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Early View

Research letter

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Lung function trajectories using different reference equations in a birth cohort study up to the age of 20 years

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Take home message: Lung function trajectories using different reference equations in a birth cohort up to the age of 20 years show a drop in FEV_1 and FVC of both asthmatic and non-asthmatic subjects at the age of 13 years regardless which reference equations were used.

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To the Editor:

New spirometry reference values of the Global Lung Function Initiative (GLI) and the LUNOKID study were published in 2012 and 2013, respectively, using a non-linear model for lung function trajectories (1) (2) (3). There is a lack of empirical testing of these new equations and reference values in longitudinal cohort studies.

In 2015 Stanojevic et al. applied the GLI reference equations in two longitudinal cystic fibrosis registry data (4). They were able to demonstrate that the use of GLI equations showed a steady rate of FEV1 decline in childhood cystic fibrosis, whereas traditional equations in part showed periods of accelerated decline in adolescence (4). So far this has been the only longitudinal study, evaluations including healthy or asthmatic subjects are missing.

To determine how lung function parameters vary over time long-term observational (birth) cohort studies with multiple time points of respiratory health assessments are superior to clinical trials examining interventions for lung or other diseases.

In the present study, we aimed to evaluate the longitudinal trajectories of lung function in a birth cohort up to the age of 20 years using different reference equations. We also aimed to assess the fit of different equations to the German cohort by separately analysing data for non-asthmatic and asthmatic subgroups from early childhood to young adulthood.

Data were used from the Multicentre Allergy Study (MAS). This German birth cohort study was initiated in 1990 with 1,314 newborns recruited from six obstetrics departments (5), containing lung function measurements at four different time points between 7 and 20 years. We computed z-scores for FEV_1, FVC and FEV_1/FVC for each follow-up by using the equations from Zapletal (6), LUNOKID (2) (3) and GLI (1) for children aged 7, 10 and 13 years. For young adults at 20 years we used equations of GLI and the European Coal and Steel Community (7) (ECSC, here referred to as 'EGKS'). Traditionally we combined Zapletal and EKGS reference data for longitudinal graphing. Cases with more than two missings in the follow-up were excluded from the analyses. We applied criteria for asthma definition at the last follow up at 20 years. As suggested and implemented by several European population-based birth cohort consortia from GA²LEN, ENRIECO and MeDALL initiatives, asthma was

defined by a positive response to at least two of the following three questions (8) (9): a parent- or self-reported physician's diagnosis of asthma (ever), current wheezing (in last 12 months), and/or current asthma medication (in last 12 months). Data were available for 700 subjects, 74 of these were classified as asthmatics at the age of 20 years. Non-linear cubic spline curves were used to model lung function trajectories by different reference systems. 95% confidence intervals were calculated to indicate differences between different time points. Maximum decreases in z-scores were assessed by calculating the difference between the highest and lowest mean z-score of three follow up time points (7, 10, 13 years). Single z-scores of non-asthmatic subjects were interpreted as sufficient fit to each reference equation in case of a value between -0,5 and 0,5 (10).

Interpreting the spline curves for FEV_1 and FVC of non-asthmatic participants mean z-scores decreased from the ages of 7 and 10 years to the age of 13 years (puberty) and increased from the age of 13 to the age of 20 years. The maximum mean decreases of FEV_1 in z-scores were 0.54 (GLI), 0.19 (LUNOKID) and 0.34 (Zapletal) and of FVC in z-scores 0.52 (GLI), 0.19 (LUNOKID) and 0.23 (Zapletal) (figure 1). This drop at 13 years was equally seen in asthmatic and non-asthmatic subjects. Spline curves of asthmatic patients were below the ones of non-asthmatic participants. The drop in lung function trajectory at 13 years was also observed when asthma diagnosis was made at the age of 13 years instead of the age of 20 years.
Spline curves for FEV_1/FVC only decreased when applying the Zapletal/EGKS equations. However, there was no drop in puberty but in early school age (7-10 years) and in young adulthood. In contrast spline curves for FEV_1/FVC using GLI or LUNOKID equations were stable during childhood and adolescence.
The FEV_1-drop at 13 years was clearly more pronounced among males than females. However, the difference was just significant for Zapletal and not for GLI. Additionally, the gap at 13 years between boys and girls was also observed for FEV_1/FVC.
Analyzing single FEV_1- and FVC z-scores showed that healthy subjects mostly had values in-between -0.5 and 0.5. In contrast FEV_1/FVC values were all above 0.5 in this group.

To our knowledge, this is the first longitudinal study applying GLI and other reference equations on multiple lung function data in a birth cohort. We found a z-score decrease in FEV_1 and FVC at the age of 13 years and a subsequent increase between the age of 13 and

20 years, considering that lung function of young teenagers can be difficult to interpret. Lung function trajectories were equal for both asthmatic and non-asthmatic subjects.

Previous studies suggested that additional parameters interfere with lung volume growth and lung function outcome in puberty, for example weight or puberty stage. Neve et al. looked at pubertal stage by Tanner scale and time since menarche and found that lung thoracic and lung development occurred predominantly more towards the end of puberty in males and rather earlier in puberty in females (11). Bekkers et al. reported a significant relationship between BMI and waist circumferences and FVC in children at 12 years of age (12). Other factors, which influence lung growth in the transition from childhood to adulthood, include bone age, growth velocity, stature, skeletal and muscle fat mass and chest circumference (13). However, none of these factors are included into reference equations.

We saw a difference in a lung volume decrease between boys and girls at the age of 13 years. This may be due to the fact that at this puberty age lung development is still occurring in boys, whereas lung development is almost finished in girls. A similar observation was made in a cross-sectional study by Hüls et al., applying GLI reference equations to original lung function data of LUNOKID and GINIplus (German Infant Study on the Influence of Nutrition Intervention plus Air pollution and Genetics on Allergy Development) at the age of 15 years (14). The authors underline that height development and therefore lung volume increase varies much between Caucasian populations, especially in puberty when growth in males is rapid. In our opinion the differences are not only present between Caucasian populations but also between local populations and individuals.

Thus, results from our present study emphasize that lung function data, especially FEV_1 and FVC should be interpreted with caution in the age group of 13 years, when pubertal cofactors might play role. Longitudinally FEV_1/FVC deviated least over time until puberty regardless which reference equations were used. Using GLI reference equations for FEV_1/FVC may even provide a reliable reference throughout to adulthood.

In our population-based birth cohort population the application of GLI reference equations did not reveal a steady spline curve of FEV_1, as shown for the cystic fibrosis patient population by Stanojevic et al (4). Reasons for that are unclear and may have been due to differences in the populations, subject numbers and/or the applied methods.

The classification of asthmatic and non-asthmatic subjects at the age of 20 years may have led to some misdiagnosis. However, the number of asthmatic subjects at 13 years who were not symptomatic at 20 years was small. Instead of a single birth cohort like MAS combined multiple cohort datasets with increased statistical power are required to analyze subphenotypes such as persistent asthma, transient asthma, asthma in remission.

Considering the non-asthmatic group as a healthy group the reference equations used seem to characterize the lung function fairly well, as z-scores of FEV_1 and FVC remained within the normal thresholds of -0.5 to 0.5. Interestingly z-scores of FEV_1/FVC were much larger than zero regardless which reference equations we used, showing less airway obstruction in this group compared to the reference population.

In summary, our results showed a drop in FEV_1 and FVC of both our non-asthmatic and asthmatic group at the age of 13 years regardless which reference equations were used.

Using FEV_1/FVC values and applying them to the reference data of GLI or LUNOKID might be useful for longitudinal follow-up analysis but further evaluations in other settings are required.

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Figures

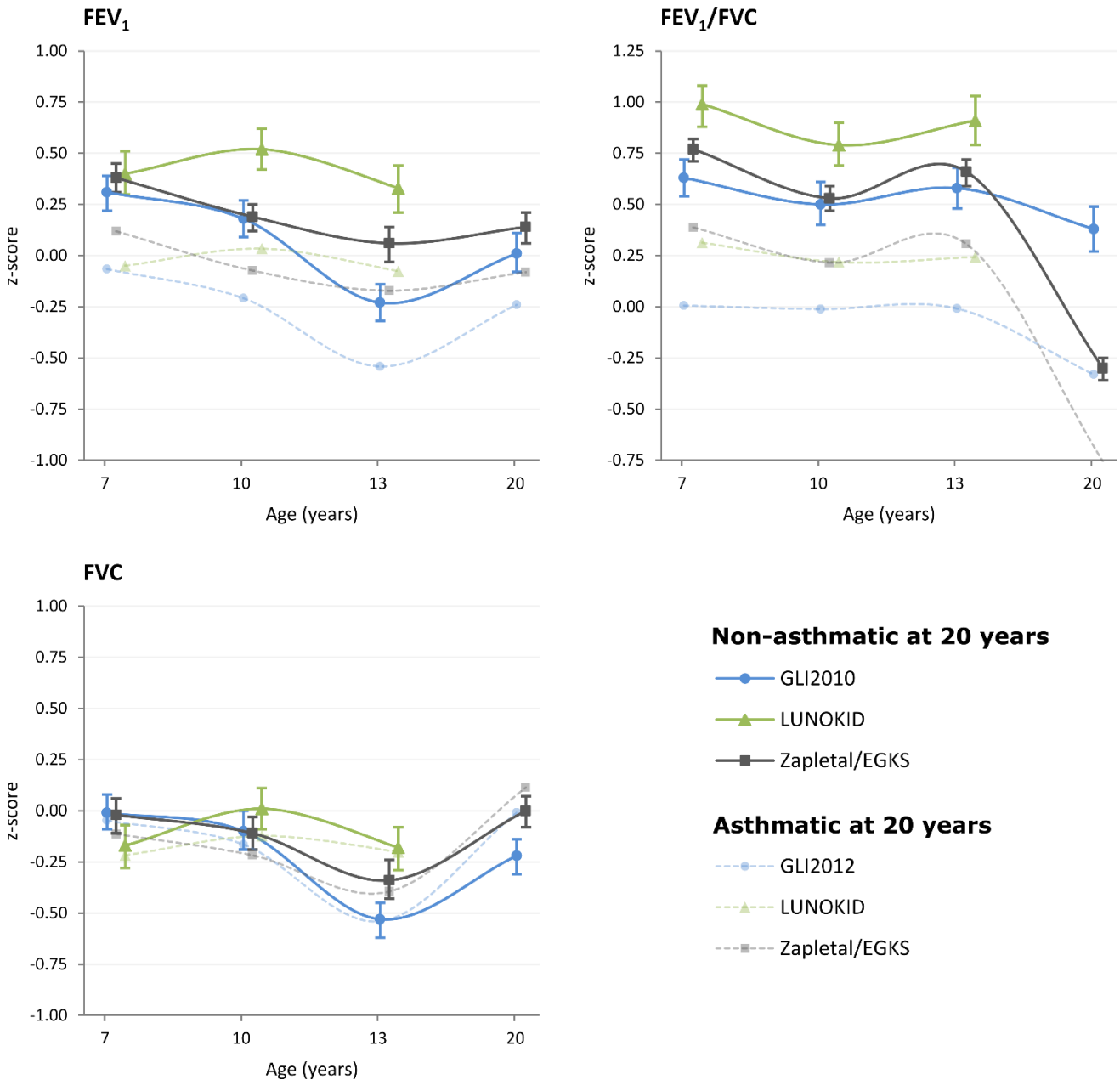

Figure 1. Longitudinal development of lung function parameters (mean z-scores and 95% confidence intervals) by asthma status at age 20 years and by reference equation used (GLI2012, LUNOKID and Zapletal/EGKS)