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**Title:** Metrics of salbutamol use as predictors of future adverse outcomes in asthma

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**Body:** Background Beta-agonist overuse is associated with adverse outcomes in asthma, however the relationships between different metrics of salbutamol use and future risk are uncertain. Aim To explore the relationship between metrics of salbutamol use and future severe exacerbations, poor asthma control and salbutamol overuse. Methods A 24-week randomised controlled trial in adult asthma included treatment with fixed-dose maintenance budesonide/formoterol and salbutamol as reliever, with actual medication use measured electronically. A nested cohort study explored the relationship between metrics of baseline salbutamol use over two weeks and future severe asthma exacerbations, poor asthma control [ACQ-5 score  $\geq 1.5$ ] or 'extreme' salbutamol overuse [ $>32$  salbutamol actuations/24-hour period]. Results Higher mean daily salbutamol use (per two actuations/day) [Odds Ratio (OR) (95% CI) 1.24 (1.06-1.46)], higher days of salbutamol use (per two days in two weeks) [OR 1.15 (1.00-1.31)] and higher maximal 24-hours use (per two actuations/day) [OR 1.09 (1.02-1.16)] were all significantly associated with future severe exacerbations. Higher mean daily salbutamol use was associated with future poor control [OR 1.13 (1.02-1.26)]. Higher mean daily salbutamol use [OR 2.73 (1.84-4.07)], number of days of use [OR 1.46 (1.24-1.71)], and maximal daily salbutamol use [OR 1.57 (1.31-1.89)] were associated with an increased risk of future extreme salbutamol overuse. Conclusion Electronically-recorded frequency of current salbutamol use is a strong predictor of risk of future adverse outcomes in asthma, with average daily salbutamol use performing the best in predicting future risk. Funding Health Research Council of New Zealand.