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Is there an association between wheezing and constipation in preschool children? Explanations from a longitudinal birth cohort

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ABSTRACT

Objective: To assess whether wheezing and atopic dermatitis were associated with constipation in preschool children and to what extent shared risk factors contribute to this relationship.

Methods: A population-based sample of 4651 preschool children was used. At the age of 24, 36 and 48 months, a parental report of functional constipation was available according to the Rome II criteria, and data on atopic dermatitis and wheezing were available using age-adapted questionnaires from the International Study of Asthma and Allergies in Childhood. Stepwise multivariate analyses were performed to assess whether body mass index, infection exposure, food allergy and infant nutrition, and parental stress explained the association between wheezing, atopic dermatitis and constipation.

Results: Out of 4651 children, 12−17% had functional constipation between 24 and 48 months. Symptoms of wheezing decreased from 20% to 12% and atopic dermatitis decreased from 30% to 18% at the age of 24 and 48 months respectively. Between the age of 24 and 48 months, wheezing symptoms were significantly associated with functional constipation (OR 1.17; 1.02 to 1.34) but these results were mainly explained by the child's exposure to infections and use of antibiotics (adjusted odds ratio 1.08; 95% CI 0.95 to 1.24). No significant association was found between symptoms of atopic dermatitis and functional constipation (OR 1.08; 95% CI 0.94 to 1.23).

Conclusions: These findings suggest that functional constipation coexists with wheezing in childhood but is mainly explained by the child's infection exposure and use of antibiotics. Therefore, an independent association between respiratory symptoms and functional bowel disorders as suggested in previous studies is questionable.

ARTICLE SUMMARY

Article focus
- Constipation, wheezing and atopic dermatitis are common symptoms in children.
- Functional bowel disorders are linked to asthma and atopy in adults.
- Functional bowel disorders, asthma and atopic disease may share common risk-factors that may explain coexistence of these symptoms.

Key messages
- Wheezing, but not atopic dermatitis, is associated with functional constipation in preschool children. The association is mainly explained by a history of infection exposure.
- Hence, the association between wheezing and functional constipation is not independent. Further research is needed to explore whether this result also applies to the outcome of asthma.

Strengths and limitations of this study
- Population-based study population. The study group were not selected according to medical care.
- This study addresses a topical area that has not been studied sufficiently and can contribute to the discussion of how asthma or atopy may be associated with functional bowel disorders.
- This study took into account multiple shared risk factors of wheezing and constipation to shed light on the suggested association in literature.
- Symptoms were available only from parental-reported questionnaires. This may lead to misclassification of the symptoms.
- Early wheezing in infancy is not a sufficient predictor of childhood asthma.
- No data were available regarding parental concerns of the child's health status. Bias may occur when parents with high concerns are more likely to report symptoms in their child as wheezing, constipation and infectious disease.
- No data were available on IgE sensitisation, thus conclusions on the assocation between allergic disease and constipation should be made with caution.

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INTRODUCTION

Functional constipation and other functional bowel diseases account for the majority of gastrointestinal symptoms worldwide and are increasing in the Western world.[1] [2] The

prevalence of atopic diseases such as asthma and atopic dermatitis is also increasing in Western countries.[3] In adults, several studies have suggested that asthma or atopy may be linked to constipation[4] or other functional gastro-intestinal disorders.[5-8] In children, different results with regard to constipation have been described.[9][10] Some pathophysiological overlaps may explain the proposed correlation between constipation and atopy. For example, atopic disease, which affects approximately 30% of the population, includes food allergies that may cause various organ dysfunctions, thus implying that the link between constipation and atopy may be explained by food allergy.[11] Likewise, a shared risk factor for both asthma and constipation is obesity. As reported in several studies, asthma is highly prevalent in children with obesity,[12] and obesity has been found to be more common in subjects with functional constipation.[13]

Since both atopy and functional bowel disorders are particularly prevalent in developed countries, a role for the 'hygiene hypothesis' in these two disorders is also proposed. The hygiene hypothesis concedes that current hygiene practices lead to reduced or altered exposure of bacteria and other micro-organisms that may result in an imbalance of the immune system and microflora early in life.[14] Early microbial colonisation of the infant's gastro-intestinal tract might reduce the risk of atopic disorders, and altered intestinal flora has been an area of interest for years in both constipation and atopy.[15][16] Finally, studies have addressed the role of stress in the aetiology both of atopic disorders[17] and constipation.[18] Prenatal and childhood stress have been suggested to disturb the regulation of immune and autonomic functions[19] that makes children vulnerable to develop both atopy and altered bowel habits.

To better understand the mechanisms playing a role in these disorders, it is warranted to examine which common risk factors explain the association between atopy and constipation as described in the literature. In addition, most of the exposures associated with disease start early in life, and the majority of adults with other functional bowel disorders experience symptoms of functional constipation that are already present during childhood.[20] The aim of our study, therefore, is to examine whether wheezing and atopic dermatitis are associated with functional constipation in childhood. A second aim is to assess if and to what extent cow's milk allergy, overweight, indices of infection exposure and parental stress contribute to the association between wheezing, atopic dermatitis and functional constipation in young children.

PATIENTS AND METHODS
Participants and study design
This study was embedded in the Generation R study, a population-based prospective cohort study from fetal life until young adulthood, and has been described in detail previously.[21][22] In total, 7893 mothers with a delivery date between April 2002 and January 2006 provided consent for follow-up. The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam, The Netherlands.

Functional constipation
At the ages of 24, 36 and 48 months, the stool pattern of the child was assessed using a questionnaire (response rates: 70%, 64% and 63% respectively). Accordingly, the outcome of functional constipation was defined in this study if at least one of the following symptoms of ROME II[23] was reported: (1) defecation frequency less than three times a week for at least 2 weeks or (2) predominantly hard faeces for the majority of stools for at least 2 weeks.

To avoid the influence of metabolic disorders and clustering, children were excluded in the analyses in case of the following: (1) twinborn (n=238), (2) siblings within the Generation R cohort (n=343), (3) presence of a congenital heart condition (n=47), (4) any history of doctor diagnosis of anaemia, collected by question-naire (n=58) or (5) growth retardation defined as height for age $<-2SD$ based on the Netherlands growth curves (n=163).[24]

Wheezing and atopic dermatitis
Information regarding atopic dermatitis and wheezing was obtained on the basis of core questions from 'International Study of Asthma and Allergies in Childhood' (ISAAC) and doctor attendance of eczema or episodes of itchy rash at the age of 24, 36 and 48 months,[25] which has been used successfully in a previous study to predict asthma.[26] In addition, the following questions were asked at the age of 24, 36 and 48 months: 'Has your child had problems with a wheezing chest during the last year?' and 'Has your child had an itchy rash that came and went during the past year?' These outcomes were analysed dichoto-mously: presence or absence of eczema and presence or absence of wheezing in the previous year at 24, 36 and 48 months of age.

Covariates
Weight and height at 24, 36 and 48 months were available from the child-health centres. Body mass index (BMI) was then calculated, and overweight was defined according to age- and gender-adapted BMI thresholds for young children from the International Obesity Task Force.[27]

At the age of 6 and 12 months, questionnaire data were available on a history of doctor-attended food allergy in the first year of life and the introduction of food allergens and breast-feeding duration that we described in detail in a previous study.[28] Briefly, parents were asked at what age they had introduced the following products in the infant's diet for the first time: milk, yogurt, porridge, egg, bread or biscuits, peanuts, nuts and soy products. The reported introduction of these food products was cross-checked with a short food-frequency questionnaire filled in at the children's age of 6 and 12 months consisting of food-products frequently

consumed according to a Dutch food-consumption survey in infants. For example, if the parent indicated at the age of 12 months that they had never introduced gluten in the infant's diet but at the infant's age of 6 months the parent had filled in that the infant consumed porridge based on gluten containing cereals for at least once, then the introduction of gluten was considered to be before or equal to the age of 6 months. Breast-feeding duration was assessed according to five variables: ever breast-feeding, cessation of breast-feeding and receiving any breast-feeding at the age of 2, 6 and 12 months.

At the age of 24, 36 and 48 months, questionnaire data were available for the following indicators which were used as proxy for infection exposure of the child: attendance of daycare and doctor attendance for fever (>38°C) accompanied by symptoms of cough, runny nose, earache, diarrhoea or vomiting in the past year, and any use of antibiotics in the previous year (yes vs no).

The level of parental stress was assessed at the child's age of 24 months using the Nijmeegse Ouderlijke Stress Index—Kort (NOSIK[29]), the Dutch version of the Parenting Stress Index—Short Form that has been shown to be reliable and valid.[30] The NOSIK comprises two domains consisting of 25 items; parenting stress due to parent factors, and parenting stress due to child factors. Only the items on the parent domain were available in this study (n=15 items on parental stress due to parent factors). Items were assessed on a four-point scale, and the scores were summed and divided by the number of fulfilled items. Higher scores indicate greater levels of parental stress. In addition, these scores were demonstrated to be an important predictor of somatic complaints in this birth cohort.[31]

Other variables possibly related to functional constipation, wheezing and atopic dermatitis were obtained from prenatal and postnatal questionnaires filled in by the parents (ethnicity, mother's educational level, maternal and paternal history of atopic dermatitis, asthma, hay fever, allergy to house dust and prenatal smoking). From obstetric records assessed in midwife practices and from hospital registries, data on gender, birth weight and gestational age were available as described previously.[21][22]

Statistical analysis

First, univariate analyses were performed using χ^2 tests for categorical variables and the Mann—Whitney U test for continuous variables. Second, logistic regression analyses using generalised estimating equations (GEE) were performed. Briefly, regression analysis using GEE assesses the association between two variables by correction for the within-subject dependence as a result of the repeated observations on wheezing, eczema and functional constipation, since repeated measurements within one individual are frequently correlated.[32] The within-subject correlation coefficient for wheezing, atopic dermatitis and functional constipation at the three time points were comparable (r=0.3−0.4). Therefore, an exchangeable working correlation struc-ture was used in the GEE analyses as adjustment for the dependency between the repeated measurements.

Logistic regression analysis with GEE was performed with functional constipation compared with no constipation as dependent variables and the presence of any wheezing or atopic dermatitis in the past year as an independent variable. In addition, model 1 was adjusted for time (ie, age), and major child characteristics as gender, mother's educational level, ethnicity (western vs non-western), birth weight, gestational age, maternal smoking and family history of atopic disorders. These covariates were selected on the basis of previous studies on factors associated with asthma-like symptoms and constipation.[28][33] Subsequently, to assess whether the association between functional constipation and atopy was dependent on BMI, infection exposure, food allergy and infant nutrition, or parental stress, the following variables were added separately to model 1: BMI (model 2); daycare attendance, use of antibiotics in previous year, and history of respiratory or gastrointestinal infections in the previous year (model 3); history of food allergy, breast-feeding duration and introduction of food allergens ≤6 months (model 4); and parental stress score (NOSIK) (model 5). To test whether the associations between wheezing, atopic dermatitis and functional constipation were different at the age of 24, 36 and 48 months, the effect modification by time was evaluated by adding the product-term of wheezing/atopic dermatitis and time (eg, wheezing×time) as an independent variable to the crude GEE model.

To reduce potential bias associated with missing data, missing values (approximately 0.1−40%) were multiple-imputed (n=5 imputed datasets). The multiple imputation was based on the correlation between each variable with missing values with the other subject characteristics as described previously by Sterne et al.[34] Data were analysed in each data set separately to obtain the desired effect sizes and standard errors. Finally, the results of the five imputed analyses were pooled and reported in this paper. In addition, the pooled OR was calculated by taking the average of the OR's of the five imputed datasets. The pooled SE to assess the 95% CI was then calculated using Ruben's rule[35]: $\sqrt{(W+(1+1/m)\times B)}$ with W the mean variance of the effect size within the imputed datasets; B the variance of the effect sizes between the imputed datasets; and m the number of imputed datasets (n=5). A p value of <0.05 was considered statistically significant. Statistical analyses were carried out using SPSS 17.0 for Windows.

RESULTS

The characteristics of the study population are presented in table 1.

A non-response analysis at 48 months showed that non-responders reported wheezing slightly more often at 36 months (17.1% vs 11.9%, p<0.01) and functional constipation at 24 and 36 months (18% vs 11.3% and 23.2 and 16.2% respectively, p<0.01), more often had mothers from a lower social economic background

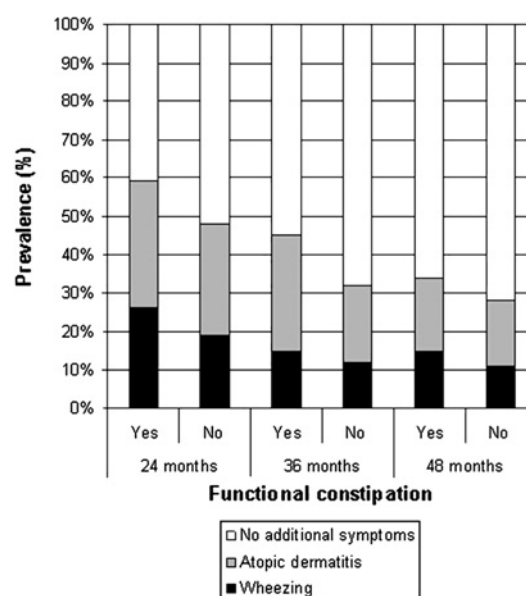**Table 1** Maternal and child characteristics of the study population (N=4651)

	N (%)
Mother	
Educational level of mother	
Low	774 (16%)
Midlow	1365 (29%)
Midhigh	1148 (25%)
High	1363 (29%)
Maternal smoking	1154 (25%)
Maternal alcohol consumption	1869 (40%)
Parental stress score mean (SD)	0.36 (0.30)
History of atopy	2238 (48%)
Child	
Male N (%)	2333 (50%)
Ethnicity N (%)	
Dutch/other Western	3421 (74%)
Non-Western	1230 (26%)
Birth-weight mean (SD)	3431 (540)
Gestational age at delivery mean (SD)	39.9 (1.6)
History of food allergy in first year of life	265 (6%)
Introduction of food allergens ≤6 months	3472 (75%)
Duration of breast-feeding in months mean (SD)	4.8 (3.8)
Crèche attendance in first 2 years of life	3579 (77%)
Overweight in second year of life	915 (20%)

Figure 1 Distribution of wheezing and atopic dermatitis symptoms in children with and without functional constipation (N=4651).

(16.6% vs 5.8% p<0.01) and a non-western ethnicity (54.5% vs 25.2%, p<0.01), and smoked more often during pregnancy (77.4% vs 65.5%, p<0.01).

The prevalence of functional constipation remained relatively stable between 12% and 14% at the ages of 24, 36 and 48 months. The highest prevalence of wheezing symptoms during childhood was at the age of 24 months (20%) and this decreased to a prevalence of 12% at 36 and 48 months. The prevalence of atopic dermatitis decreased from 30% at the age of 24 months to 20% and 18% at the age of 36 and 48 months respectively. Out of 4651 children, 3−4% had persistent symptoms of functional constipation, atopic dermatitis or wheezing at all time points (ie, at 24, 36 and 48 months).

At the age of 48 months, functional constipation was more prevalent in girls (16% vs 13%, p<0.01), children of non-western origin (23% vs 12%, p<0.01), children with a history of respiratory-tract- and gastrointestinal infections in the previous year (12% vs 20% and 14% vs 18%, p<0.01), and children whose mothers smoked during pregnancy (14% vs 16%, p<0.01). Children with functional constipation at 48 months had a lower birth weight (3373 vs 3488 g, p<0.01) and had a higher parental stress score (0.37 vs 0.29, p<0.01) than children with no functional constipation.

The distribution of wheezing and atopic dermatitis in children with and without functional constipation between 24 and 48 months is shown in figure 1.

Wheezing symptoms were significantly associated with symptoms of functional constipation in childhood, but no significant association was found between atopic dermatitis and functional constipation in univariate analyses (table 2). After adjustment for age, gender, birth weight, gestational age, maternal smoking, maternal educational background, ethnicity and parental history of atopy, wheezing remained significantly associated with functional constipation (table 2; model 1), which was also the case after stepwise adjustment for BMI, history of food allergy and infant nutrition, and parental stress (table 2; models 2, 4 and 5). The greatest alteration in the effect estimate in the analyses of wheezing and functional constipation was found after adjustment for infection exposure and use of antibiotics for the child, which mainly explained the association between wheezing and constipation (table 2; model 3). Adjustment in addition to model 1 for other potential shared risk factors did not explain the association between wheezing and functional constipation (table 2).

The results between wheezing and constipation did not differ significantly by the different time points of 24, 36 and 48 months (p=0.57 for statistical interaction between wheezing and age and p=0.43 for statistical interaction between eczema and age).

DISCUSSION

This study shows that wheezing symptoms and functional constipation frequently coexist in preschool children, but this relationship was markedly influenced by infection exposure of the child. Other potential shared risk factors such as BMI, history of food allergy, infant nutrition and parental stress did not explain the association between wheezing and constipation.

Several studies in adults showed a link between functional bowel disorders and asthma,[5−8] but different

Table 2 Longitudinal logistic regression models on the association between wheezing, eczema and functional constipation between 24 and 48 months of age (N=4651)

	No constipation	Functional constipation OR (95% CI)
Wheezing		
Unadjusted	Reference	1.17* (1.02 to 1.32)
Model 1	Reference	1.16* (1.01 to 1.31)
Model 2 (body mass index)	Reference	1.16* (1.01 to 1.32)
Model 3 (infection exposure and use of antibiotics)	Reference	1.10 (0.96 to 1.25)
Model 4 (food allergy and infant nutrition)	Reference	1.15* (1.01 to 1.32)
Model 5 (parental stress)	Reference	1.14* (1.00 to 1.30)
Eczema		
Unadjusted	Reference	1.08 (0.94 to 1.23)
Model 1	Reference	1.04 (0.91 to 1.18)
Model 2 (body mass index)	Reference	1.04 (0.91 to 1.18)
Model 3 (infection exposure and use of antibiotics)	Reference	1.04 (0.91 to 1.19)
Model 4 (food allergy and infant nutrition)	Reference	1.03 (0.60 to 1.18)
Model 5 (parental stress)	Reference	1.03 (0.90 to 1.18)

Model 1, baseline model adjusted for age, gender, mothers educational level, ethnicity, birth weight, gestational age, maternal smoking and family history of atopy; Model 2, model 1+ adjustment for body mass index; Model 3, model 1+ adjustment for history of respiratory-tract- or gastrointestinal infections in past year and daycare attendance in first 2 years of life, and use of antibiotics in the previous year; Model 4, model 1+ adjustment for history of food allergy, breast-feeding duration and introduction of food allergens ≤6 months; Model 5, model 1+ parental stress.
*p<0.05.

results in children have been described so far. In addition, Caffarelli *et al* demonstrated no difference in constipation in allergic children compared with controls[36] but reported that other gastrointestinal symptoms such as diarrhoea and vomiting are more prevalent in children with atopic eczema than in controls.[10] Also, Simeone *et al* showed no association between constipation and atopy in young children,[9] whereas a small increase in the prevalence of irritable bowel syndrome over time was observed in subjects with asthma aged 5–65 years.[7] Yet, Leander *et al*[4] showed recently that constipation was associated with asthma independently of age.[9]

The strength of our study lies in the large study population not selected according to medical care, thereby diminishing any selection bias. Earlier studies have been carried out in selected populations of patients seeking medical care. This could lead to selection, for instance, towards children at high risk for atopic constitution who may have a higher proportion of functional bowel disorders than in the general population. Also, most studies did not take account for potential shared risk factors that may suggest incorrectly that the relationship is independent. The broad range of available data of potential confounders in our study elucidates the contribution of shared risk factors in the association between atopy and functional bowel disorders.

Our study confirmed that the association between wheezing and functional constipation was influenced by infection exposure. This finding can be explained in several ways. First, respiratory infections are risk factors for wheezing and asthma[26] but gastro-intestinal infec-

tions are also associated with constipation.[37] For example, during a flu-like illness, both respiratory and gastrointestinal symptoms may coexist,[38 39] and this may clarify that our association between wheezing and constipation is explained by a history of infections as defined by fever accompanied by diarrhoea or respiratory symptoms. Second, from animal studies it is known that very early exposure to micro-organisms, for example, by crowding or infections earlier in life, is required for proper maturation of the immune system in and outside the gut, which may have a protective effect on allergic disease.[40] Also, it is speculated that frequent exposure to childhood infections is responsible for the low prevalence of functional bowel disorders in developing countries and that early colonisation may enable the intestinal epithelium to respond efficiently to antigenic challenge, which may result in a pronounced amelioration of gastro-intestinal symptoms after infections.[41] However, if the latter were the case in our study, we would expect adjustment for infection exposure to make the association between wheezing and constipation even stronger instead of weaker. Further in-depth research to explore the process of colonisation may elucidate the contribution of infections and exposure to micro-organisms in the association between wheezing and constipation.

Underlying mechanisms such as altered contractility of smooth muscles cells and dysfunction of the autonomic nervous system that can be triggered by emotional stress are suggested to play a common role in asthma and constipation.[17 18] Since parental stress was

demonstrated to be an important predictor of somatic symptoms in children in a previous study,[31] we expected a certain explanatory effect of parental stress on the association between wheezing and constipation. However, adjustment for parental stress only slightly weakened the association between wheezing and functional constipation. Nevertheless, it may well be that stress operates at the spectrum of infection exposure of the child, since prenatal and postnatal stress can be associated with an increased risk of infectious disease in the offspring,[42 43] which itself was thus of major importance in explaining the association between wheezing and constipation.

To appreciate the results, some limitations of this study should be considered. We had data on functional constipation using parental-derived questionnaires, and no additional information from medical records or physical examinations was available. Therefore, some subjects may be misclassified concerning the diagnosis of functional constipation. However, only if this misclassification is also related to wheezing would this misclassification have overestimated our results.

Loss to follow-up is a common phenomenon in large birth-cohort studies. Relative to other birth-cohort studies, the participation rate of our study was high (60−70% in our study group versus 30−40% in other studies).[44] As in most other studies, the non-response analyses showed that the participation in our study was selective. Nevertheless, this would have influenced our results only if the association between wheezing and constipation were completely different among participants of this study relative to those who did not participate.[44] It has been suggested that food allergy in early infancy may be a risk factor for wheezing attacks.[45] The limited clarifying effect of food allergy on our study results might be explained by the fact that not all food-sensitised children have manifest food allergy.[46] Consequently, sensitisation to food allergens, as demonstrated by tests of specific serum IgE, might be a better explanation rather than a report of food allergy or timing of introduction of food allergens in the association between atopic disorders and functional constipation. We did not have any other evidence of food allergy in the first year available than the parental report of doctor-diagnosed food allergy. It is known that self-report of food allergy overestimates the true prevalence of food allergy. On the other hand, we expect that this information bias may have led to overadjusted ORs and thereby an underestimation of the final results because parents who believe that their child had a food allergy may also have reported symptoms related to atopic diseases or constipation more frequently. Nevertheless, some bias may occur when parents with high concerns are more likely to report symptoms in their child as wheezing, constipation and infectious disease. Adjustment for the NOSIK score may reduce this effect slightly. However, it only consisted of information on parental stress due to parent factors but not stress due to the child's health status.

At last, previous studies on functional bowel disorders have focused on the link with asthma and allergic disease. Early wheezing in infancy is not a major predictor of childhood asthma,[26] and we did not have any data on allergic sensitisation as measured by IgE. Hence, our results do not allow for conclusions regarding functional constipation and childhood asthma and allergic disease. Although we took several shared-risk factors into account when analysing the association between wheezing and constipation, other determinants may also explain the association between asthma and functional bowel disorders in other studies. Recently, it has been demonstrated that consumption of fruit and vegetables is associated with a lower prevalence of asthma[47] but also with lower rates of constipation.[48] Another symptom that may overlap wheezing with constipation is gastro-oesophageal reflux disease. Gastro-oesophageal reflux disease is a relatively common disorder in infants and children that has been demonstrated to be associated with respiratory symptoms[49] and functional bowel disorders.[50] Therefore, explaining the association between other respiratory symptoms and asthma, and functional constipation in both children and adults needs further clarification.

CONCLUSION

In a population-based setting, functional constipation and wheezing symptoms may coexist in preschool children. However, this association is not independent and can be mainly explained by infection exposure of the child and antibiotic use. Other potential shared risk factors such as BMI, food allergy, infant nutrition and parental stress do not explain this association. Further research should elucidate whether colonisation plays a role in the explanatory effect of infectious disease in the association between wheezing and constipation, and whether these results also apply to the adult population and to secondary-care patients.

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