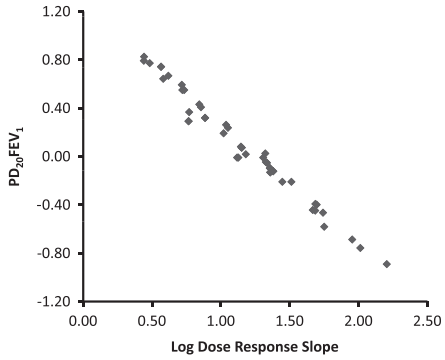

Figure 1 Log dose–response slope and log$PD_{20}FEV_1$ in 41 subjects with asthma after histamine challenge ($r=-0.97$, $p<0.0001$). Data from these subjects have been reported previously.[2]

Thirdly, there are inconsistencies in the data in their figure 2.[1] Seven subjects have PD_{20} values close to zero (possibly 0.1 μmol?), and therefore should have DRS values of ~200 (ie, 20% fall/0.1 μmol) and CIR values of ~2.3 (ie, log 200). These subjects do not appear in figure 2B,C. Furthermore, the distribution of AQLQ differs between figure 2A and B.

The advantage of a continuous measure of airway responsiveness such as DRS, rather than PD_{20}, is not that DRS provides qualitatively different information but rather that it yields an estimate of airway responsiveness in all subjects, not just the subset with AHR. Airway responsiveness is a continuum, with the cut-off point for AHR defined arbitrarily. However, AHR can be normalised with inhaled corticosteroid therapy,[3] and subjects with asthma can move in and out of the abnormal range. A more appropriate interpretation of the difference between PD_{20} and 'reactivity' in their relationships with AQLQ reported by Cisneros *et al*[1] would be that quality of life is worse in subjects with AHR, but does not worsen with increasing severity of AHR.

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Authors' response

We read with great interest the comment by Salome and coworkers on our recently published article.[1] We are grateful for their interest in our work, although they attribute to us a conclusion that does not appear in our paper. We conclude that bronchial reactivity indices are independent predictors for the health-rated quality of life of patients with asthma and we propose that they might be of use in clinical practice. In our conclusion, however, no comparison is established between bronchial reactivity and sensitivity.

We agree that the analysed indices of bronchial reactivity represent different expressions of the slope of the dose–response curve. Certainly, the differences in their relationship with the Asthma Quality of Life Questionnaire are attributable to changes in shape or linearity due to the mathematical transformation applied in their calculation.

Nevertheless, we do not agree with the assimilation between the provocative dose causing a 20% fall in forced expiratory volume in 1 s (FEV_1) (PD_{20}) and dose–response slope (DRS). Both parameters seem to be qualitatively different since the dose–response curves plotted in their determination are also different. PD_{20} is obtained from curves plotted on a semilogarithmic scale whereas DRS is obtained from a linear dose axis. Moreover, the calculation of PD_{20} uses the fall in FEV_1 between the last and penultimate doses while, for DRS determination, the fall in FEV_1 is considered that between the last dose and the post-diluent baseline value. These different approaches provide necessarily different values. In fact, and in contrast to Salome and coworkers, in our patients with asthma the relationship between PD_{20} and DRS is slight ($r=0.416$, $r=0.042$).

We therefore believe that DRS and PD_{20} are not completely equivalent. DRS allows for airway responsiveness to be assessed in all individuals, including those who do not reach the threshold PD_{20}. Several studies, including some of their own group,[2] have already shown that DRS to methacholine or histamine is associated with asthma diagnosis and symptoms. Moreover, DRS allows for a better separation of patients with and without asthma than PD_{20}.[3] It has recently been shown that adolescents with asthma remission had a significant decrease in speed of bronchial constriction (bronchial reactivity) whereas the threshold of methacholine (bronchial sensitivity) was not altered.[4]

Finally, and in agreement with Porsbjerg *et al*,[5] we consider that the differences in the estimation procedure and the non-censored character of the DRS, continuous index of responsiveness and bronchial reactivity index should justify their stronger relationship with health-related quality of life than PD_{20}.

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Outcome after bronchiolitis depends on disease definition

Sigurs *et al* recently published their 18-year prospective controlled follow-up study of 47 subjects hospitalised for respiratory syncytial virus (RSV) bronchiolitis at age <12 months.[1] In the cohort the prevalence of wheezing and asthma was higher than in population-based controls at 3, 7 and 13 years of age.

Asthma was present, depending on definition, in 33–39% of 46 study subjects and in 7–9% of 92 controls,[1] in line with an asthma prevalence of 9.5% in Swedish young adults.[2] The risk of adulthood asthma after

RSV bronchiolitis was therefore 3.5–4.1-fold compared with the population.

Lung function by forced expiratory volume in 1 s (FEV_1), ratio of FEV_1 to forced vital capacity (FVC) and mid forced expiratory flow (FEF_{25-75}) was reduced in the former patients with RSV bronchiolitis with and without current asthma but not in asthmatic controls.[1] The differences were significant in both pre- and post-bronchodilator measurements, suggesting the permanence of the changes. Instead, no evidence was found for permanent small airway dysfunction by lung clearance calculation.[1]

In our study, 100 infants aged <24 months were hospitalised with bronchiolitis in 1992–3. Eighty-one attended the control visit at age 12 years; asthma was present in 20% of former patients with RSV and in 52% of former non-RSV patients (OR 0.27, 95% CI 0.09 to 0.82), and in 58% of former patients with rhinovirus and in 34% of former non-rhinovirus patients (OR 2.6, 95% CI 0.89 to 7.94).[3] RSV bronchiolitis was associated with a restrictive pattern of lung function documented by reduced FVC.[4]

A post-questionnaire study including population-based controls was performed in 2008 when the study subjects were 17–18 years of age (unpublished). Sixty-seven former patients with bronchiolitis and 155 controls attended, and current asthma was present in 30% and 5%, respectively (OR 7.9, 95% CI 3.3 to 19.3). Asthma was present in 25% of the former patients with RSV and in 26% of the former patients with rhinovirus. As in the study of Sigurs *et al*,[1] asthma was common after early life bronchiolitis but a viral aetiology of bronchiolitis no longer had a predictive value.

Sigurs *et al* enrolled only RSV-positive patients with bronchiolitis aged <12 months treated in hospital, and >90% of the cases were aged ≤6 months.[1] In the Tucson birth cohort study from which our current concept about childhood wheezing phenotypes originates, patients with bronchiolitis were aged <24 months with parent-reported wheezing treated usually at home.[5] In the Finnish post-bronchiolitis studies highlighting the role of rhinovirus aetiology, RSV predominated in infants aged <6 months ('European bronchiolitis') and rhinovirus in those aged 6–24 months ('American bronchiolitis').[3 4] In future studies of bronchiolitis, stratified analyses by age and viral findings are mandatory.

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Authors' response

We thank Dr Hyvärinen and colleagues for their insightful comments on our recent paper on asthma and allergy outcome at age 18 years after severe respiratory syncytial virus (RSV) bronchiolitis during the first year of life[1] and for their contribution of as yet unpublished findings from their 18-year follow-up of the Finnish cohort.[2] Their data, obtained in subjects previously hospitalised with bronchiolitis in the first 2 years of life (25/81 cases tested for RSV were positive and 19/66 were positive for rhinovirus), confirm our findings of increased asthma rates up to early adulthood. The Finnish study extends these findings by including severe bronchiolitis due to other viral agents, most notably rhinovirus, which is today a well-recognised risk factor for later wheezing illness.[3] Interestingly, in the Finnish cohort of hospitalised subjects aged <24 months, RSV predominated in those aged <6 months and rhinovirus in those aged 6–24 months. While rhinovirus carried the greatest risk of asthma at age 12 years, the increased rates of asthma at age 18 were similar in former RSV- and rhinovirus-infected subjects. What remains unclear, regardless of the underlying viral aetiology, is whether these episodes of severe bronchiolitis are simply identifying those infants already at a predisposed risk of subsequent wheezing illness in later childhood or whether a true causative role of viral infection exists. In our cohort only one of the infants had a previous episode of wheezing, and we are therefore confident that their RSV bronchiolitis represents their first lower respiratory tract insult.

If stratification by age and viral type are incorporated in future studies, it would be important to ensure that the confounding effects of previous viral infections are taken into account if a causal relationship is to be investigated. Ideally, such studies should also include premorbid assessment of lung function and allergic sensitisation, and identified genetic risk factors.

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Longitudinal change of prebronchodilator spirometric obstruction

We read with interest the article by Probst-Hensch *et al* about longitudinal changes of prebronchodilator spirometric values.[1] They reported a non-persistent obstruction rate of 20.9% and concluded that prebronchodilator spirometry values only might misclassify chronic obstructive pulmonary disease (COPD). We are surprised by this high non-persistence rate and we believe that there are some issues that have to be taken into account regarding the obtained lung function values, irrespective of the quality control.[2]

First, we noticed that ~40% of the non-persistent subjects were never-smokers and