The role of the small airways in asthma- and their importance in relation to pulmonary symptoms, whether related to smoking or not, has long been underestimated. Although, nowadays, the small airways are no longer referred to as ‘the silent zone’ and smokers are no longer systematically excluded in pulmonary research, a lot remains unknown. In the current thesis, the small airways are extensively explored. We covered three aspects of small airways: the importance of inhaled drug particle size, the contribution of small airways to airway hyperresponsiveness, and a search for an easily measured, reliable, and meaningful parameter of small airways disease.

In Chapter 2, we describe an open-label, randomized, three-way cross-over study to confirm our hypothesis that extrafine particle inhaled corticosteroids (ICS) improve small airways function more than non-extrafine particle ICS in asthmatic (ex-)smokers. This was investigated because asthmatic (ex-)smokers tend to respond less to ICS treatment compared to asthmatics who have never smoked. The worse treatment response is assumed to be due to smoking-induced changes, especially in the small airways. Since these small airways are insufficiently reached by standard non-extrafine ICS, the hypothesis was that targeting the small airways may be an important step forward in increasing treatment response and asthma control in asthmatic (ex-)smokers. However, this hypothesis could not be confirmed. Both extrafine and non-extrafine particle ICS were found to be equally effective with similar improvements in small airways function (adenosine provocation, spirometry, impulse oscillometry, and multiple breath nitrogen washout) and questionnaire-assessed symptoms (ACQ-6 and BHQ). Hence, as (ex-)smokers with asthma seem to respond equally well to extrafine and non-extrafine ICS, just reducing the particle-size of the ICS does not lead to better asthma control in (ex-)smokers.

In Chapter 3, we assessed the effects of two types of inhaled stimuli on the dyspnea sensation in asthmatic (ex-)smokers. The inhaled stimuli differed in particle size and were either targeting the small airways, or the larger, more central airways. To this end, dry powder adenosine with a particle size of 2.6–2.9 µm, designed to better reach the small airways, was compared to
nebulized adenosine 5'-monophosphate (AMP) consisting of 5.1–8.5 µm sized particles. It was explored if the experienced dyspnea sensation would be more pronounced with the provocation of the smaller airways. This question arose from patient reports that provocation-induced dyspnea sensation seems to differ from day-to-day dyspnea, the observation that a drop in forced expiratory volume exhaled in one second (FEV₁) associates poorly with experienced dyspnea, and the fact that provocation is commonly only evaluated with the large airways parameter FEV₁, while dyspnea was previously associated with both large and small airways. As expected, this study showed that provocation targeting either the large- or small airways evoked a similar drop in the FEV₁, but contrary to our hypothesis, dyspnea sensation was not more pronounced when targeting the small airways. Nevertheless, in multivariate regression, an association between induced dyspnea and changes in several small airways function parameters was found for small-sized dry powder adenosine while no association was found for large-sized AMP-induced dyspnea with either large- or small airways parameters. Therefore, we speculate that other factors than airway caliber or resistance—which is measured with pulmonary function tests—play an important role in dyspnea sensation.

In Chapter 4, we investigated the unexpected finding of airway hyperresponsiveness (AHR) to nebulized AMP in healthy asymptomatic never- or current smokers who were unresponsive to methacholine. All subjects were meticulously characterized as they were part of a cohort of healthy controls for pulmonary research. None exhibited respiratory symptoms and all had normal pulmonary function including the absence of AHR to methacholine. Interestingly, a subset exhibited AHR when provoked with nebulized AMP. Methacholine is a stimulus directly acting on the smooth muscle surrounding the airways, while AMP acts via the release of inflammatory mediators, mainly from mast cells, thereby indirectly causing AHR. This study was performed aiming to explain this unexpected AHR in the subset of subjects. The following factors were found to be associated with a higher risk of AHR to AMP in these subjects: 1. smoking, both expressed as status and as quantity, 2. worse small airways function and diffusion capacity, 3. higher percentage of sputum eosinophils, and 4. lower scores on
questionnaire evaluating the quality of life and COPD control (note: none of these subjects were diagnosed with COPD). These findings lead to the speculation that AHR to AMP could be indicative of a higher risk to develop pulmonary complaints later in life.

In Chapter 5, we revisited the FVC adjustment of the forced expiratory flows (FEFs), mentioned throughout literature since the 1970ies to reduce the variability of these FEFs. Often, the lack of reference equations is presented as one of the reasons this adjustment failed to become established. To obtain these equations, 80% of the almost 14,500 pulmonary healthy, never-smoker adults from the LifeLines biobank were used. The remaining 20% of the LifeLines data combined with almost 340 healthy controls from two cohorts of healthy controls (NORM and Fiddle) were used to validate the equations. The presented equations provide predicted normal values for the adjusted FEFs based on sex, age, height, and weight. Importantly, this study confirmed that the FVC adjustment of the FEFs indeed decreases the variability of the FEFs.

In Chapter 6, we assessed the clinical applicability of the adjusted FEFs as small airways parameter in asthmatics. To this end, the adjusted FEFs were correlated to the unadjusted FEFs and evaluated for the level of agreement in defining abnormal pulmonary function. Furthermore, the adjusted and unadjusted FEFs were compared for their levels of association with established large and small airways parameters, disease severity, and asthma control. In the end, the unadjusted FEFs showed higher correlations with established small airways parameters and explained larger proportions of the variance in GINA severity and ACQ6. Therefore, even though the adjustment of the FEFs decreases the variability, it failed to improve the clinical applicability of measuring small airways function in asthma based on spirometry.