers that met spirometry quality criteria (Figure S1). Compared to excluded, included participants' parents were higher educated and less likely to smoke during pregnancy. Included children were breastfed longer, less likely to grow up with pets, and more exposed to gas from cooking or heating during pregnancy, and had more allergic conditions (Table S3). Half of the participants were girls, 16% were exposed to maternal smoking during pregnancy, and 39% had at least one allergic disease at 4 years (Table 1).

Table 1: Characteristics of included children by sex

Variable name	Total n (%)‡ 1151 (100%)	Girls n (%)‡ 570 (50%)	Boys n (%)‡ 581 (50%)
Demographics and birth characteristics			
Ethnicity – Caucasian (ref. Other)	1121 (98%)	557 (99%)	566 (97%)
Season of birth			
Winter	295 (26%)	144 (25%)	151 (26%)
Spring	333 (29%)	169 (30%)	164 (28%)
Summer	387 (21%)	132 (23%)	155 (27%)
Fall	238 (21%)	126 (22%)	112 (19%)
Type of birth			
Vaginal	761 (68%)	402 (73%)	359 (63%)
Instrumental	180 (16%)	81 (15%)	99 (17%)
Cesarean	180 (16%)	69 (13%)	111 (20%)
Parity			
Nulliparous	597 (54%)	302 (55%)	295 (53%)
One child	399 (36%)	192 (35%)	207 (37%)
Two or more children	109 (10%)	53 (9%)	56 (10%)
Daycare attendance before age 1y – yes	330 (27%)	158 (26%)	167 (27%)
Maternal age at birth (years), mean (sd)	30.5 (4.1)	30.4 (4.1)	30.6 (4.1)
Maternal education			
Primary school	331 (28%)	154 (27%)	167 (29%)
Secondary school	452 (39%)	225 (39%)	227 (39%)
Post-secondary school	380 (33%)	192 (34%)	188 (32%)
Paternal education			
Primary school	436 (38%)	214 (37%)	222 (38%)
Secondary school	469 (41%)	228 (42%)	231 (40%)
Post-secondary school	248 (22%)	119 (21%)	129 (22%)
Gestational age (weeks) mean (sd)	39.6 (1.6)	39.5 (1.7)	39.6 (1.6)
Gestational weight (g) mean (sd)	3242 (459)	3178 (455)	3305 (455)
Small for gestational age for weight – yes	30 (11%)	82 (14%)	48 (8%)
Large for gestational age for weight - yes	98 (8%)	48 (8%)	69 (8%)
Breastfeeding (weeks) mean (sd)	23.0 (20.2)	23.3 (20.6)	22.7 (19.7)
Allergic diseases and respiratory tract infections			
Maternal ever asthma – yes	79 (7%)	37 (6%)	42 (7%)
Maternal ever rhinitis – yes	188 (16%)	98 (17%)	90 (15%)
Maternal ever eczema – yes	164 (14%)	84 (15%)	80 (14%)
Number of maternal allergic diseases*			
0	824 (71%)	409 (72%)	415 (71%)
1	244 (21%)	114 (20%)	130 (22%)
2	68 (6%)	39 (7%)	29 (5%)
3	17 (1%)	9 (2%)	8 (1%)
Paternal ever asthma – yes	72 (7%)	33 (6%)	39 (7%)
Paternal ever rhinitis – yes	164 (14%)	75 (13%)	89 (15%)
Paternal ever eczema – yes	91 (8%)	47 (9%)	44 (8%)
Number of paternal allergic diseases*			
0	840 (76%)	420 (77%)	420 (75%)
1	218 (20%)	105 (19%)	113 (20%)
2	41 (4%)	19 (3%)	22 (4%)
3	6 (1%)	3 (1%)	3 (1%)
Child ever asthma until age 4 years – yes	45 (4%)	25 (4%)	20 (3%)
Child ever rhinitis until age 4 years – yes	31 (3%)	13 (2%)	18 (3%)
Child ever eczema until age 4 years – yes	411 (36%)	195 (34%)	216 (37%)
Number of child allergic diseases at 4 years*			
0	714 (62%)	361 (64%)	353 (61%)
1	399 (35%)	192 (33%)	207 (36%)
2	32 (3%)	13 (3%)	19 (3%)
3	3 (1%)	5 (1%)	3 (1%)
Child ever asthma until age 7 years – yes	78 (7%)	37 (6%)	41 (7%)
Child ever rhinitis until age 7 years – yes	260(23%)	120 (21%)	140 (24%)
Child ever eczema until age 7 years – yes	187 (16%)	110 (19%)	77 (13%)
Number of child allergic diseases at 7 years			
0	617 (54%)	310 (54%)	307 (53%)
1	401 (35%)	198 (35%)	203 (35%)
2	109 (9%)	49 (9%)	60 (10%)
3	22 (2%)	12 (2%)	10 (2%)
Child remittent asthma from 4 to 7 years – yes	15 (1%)	9 (2%)	6 (1%)
Child remittent rhinitis from 4 to 7 years – yes	14 (1%)	7 (1%)	7 (1%)
Child remittent eczema from 4 to 7 years – yes	231 (20%)	111 (19%)	120 (21%)
Lower respiratory tract infections at age 4 years	290 (25%)	146 (26%)	144 (25%)

Smoking and other environmental exposures			
Maternal smoking during pregnancy - yes	180 (16%)	90 (16%)	90 (15%)
Paternal smoking during pregnancy - yes	396 (36%)	210 (38%)	186 (33%)
Maternal smoking at child's age of 4 years - yes	273 (25%)	139 (26%)	134 (24%)
Paternal smoking at child's age of 4 years - yes	371 (34%)	198 (37%)	173 (31%)
Maternal packyears from pregnancy to child's age of 4 years mean (sd)[†]	0.30 (0.67)	030 (0.67)	0.29 (0.64)
Pets at home during pregnancy - yes	411 (38%)	201 (37%)	210 (38%)
Pets at home during childhood - yes	273 (29%)	139 (31%)	134 (28%)
Gas heating at home during childhood – yes	729 (63%)	372 (65%)	357 (61%)
Gas cooking at home during childhood – yes	549 (48%)	256 (45%)	293 (50%)
Gas heating or cooking at home during childhood – yes	698 (64%)	353 (65%)	345 (62%)
Health behaviours and body mass			
Physical activity at age 4 years			
Sedentary	10 (1%)	6 (1%)	4 (1%)
Little active	63 (6%)	35 (6%)	28 (5%)
Moderately active	426 (38%)	242 (44%)	184 (32%)
Active	480(43%)	205 (37%)	275 (48%)
Very active	137 (12%)	60 (11%)	77 (14%)
Physical activity at age 7 years			
Sedentary	24 (2%)	12 (2%)	12 (2%)
Little active	157 (14%)	88 (16%)	69 (12%)
Moderately active	416 (37%)	221 (39%)	195 (34%)
Active	343 (30%)	160 (28%)	183 (32%)
Very active	194 (17%)	85 (15%)	109 (19%)
Physical activity between 4 and 7 years[§]			
Low	394 (36%)	227 (42%)	167 (30%)
Moderate	282 (26%)	142 (26%)	140 (25%)
Active	421 (38%)	174 (32%)	247 (45%)
BMI at age 4 years mean (sd)	16.3 (1.5)	16.2 (1.6)	16.3 (1.5)
BMI at age 7 years mean (sd)	17.2 (2.5)	17.2 (2.5)	17.2 (2.5)
zBMI at age 4 years mean (sd)	0.64 (0.99)	0.57 (0.96)	0.71 (1.02)
zBMI at ages 7 years mean (sd)	0.80 (1.16)	0.74 (1.06)	0.85 (1.23)
zBMI growth per year between 4 and 7 years mean (sd)	0.05 (0.26)	0.06 (0.24)	0.05 (0.24)
Daily ingested calories (kcal)	1578 (360)	1549 (343)	1607 (375)

[‡] Categorical variables are presented as number of study participants and percent of study population. Number of participants were calculated based on corresponding percent derived from 20 datasets generated through multiple imputations and due to rounding, not all percentages add up to exactly 100%. Continuous variables are presented as means and standard deviations.

[*]Allergic diseases include: asthma, rhinitis and eczema.
[†]Paternal packyears could not be calculated as required variables were not available.
[§] See supplemental material for generation of physical activity variable.

Abbreviations: sd: standard deviation, g: grams; zBMI: z-score of body mass index

Lung function trajectories

We identified four distinct lung function growth trajectories for $zFEV_1$ and zFVC (Figures 1 and 2, and Tables S4-S6). Three trajectories run in parallel, were characterized by different starting levels at the age of 4 years, and were labelled as: "low" ($zFEV_1$ analyses: n (%) of participants = 219 (19.3%) and zFVC: 218 (18.9%)), "normal" (708 (62.4%) and 722 (62.6%)), and "high" (182 (16.0%) and 150 (13.0%)).

A fourth trajectory started out at lung function values below the low trajectory, exhibited accelerated growth between the ages of 4 and 10 years, subsequently followed the normal trajectory from the age of 10 years onwards, and was labelled "catch-up" (26 (2.3%) in $zFEV_1$; 63 (35.5%) in zFVC). Children were assigned to identical trajectories for $zFEV_1$ and zFVC in 74% of the cases with moderate agreement (kappa= 0.53, Table S7). Tables S8 and S9 show participant demographics of each trajectory.

Predictors of lung function trajectories

In Tables S8 and S9, we present the distributions of all assessed potential predictors of lung function growth across the four $zFEV_1$ and zFVC trajectories, respectively. Figures 3 and 4, and Tables S10 and S11 show the predictors of normal, high, and catch-up lung function growth using the low trajectory as reference because it is the most relevant comparator for catch-up growth. Children's physical activity between 4 and 7 years of age (relative risk ratio (RRR): 1.59 per physical activity category (95% confidence interval (CI): 1.03 – 2.46)) was significantly associated with the $zFEV_1$ catch-up trajectory when compared to the low trajectory. A trend of higher zBMI at 4 years being associated with a greater likelihood to be assigned to the catch-up compared the low trajectory was found for $zFEV_1$ (1.47 per zBMI score (0.97 – 2.23). Number of child allergic diseases at 4 years, and zBMI scores at 4 years were associated with the normal and high trajectories, compared to the low, in a dose-response manner (0.75 (0.58 – 0.98)

and 0.67 (0.47 – 0.97) per additional disease for normal and high trajectories, respectively, p-for-trend=0.016; and 1.20 (1.01 – 1.44) and 1.29 (1.04 – 1.60) per zBMI unit for normal and high trajectories, respectively, p-for-trend=0.024).

Predictors of zFVC trajectories were similar in pattern and magnitude of associations for the normal and high trajectories. No predictors were identified for the catch-up compared to the low zFVC trajectory.

To provide complementary interpretation, we repeated multinomial regression using the normal trajectory as reference without revealing any novel predictors or different magnitudes of associations (Tables S12 and S13).

***Post hoc* analyses**

Due to the finding that the catch-up trajectory group exhibited very low lung function levels, we conducted a *post hoc* analysis testing the determinants of very low lung function (defined as z-scores of lung function parameters below -3). Previously known determinants of low lung function including c-section deliveries, low parental education levels, and maternal packyears smoked between pregnancy and the children's age of 4 years were predictors of very low lung function at 4 years, both for FEV_1 and FVC (see Tables S14 and S15). Additionally, we compared observed $zFEV_1$ and zFVC values to the expected distribution of a normalised variable (i.e., reference GLI z-scores), which led to the identification of a poor fit of the GLI-scores in our study population at 4 years, but less so at 7 years.

Secondary, exploratory, and sensitivity analyses

We found very similar trajectories (low, normal, high and catch-up) for the ratio of $zFEV_1$/FVC, with the difference that the magnitude of catch-up was higher (Figure S4).

Modelling lung function growth trajectories for boys and girls separately resulted in the same trajectories (Figures S5-S7). All sensitivity analyses confirmed findings of the primary analysis with respect to trajectories (low, normal, high, and catch-up), and their predictors (children's allergic diseases, physical activity, and zBMI levels at 4 years) (Figures S8-S11). Due to the reduction in sample size in sex-specific trajectories and after applying restrictions, some associations between predictors and trajectories lost precision. When replacing the continuous zBMI variable by the BMI categories (overweight/obese vs normal/underweight), no additional trends were found (Tables S16 and S17).

DISCUSSION

Using repeated spirometry measures from 1151 children between the ages of 4 and 18 years, we identified four distinct lung function growth trajectories for $zFEV_1$ and zFVC. We replicated the existence of the catch-up trajectory, characterized by normal lung function from 10 years of age and onwards despite initial below-average values at 4 years of age. We identified children's physical activity levels between 4 and 7 years of age, and body mass at 4 years as predictors of $zFEV_1$ catch-up growth and confirmed children's allergic diseases and body mass at 4 years as predictors of the normal and high lung function growth patterns. Our three parallel-running lung function trajectories separated by approximately one standard deviation resemble the parallel-running trajectories from the Tucson,[5] ALSPAC,[6] MAAS,[6] TAHS,[2] Raine,[7] BAMSE,[8] and PIAMA[8] cohorts. Our identification of catch-up lung function growth during childhood differs from the Tucson,[5] ALSPAC,[6] MAAS,[6] and Raine[7] cohorts. It is possible that these cohorts did not identify catch-up growth because their first lung function assessments occurred at a later age (>7 years) at which our children in the catch-up

trajectory were already approaching lung function levels of the normal trajectory. However, our results are consistent with similar catch-up growth curves observed in the TAHS,[2,9] BAMSE,[8] and PIAMA[8] cohorts, although our findings slightly differ in the prevalence and magnitude of catch up. Previous studies found a prevalence of catch-up trajectory ranging from 3 to 13%, higher than our observed range in the main, exploratory, and sensitivity analyses between 2% and 6%. The varying range can be explained by random sampling error across the diverse analyses performed. Differences in population type and size, data assessment time points, environmental exposures, cultural specifics and regional lifestyle behaviours might serve as underlying causes for differences in the prevalence of catch-up growth across the different birth cohorts that demand further research.[8]

It can be argued that the magnitude of catch-up growth in our study from -3 to zero between 4 and 10 years is tremendous and unlikely to be true. Indeed, previous reports on the catch-up trajectory observed an increase ranging between 1.5 and 3 standard deviations, beginning at different starting points just below -1 and reaching values between 0 and almost 2.[2,8,9] We acknowledge that a poor cognitive understanding of the spirometry technique and a poor fit of the GLI-recommendations at 4 years can be responsible of the very low z-scores at that age. Also, random error derived from the use of different spirometers, the test administration by different field technicians, and small sample size in some analyses may have contributed to this large magnitude of catch-up growth. However, our *post hoc*, secondary and sensitivity analyses support the existence of the catch-up group. First, the fact that most children assigned to the catch-up trajectory come from two different regions and the replication of findings when analysis was restricted to children with stricter spirometry criteria at every assessment reduces concerns regarding possible bias introduced by equipment, study technicians or

suboptimal spirometry maneuvers. Second, the agreement of our findings about predictors of very low lung function at 4 years with the available literature[4] (indirect known-groups validity analysis) further supports the plausibility of the (very) low lung function levels. Third, the replication of the catch-up trajectory when modelling percent predicted lung function parameters or the $zFEV_1/FVC$ reinforces our primary results. Finally, the consistency with the TAHS[2,9], BAMSE[8] and PIAMA[8] cohorts, and the replication of results when restricted to children without respiratory conditions, minimises the possibility of selection bias as an explanation. All in all, we consider that the catch-up growth observed in INMA is a robust finding, although we acknowledge that the magnitude of the z-scores as per GLI-equations should be interpreted with caution.

We identified children's physical activity and body mass during childhood as predictors of FEV_1 (but not FVC) growth to the extent of catching up from low to normal lung function. Children with higher body mass at 4 years were more likely to be assigned to the normal and high, compared to the low trajectory, both for FEV_1 and FVC. Contrarily to hypothesised,[18] we did not find that being small or large for gestational age was associated with catch-up trajectories, which could be attributed to the small proportion of fetal growth restriction in a population-based study. Previous longitudinal research has also shown positive associations between physical activity and lung function levels in girls and boys.[19,20] Furthermore, previous longitudinal studies have reported that accelerated gain in BMI in the first four years of life, as well as higher lean and lower fat mass during childhood are related with higher lung function levels or growth in childhood and adolescence.[21–24] Due to the loss of statistical power when categorizing BMI into body mass categories across the four trajectories, our sensitivity analysis using IOFT body mass criteria did not result in any additional findings.

Several pathways support the plausibility of the observed association between physical activity and body mass with FEV_1 catch-up. Firstly, regular physical activity and accompanying increased breathing rates and volumes might strengthen respiratory muscles[25] and optimize their neuro-motor coordination, which might result in a better spirometry value. It is possible, that this positive effect on respiratory muscle strength and neuro-motor coordination is particularly reflected in better FEV_1 rather than FVC values due to the explosive exhalation upon maximal inhalation that underlies the assessment of FEV_1. Secondly, physical activity has anti-inflammatory properties[26] while fat mass (inversely associated with physical activity[27]) has pro-inflammatory characteristics.[28] Previous data supports a role for inflammatory pathways on lung function growth.[28] Third, greater proportions of fat-free mass (that could result from physical activity) reduce the risk of compression of the lungs and diaphragm thus resulting in increased lung function.[29] We were unable to test hypotheses that link lean body mass with lung function growth due to the lack of data on lean and fat mass.[24]

Our study confirms and goes beyond previous research on well-known predictors of lung function.[2,30,31] Children with fewer cumulative allergic diseases were more likely to be assigned to normal or high $zFEV_1$ trajectories compared to the low trajectory. This supports previous evidence of children's allergic conditions to predict lung function growth [2,5–7,10,30,32,33].

Surprisingly, we did not find an association between maternal smoking during pregnancy or early childhood, like the Tucson study.[5] However, in agreement with a large body of literature,[34,35] maternal smoking was actually related to individual FEV_1 and FVC levels in our study, and the lack of association with the trajectories could be attributed to small sample size in some trajectory groups combined with the small proportion of smokers in our population. Similarly, although lower respiratory tract infections during

early childhood were related to the levels of lung function in our study (data not shown), they did not relate to the lung function trajectories.

We tested whether remission of allergic diseases, decrease in smoking exposure, and increase in BMI body growth between 4 to 7 years related to catch-up growth, as persistent (but not transient) wheeze or asthma had been associated with reduced FEV_1.[36] Our results did not confirm such hypotheses, in agreement with the MAAS cohort.[6] However, we suggest caution in interpreting these results, as the proportion of children experiencing these changes is small at the population level and reduced statistical power could have driven our results.

The key finding of our study is that low lung function in early childhood does not automatically translate into poor lung function in early adulthood, but that accelerated growth can recover early-life lung function deficits and result in normal values in adolescence. Implications include, first, future research should confirm the role of physical activity and body mass in catch-up growth of lung function, and investigate underlying mechanisms and optimal stimuli (e.g., volume, intensity, type) of physical activity and body mass during childhood to enhance lung function growth. Second, public health policies should support and promote a healthy diet and high physical activity levels in children, not only to prevent obesity and other metabolic diseases but also to improve respiratory health in childhood and adulthood. Third, clinical management should encourage parents and children who have low initial lung function values, suboptimal environmental settings, or allergies to participate in physical activity and adhere to a healthy diet to overcome early lung function growth limitations.

Important strengths of this study include the population-based nature and the availability of detailed information of possible pre- and postnatal predictors of lung function growth.

The availability of measures starting at 4 years allowed us not only to identify catch-up lung function growth, but also to analyse which potentially modifiable factors during early childhood could induce the observed lung function recovery. The use of an accelerated cohort design[12] permitted us to investigate nearly the entire lung function growth phase covering the period between 4 and 18 years of age. Furthermore, lung function measures were derived from forced spirometry, and not a combination of various assessment methods as done in previous work.[6]

Our study has limitations. First, smoking and physical activity levels could show misclassification when relying on parent-reported questionnaires. However, we used a validated smoking questionnaire and conducted an internal validation for physical activity using an activity monitor as gold standard (see supplemental material). Given the lack of public awareness that physical activity may affect lung growth, any potential misclassification would be non-differential with respect to lung function trajectories, which would suggest that the real association is likely stronger than observed.[37] Second, using an accelerated cohort study design prevented us from providing an overview of the changes in clinical features during follow-up because not all children were followed up at exactly the same periods. Third, differences between included and non-included mother-child pairs in parameters that were actually identified as predictors of lung function trajectories (maternal age at birth, maternal smoking, children allergic diseases) could be the source of selection bias. To minimize it, we imputed missing data using the full dataset (Table S2) thus reproducing the covariates' pattern from the full population. Fourth, detailed information on some potential determinants of lung function growth, such as dietary patterns and air pollution exposure in early childhood were not available or only available in a subsample of the study. However, we were able to account for a wide range of potential predictors and their changes over time. Finally, regional

differences in environmental exposures and health behaviours between our study sample and other populations could limit the generalizability of our results. Future studies with more frequent spirometry and predictor assessments in shorter time intervals between the ages of 4 and 25 years are needed to better understand the shape, further define the critical age window, and identify further predictors that facilitate catch-up lung function growth as opposed to low lung function growth, as well as the discovery of possible additional trajectories.

In summary, we identified four distinct $zFEV_1$ and zFVC growth patterns, three parallel-running and one catch-up growth trajectory, in an accelerated population-based cohort design covering from 4 to 18 years. Higher physical activity levels and body mass between the ages of 4 and 7 years were found predictors of $zFEV_1$ catch-up. For optimal lung function growth, efforts in research, public health, and clinical management should be directed towards advancing our understanding of underlying mechanisms and facilitating increases in physical activity levels and a healthy body mass in children.

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JGA and MC conceptualized this project and provided supervision. MT, FB, CI, AL, MG, MV, JS, MC, and JGA were responsible for the project administration, data collection, and resource management. SK, AEC and JGA verified the underlying data. SK, AEC, AB, CR, MG, JS, MC, JGA were responsible for data curation. SK, GPP, AEC, AA, and JGA performed the data analyses. GPP and EAC provided support with respect to used analysis software. SK, GPP, AEC, AA, MG, MV, MC, JGA were responsible for the data interpretation. SK and JGA wrote the original draft, and GPP, AEC, AA, CR, MT, FB, CI, AL, MG, MV, JS, and MC contributed substantially to the manuscript writing.

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Data sharing: Data are not publicly available but can be obtained from a third party after acceptance of a proposal by the INMA research committee.

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Figure captions:

Figure 1: Longitudinal lung function growth trajectories for z-scores of forced expiratory volume in one second ($zFEV_1$) in 4- to 18-year-old children. Dots represent group mean at each time point.

Figure 2: Longitudinal lung function growth trajectories for z-scores of forced vital capacity (zFVC) in 4- to 18-year-old children. Dots represent group mean at each time point.

Figure 3: Relative risk ratios and 95% confidence intervals for predictors of $zFEV_1$ trajectories.

See values in Table S10 in the supplemental material.

Abbreviations: zBMI: z-scores of body mass index.

Maternal smoking was included due to previously reported significant effects on lung function growth.

Figure 4: Relative risk ratios and 95% confidence intervals for zFVC trajectories.

See values in Table S11 in supplemental material.

Abbreviations: zBMI: z-scores of body mass index.