



**Co-existence of wheezing and constipation in childhood:
explanations from an epidemiological study"**

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4 1 **Co-existence of wheezing and constipation in childhood:**
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6 2 **explanations from an epidemiological study**
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27 12 **Keywords:** functional constipation, wheezing, eczema
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38 18 **Financial disclosure and conflict of interest:** none
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40 19

41 20 **Abbreviations:** IBS, irritable bowel syndrome; AD, atopic dermatitis; ISAAC, international study of
42
43 21 asthma and allergies in childhood; BMI, body mass index; NOSIK, nijmegenese ouderlijke stress
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45 22 index—kort (parenting stress index—short form); OR, odds ratio; CI, confidence interval; HPA,
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47 23 hypothalamic pituitary-adrenal
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3 30 **CONTRIBUTOR'S STATEMENT:**
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7 32 Jessica Kieffe-de Jong has analyzed the data, written the first draft of the paper, had full access to all
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9 33 the data in the study and takes responsibility for the integrity of the data and the accuracy of the data
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11 34 analysis. She fulfils the criteria as described by the ICMJE as follows:

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13 35 1. Substantial contributions to conception and design, acquisition of data, and analysis and
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15 36 interpretation of the data.
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17 37 2. Drafting the article .
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19 38 3. Final approval of the version to be published.
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23 40 Ankie Lebon has participated in the data analysis and had access to all the data in the study. She
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27 42 1. Substantial contributions to conception and design, acquisition of data, analysis and interpretation
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29 43 of the data.
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33 45 3. Final approval of the version to be published.
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51 54 Henriëtte Moll supervised the study. She fulfils the criteria as described by the ICMJE as follows:

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53 55 1. Substantial contributions to conception and design, acquisition of data, and analysis and
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55 56 interpretation of the data.
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57 57 2. Critical revisions of the paper.
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59 58 3. Final approval of the version to be published
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59 **ABSTRACT**

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61 **Objective:** To assess whether wheezing and atopic dermatitis were associated with constipation in
62 pre-school children and to what extent shared risk-factors contribute to this relationship.

63 **Methods:** A population-based sample of 4651 pre-school children was used. At the age of 24, 36 and
64 48 months, parental report of functional constipation was available according to the ROME II criteria
65 and data on atopic dermatitis and wheezing was available using age-adapted questionnaires from the
66 International Study of Asthma and Allergies in Childhood. Stepwise multivariate analyses were
67 performed to assess whether body mass index, infection exposure, food allergy and infant nutrition,
68 and parental stress explained the association between wheezing, atopic dermatitis and constipation.

69 **Results:** Out of 4651 children, 12-17% had functional constipation between 24 and 48 months.
70 Symptoms of wheezing and atopic dermatitis decreased from 20% and 30% at 24 months to 10% and
71 18% at 48 months. Between the age of 24 and 48 months, wheezing symptoms were significantly
72 associated with functional constipation (aOR: 1.16; 95%CI: 1.01, 1.33) but these results were mainly
73 explained by the child's infections exposure (aOR: 1.10; 95%CI: 0.96 – 1.25). No significant
74 association was found between symptoms of atopic dermatitis and functional constipation (aOR: 1.04;
75 95%CI: 0.91, 1.18).

76 **Conclusions:** These findings suggest that functional constipation frequently co-exists with wheezing
77 in childhood but is mainly explained by the child's infection exposure. Therefore, an independent
78 association between respiratory symptoms and functional bowel disorders as suggested in previous
79 studies may be discussed.

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3 80 **ARTICLE SUMMARY**
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7 82 **Article focus**
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- 9 83 • Both constipation, wheezing and atopic dermatitis are common symptoms in the paediatric
10 population.
11 84
12 85 • Functional bowel disorders is linked with asthma and atopy in previous studies in adults but in
13 children these results are equivocal.
14 86
15 87 • Functional bowel disorders, asthma and atopic disease may share common risk-factors which
16 include overweight, stress, infection exposure, food allergy and nutritional practice during
17 infancy. However, most studies did not take into account for these potential confounders.
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25 91 **Key messages**
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- 27 92 • Wheezing but not atopic dermatitis is associated with functional constipation in pre-school
28 children but this is mainly explained by a history of infections of the child whereas other
29 potential shared-risk factors as BMI, food allergy, timing of introduction of food allergens,
30 breast-feeding duration and parental stress do not have a major role in explaining the
31 association between wheezing and constipation..
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35 96
36 97 • This study suggests that the association between wheezing and functional constipation is not
37 independent in childhood. Further research is needed to explore whether this result also apply
38 to the outcome of asthma.
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45 101 **Strengths**
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- 47 102 • Population-based study population. This study includes a large study population who were not
48 selected according to medical care and, therefore, a high external validity applies to this
49 study.
50 103
51 104
52 105 • This study addresses a topical area that has not had sufficient study and can have a
53 contribution on the discussion how asthma or atopy may be associated with functional bowel
54 disorders. This study took multiple shared risk-factors of wheezing, atopic dermatitis and
55 constipation into account that sheds light on the suggested association in literature.
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110 **Limitations**

- 111 • Symptoms were available only from parental-reported questionnaires. This could have led to
112 misclassification of wheezing, atopic dermatitis and constipation since doctor diagnosis
113 provides a more accurate diagnosis.
- 114 • Early wheezing in infancy is not a sufficient predictor of childhood asthma. Hence, our study
115 precludes conclusions with respect to functional bowel disorders and its link with asthma.
- 116 • No data was available regarding parental concerns of the child's health status. Bias may
117 occur when parents with high concerns are more likely to report symptoms in their child as
118 wheezing, constipation and infectious disease.

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3 119 **INTRODUCTION**
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7 121 Functional bowel disease accounts for the majority of gastrointestinal symptoms worldwide (1). The
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9 122 prevalence of atopic diseases such as asthma and atopic dermatitis is also increasing in Western
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11 123 Countries(2). Several studies linked asthma and atopy in adults with the irritable bowel syndrome
12
13 124 (IBS)(3-6), but in children different results have been described(7-8).

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15 125 Some pathophysiological overlaps may explain the correlation between IBS and atopy. For example,
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17 126 atopic disease, which affects approximately 30% of the population, include food allergies that may
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19 127 cause various organ dysfunction implying that the link between IBS and atopy may be explained by
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21 128 food allergy(9). Likewise, a shared risk-factor for both asthma and functional bowel disorders is
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23 129 obesity. As reported in several studies, asthma is highly prevalent in children with obesity(10) and
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25 130 obesity has been found to be more common in subjects with functional constipation(11).

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27 131 Since both atopy and functional bowel disorders are particularly prevalent in developed countries, a
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29 132 role for the 'hygiene hypothesis' in these two disorders is also proposed. The hygiene hypotheses
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31 133 concedes that current hygiene practices lead to reduced or altered exposure of bacteria and other
32
33 134 micro-organisms that may result in an imbalance of the immune system and microflora early in life
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35 135 (12). Early microbial colonization of the infant's gastro-intestinal tract might reduce the risk of atopic
36
37 136 disorders and altered intestinal flora has been an area of interest for years in both IBS and atopy (13-
38
39 137 14). Finally, studies have addressed the role of stress in the aetiology both of atopic disorders(15)
40
41 138 and functional bowel disorders(16). Prenatal and childhood stress have been suggested to disturb
42
43 139 the regulation of immune and autonomic functions(17) that makes children vulnerable to develop both
44
45 140 atopy and altered bowel habits.

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47 141 To better understand the mechanisms playing a role in these disorders, it is warranted to examine
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49 142 which common risk-factors explain the association between atopy and functional bowel disorders as
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51 143 described in the literature. In addition, most of the exposures associated with disease start early in life
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53 144 and the majority of IBS subjects experience symptoms of constipation that are already present during
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55 145 childhood(18). The aim of our study, therefore, is to examine whether wheezing and atopic dermatitis
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57 146 are associated with functional constipation in childhood. A second aim is to assess if and to what
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59 147 extent cow's milk allergy, overweight, indices of infection exposure and parental stress contribute to
60
148 the association between wheezing, atopic dermatitis and functional constipation in young children.

149 PATIENTS AND METHODS

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151 Participants and study design

152 This study was embedded in the Generation R study, a population-based prospective cohort study
153 from foetal life until young adulthood and has been described in detail previously (19-20). In total,
154 7893 mothers with a delivery date between April 2002 and January 2006 provided consent for follow-
155 up. The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre,
156 Rotterdam, The Netherlands.

157

158 Functional constipation

159 At the age of 24, 36 and 48 months, stool pattern of the child was assessed by using a questionnaire
160 (response rates: 70%, 64% and 63% respectively). Accordingly, the outcome of functional
161 constipation was defined in this study if at least one of the following symptoms of ROME II(21) were
162 reported: 1) defecation frequency <3 times a week for at least 2 weeks or 2) predominantly hard
163 faeces for the majority of stools for at least 2 weeks.

164 To avoid the influence of metabolic disorders and clustering, children were excluded in the analyses
165 in case of the following: 1) twinborn ($n=238$), 2) siblings within the Generation R cohort ($n=343$) 3)
166 presence of a congenital heart condition ($n=47$), 4) history of anaemia ($n=58$) or 5) growth
167 retardation defined as height for age < -2SD based on the Netherlands growth curves ($n=163$)(22).

168

169 Wheezing and atopic dermatitis

170 Information regarding atopic dermatitis and wheezing was obtained using core questions from an age-
171 adapted version of the validated "International Study of Asthma and Allergies in Childhood" (ISAAC)
172 and doctor-attendance of eczema or episodes of itchy rash at the age of 24, 36 and 48 months(23).
173 These outcomes were defined dichotomously: presence or absence of eczema and presence or
174 absence of wheezing at 24, 36 and 48 months of age.

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179 **Covariates**

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

183 At the age of 6 and 12 months, questionnaire data were available about a history of doctor-attended
184 food allergy in the first year of life and the introduction of food allergens and breast-feeding duration
185 that we described in detail in a previous study (25).

186 At the age of 24, 36 and 48 months, questionnaire data was available for the following indicators
187 which were used as proxy for infection exposure of the child: attendance of daycare and doctor-
188 attendance for fever ($> 38^{\circ}\text{C}$) accompanied with symptoms of cough, runny nose, earache, diarrhoea
189 or vomiting in the past year.

190 The level of parental stress was assessed at the child's age of 24 months by using the Nijmeegse
191 Ouderlijke Stress Index—Kort (NOSIK(26)), the Dutch version of the Parenting Stress Index—Short
192 Form that has been shown to be reliable and valid(27). The NOSIK comprises two domains consisting
193 of 25 items; parenting stress due to parent factors and parenting stress due to child factors. Only the
194 items on the parent domain were available in this study ($n=15$). Items were assessed on a 4-point
195 scale and the scores were summed and divided by the number of fulfilled items. Higher scores
196 indicate greater levels of parental stress. In addition, these scores were demonstrated to be an
197 important predictor of somatic complaints in this birth cohort (28).

198 Other variables possibly related to functional constipation, wheezing and atopic dermatitis were
199 obtained from prenatal and postnatal questionnaires filled in by the parents (ethnicity, mother's
200 educational level, maternal and paternal history of atopic dermatitis, asthma, hay fever, allergy to
201 house dust and prenatal smoking). From obstetric records assessed in mid-wife practices and from
202 hospital registries data on gender, birth weight and gestational age were available as described
203 previously(19-20).

204

205 **Statistical analysis**

206 Firstly, univariate analyses were performed by using Chi-square tests for categorical variables and the
207 Mann-Whitney U test for continuous variables. Secondly, hierarchical logistic regression analyses (29)
208 by using generalized estimating equations (GEE) were performed. GEE analysis assesses the

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3 209 association by correction for the within subject's dependence as a result of the repeated observations
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5 210 on wheezing, eczema and functional constipation (30). Since the within-subject correlation coefficient
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7 211 for wheezing, atopic dermatitis and functional constipation at the three time points were comparable
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9 212 ($r=0.3-0.4$), an exchangeable working correlation structure was used in the GEE analyses.
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11 213 Generalized Estimation equations were performed with functional constipation compared to no
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13 214 constipation as dependent variables and the presence of any wheezing or atopic dermatitis in the past
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15 215 year as independent variable. In addition, model 1 was adjusted for time, and major child
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17 216 characteristics as gender, mother's educational level, ethnicity (western versus non-western), birth
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19 217 weight, gestational age, maternal smoking and family history of atopic disorders (ie. asthma or atopic
20
21 218 dermatitis). Subsequently to assess whether the association between functional constipation and
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23 219 atopy was dependent on BMI, infection exposure, food allergy and infant nutrition, or parental stress;
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25 220 the following variables were added separately to model 1: BMI (model 2), daycare attendance and
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27 221 history of respiratory or gastrointestinal infections in the previous year (model 3), history of food
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29 222 allergy, breast-feeding duration, and introduction of food allergens ≤ 6 months (model 4) and NOSIK
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31 223 score (model 5). To test whether the associations between wheezing, atopic dermatitis and functional
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33 224 constipation were different at the age of 24, 36 and 48 months, effect modification by time was
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35 225 evaluated by adding the product-term of wheezing/atopic dermatitis and time (e.g. wheezing*time) as
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37 226 independent variable to the crude GEE model.
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39 227 Non-response analysis at 48 months showed that non-responders slightly reported more often
40
41 228 wheezing at 36 months (17.1% vs. 11.9%, $P<0.01$), functional constipation at 24 and 36 months (18%
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43 229 vs. 11.3% and 23.2 and 16.2% respectively, $P<0.01$), had more often mothers with a lower social
44
45 230 economic background (16.6% vs. 5.8% $P<0.01$) and a non-western ethnicity (54.5% vs. 25.2%,
46
47 231 $P<0.01$) and smoked more often during pregnancy (77.4% vs. 65.5% $P<0.01$). To reduce potential
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49 232 bias associated with missing data, missing values (approximately 0.1% - 40%) were multiple imputed
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51 233 ($n=5$ imputed datasets). The multiple imputation was based on the correlation between each variable
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53 234 with missing values with the other subject characteristics as described previously by Sterne et al(31).
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55 235 Data were analyzed in each data set separately to obtain desired effect sizes and standard errors.
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57 236 Finally, the results of the 5 imputed analyses were pooled and reported in this paper as odds ratios
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59 237 (OR) and 95% confidence interval (95%CI). A P -value <0.05 was considered as statistically
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3 238 significant. Statistical analyses were carried out by using SPSS 17.0 for Windows (SPSS Inc,
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5 239 Chicago, IL).
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240 **RESULTS**

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242 Characteristics of the study population are presented in table 1. Prevalence of functional constipation
243 remained relatively stable between 12% and 14% at the age of 24, 36 and 48 months. The highest
244 prevalence of wheezing symptoms during childhood was at the age of 24 months (20%) and this
245 decreased to a prevalence of 12% at 36 and 48 months. The prevalence of atopic dermatitis
246 decreased from 30% at the age of 24 months to 20% and 18% at the age of 36 and 48 months
247 respectively. Out of 4651 children, 3-4% had persistent symptoms of functional constipation, atopic
248 dermatitis or wheezing at all time points (i.e. at 24, 36 and 48 months).

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

255 The distribution of wheezing and atopic dermatitis in children with and without functional constipation
256 between 24 and 48 months is shown in figure 1. Wheezing symptoms were significantly associated
257 with symptoms of functional constipation in childhood but no significant association was found
258 between atopic dermatitis and functional constipation after adjustment for gender, birth weight,
259 gestational age, maternal smoking, maternal educational background, ethnicity and parental history of
260 atopy (Table 2; model 1). The greatest alteration in the effect estimate in the analyses of wheezing
261 and functional constipation was found after adjustment for infection exposure of the child, which
262 mainly explained the association between wheezing and constipation (Table 2; model 3). Adjustment
263 in addition to model 1 for other potential shared risk-factors did not explain the association between
264 wheezing and functional constipation (Table 2).

265 No effect modification by the different time points (ie. 24, 36 and 48 months) was found for the
266 analyses between wheezing, atopic dermatitis and functional constipation ($P=0.57$ for statistical
267 interaction between wheezing and time and $P=0.43$ for statistical interaction between eczema and
268 time).

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3 269 **DISCUSSION**
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7 271 This study shows that wheezing symptoms and functional constipation frequently coexist in pre-school
8 children but this relationship was markedly influenced by infection exposure of the child. Other
9 272 potential shared-risk factors as BMI, history of food allergy, infant nutrition, and parental stress did not
10 273 explain the association between wheezing and constipation.
11 274

12 275 Several studies in adults showed a link between IBS and asthma (3-6), but results in children are
13 276 inconsistent so far. In addition, Caffarelli et al. demonstrated no difference in constipation in allergic
14 277 children compared to controls(8). Also, Simeone et al. showed no association between constipation
15 278 and atopy in young children(7) whereas a small increase in IBS prevalence over time was observed in
16 279 subjects with asthma aged 5-65 years(5).

17 280 The strength of our study lays in the large study population who were not selected according to
18 281 medical care, thereby diminishing selection bias. Earlier studies have been carried out in selected
19 282 populations of patients seeking medical care. This could lead to selection towards for instance
20 283 children at high risk for atopic constitution that may have a higher proportion of IBS than in the
21 284 general population. Also, most studies did not take account for potential shared risk-factors that may
22 285 improperly suggest that the relationship is independent. The broad range of available data of potential
23 286 confounders in our study elucidates the contribution of shared risk-factors in the association between
24 287 atopy and functional bowel disorders.

25 288 Our study confirmed that the association between wheezing and functional constipation was
26 289 influenced by infection exposure. Respiratory infections are risk-factors for asthma(32) but gastro-
27 290 intestinal infections are also associated with IBS(33). It is, therefore, more likely that infection
28 291 exposure of the child increases the risk of wheezing and constipation rather than that it acts
29 292 protectively as suggested by other studies. In addition, from animal studies it is known that early
30 293 exposure to micro-organisms is required to have a proper maturation of the immune system in and
31 294 outside the gut that may have a protective effect on allergic disease (34). Also, it is speculated that
32 295 childhood exposure to infection is responsible for low prevalence of IBS in developing countries and
33 296 that early colonization may enable the intestinal epithelium to respond efficiently to antigenic
34 297 challenge that may result in a pronounced amelioration of gastro-intestinal symptoms after
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3 298 infections(35). Further in-depth research exploring the process of colonization may elucidate the
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5 299 contribution of infections in the association between wheezing and constipation.

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7 300 Underlying mechanisms as altered contractility of smooth muscles cells and dysfunction of the
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9 301 autonomic nervous system that can be triggered by emotional stress is suggested to play a common
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11 302 role in asthma and bowel disorders (15). Since parental stress was demonstrated to be an important
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13 303 predictor of somatic symptoms in children in a previous study (28) we expected a certain explanatory
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15 304 effect of parental stress on the association between wheezing and constipation. However, adjustment
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17 305 for parental stress only slightly weakened the association between wheezing and functional
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19 306 constipation. Nevertheless, it may well be that stress operates at the spectrum of infection exposure
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21 307 of the child since prenatal and postnatal stress can be associated with an increased risk of infectious
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23 308 disease in the offspring (36-37) which itself was thus of major importance in explaining the association
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25 309 between wheezing and constipation.

26
27 310 To appreciate the results some limitations of this study should be considered. We had data on
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29 311 functional constipation by the use of parental derived questionnaires and no additional information
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31 312 from medical records or physical examinations was available. Therefore, some subjects may be
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33 313 misclassified concerning the diagnosis of functional constipation. However, only if this
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35 314 misclassification is also related to wheezing, this misclassification has overestimated our results.

36
37 315 It has been suggested that food allergy in early infancy may be a risk factor for wheezing attacks(38).
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39 316 The limited clarifying effect of food allergy on our study results might be explained by the fact that not
40
41 317 all food-sensitized children have manifest food allergy(39). Consequently, sensitization to food
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43 318 allergens, as demonstrated by tests of specific serum IgE, might be a better explanation rather than
44
45 319 report of food allergy or timing of introduction of food allergens in the association between atopic
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47 320 disorders and functional constipation. We did not have other evidence of food allergy in the first year
48
49 321 available than the parental report of doctor-diagnosed food allergy. It is known that self-report of food
50
51 322 allergy overestimates the true prevalence of food allergy. On the other hand, we expect that this
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53 323 information bias may have led to over-adjusted odds ratios and thereby an underestimation of the
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55 324 final results because parents who believe that their child had food allergy may also have reported
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57 325 symptoms related to atopic diseases or constipation more frequently. Nevertheless, bias may occur
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59 326 when parents with high concerns are more likely to report symptoms in their child as wheezing,
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327 constipation and infectious disease. Adjustment for NOSIK score may slightly reduce this effect.

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3 328 However, it only consisted of information on parental stress due to parent factors but not stress due to
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5 329 the child's health status.

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7 330 At last, previous studies on functional bowel disorders focused on the link with asthma. Early
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9 331 wheezing in infancy is not a major predictor of childhood asthma(32). Hence, our results do not allow
10
11 332 for conclusions regarding functional constipation and childhood asthma. Although we took several
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13 333 shared-risk factors into account when analyzing the association between wheezing and constipation,
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15 334 other determinants may also explain the association between asthma and functional bowel disorders
16
17 335 in other studies. Recently it has been demonstrated that consumption of fruit and vegetables is
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19 336 associated with a lower prevalence of asthma (40) but also with constipation in children(41). Another
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21 337 symptom that may overlap wheezing with constipation is gastro-oesophageal reflux disease. Gastro-
22
23 338 oesophageal reflux disease is a relatively common disorder in infants and children which has been
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25 339 demonstrated to be associated with respiratory symptoms(42) and functional bowel disorders(43).
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27 340 Therefore, explaining the association between other respiratory symptoms and asthma, and functional
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29 341 constipation in both children and adults needs further clarification.

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31 342

32 33 343 **Conclusion**

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35 344 In a population-based setting, functional constipation and wheezing symptoms may coexist in pre-
36
37 345 school children. However, this association is not independent and can be mainly explained by
38
39 346 infection exposure of the child. Other potential shared risk-factors as BMI, food allergy, infant nutrition
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41 347 and parental stress do not explain this association. Further research should elucidate whether
42
43 348 colonization plays a role in the explanatory effect of infectious disease in the association between
44
45 349 wheezing and constipation and if these results do also apply to the adult population and to secondary
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47 350 care patients.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	X
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	X
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	X
		(b) Describe any methods used to examine subgroups and interactions	X
		(c) Explain how missing data were addressed	X
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X
		(b) Give reasons for non-participation at each stage	X (non-response Analyse described)
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	X
		(b) Indicate number of participants with missing data for each variable of interest	

		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	X
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X
		(b) Report category boundaries when continuous variables were categorized	X
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	X
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X
Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

Table 1. Maternal and Child Characteristics of the Study Population (N=4651)

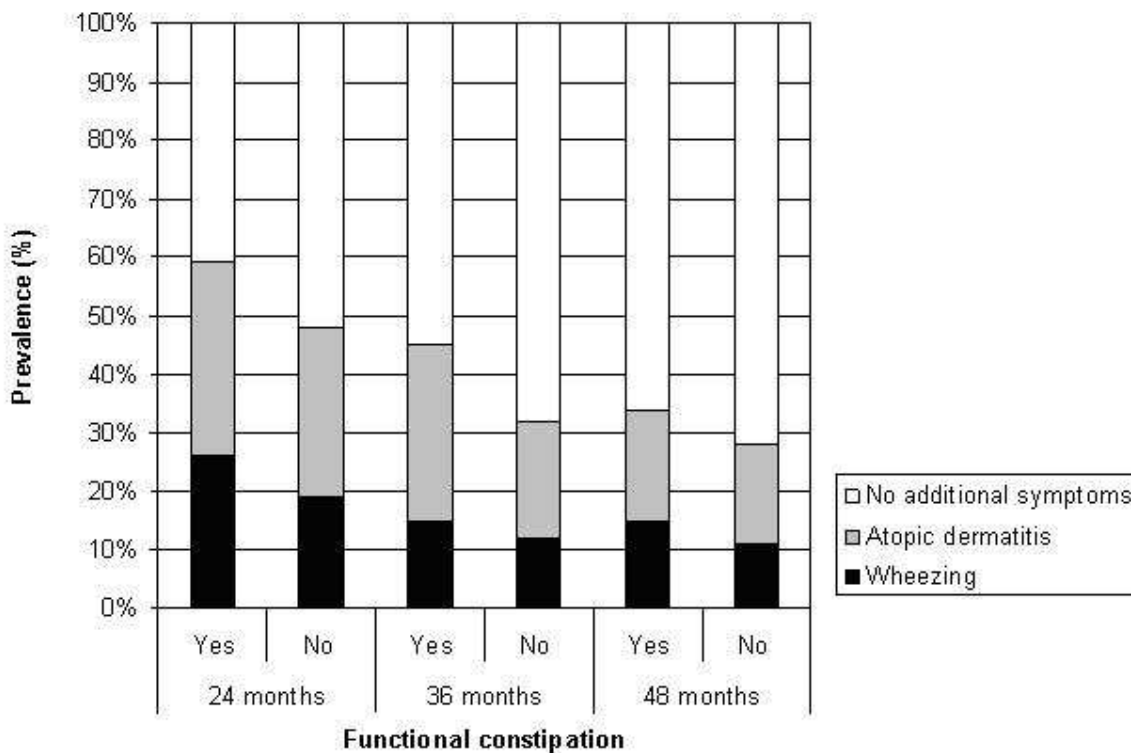
	N
	(%)
Mother	
Educational level of mother	
Low	774 (16%)
Midlow	1365 (29%)
Midhigh	1148 (25%)
High	1363 (29%)
Maternal smoking	1154 (25%)
Maternal alcohol consumption	1869 (40%)
Parental stress score mean (SD)	0.36 (0.30)
History of atopy	2238 (48%)
Child	
Male N (%)	2333 (50%)
Ethnicity N (%)	
Dutch/other 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 \leq 6 months	3472 (75%)
Duration of breast-feeding in months mean (SD)	4.8 (3.8)
Crèche attendance in first two years of life	3579 (77%)
Overweight in second year of life	915 (20%)

Table 2. Hierarchical logistic 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		
Crude	Reference	1.11 (0.98 – 1.27)
Model 1	Reference	1.16* (1.01 – 1.31)
Model 2 (body mass index)	Reference	1.16* (1.01 – 1.32)
Model 3 (infection exposure)	Reference	1.10 (0.96 – 1.25)
Model 4 (food allergy & infant nutrition)	Reference	1.15* (1.01 – 1.32)
Model 5 (parental stress)	Reference	1.14* (1.00 – 1.30)
Eczema		OR
		95%CI
Crude	Reference	1.03 (0.91 – 1.16)
Model 1	Reference	1.04 (0.91 – 1.18)
Model 2 (body mass index)	Reference	1.04 (0.91 – 1.18)
Model 3 (infection exposure)	Reference	1.04 (0.91 – 1.19)
Model 4 (food allergy & infant nutrition)	Reference	1.03 (0.60 – 1.18)
Model 5 (parental stress)	Reference	1.03 (0.90 – 1.18)

OR: odds ratio; 95%CI: 95% confidence interval; * $P < 0.05$; Model 1: baseline model adjusted for time, 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 two years of life; 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.

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



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Association between wheezing and childhood in pre-school children: explanations from a longitudinal birth cohort.

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Manuscripts

Is there an association between wheezing and constipation in pre-school children?**Explanations from a longitudinal birth-cohort**

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Keywords: functional constipation, wheezing, eczema

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Financial disclosure and conflict of interest: none

Abbreviations: IBS, irritable bowel syndrome; AD, atopic dermatitis; ISAAC, international study of asthma and allergies in childhood; BMI, body mass index; NOSIK, nijmegenese ouderlijke stress index—kort (parenting stress index—short form); OR, odds ratio; CI, confidence interval; HPA, hypothalamic pituitary-adrenal

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3 31 **CONTRIBUTOR'S STATEMENT:**
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7 33 Involvement in the design, planning, conducting the study and data collection: H.A. Moll, V.W.V.

8
9 34 Jaddoe, A. Hofman, J.C. de Jongste, J.C. Kiefte-de Jong. Statistical analyses, interpreting data: J.C.

10
11 35 Kiefte-de Jong, H.A. Moll, A. Lebon. Drafting the final manuscript: J.C. Kiefte-de Jong, H.A. Moll.

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13 36 All authors critically reviewed the manuscript and approved the final version of the manuscript to be

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38 **ABSTRACT**

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40 **Objective:** To assess whether wheezing and atopic dermatitis were associated with constipation in
41 pre-school children and to what extent shared risk-factors contribute to this relationship.

42 **Methods:** A population-based sample of 4651 pre-school children was used. At the age of 24, 36 and
43 48 months, parental report of functional constipation was available according to the ROME II criteria
44 and data on atopic dermatitis and wheezing was available using age-adapted questionnaires from the
45 International Study of Asthma and Allergies in Childhood. Stepwise multivariate analyses were
46 performed to assess whether body mass index, infection exposure, food allergy and infant nutrition,
47 and parental stress explained the association between wheezing, atopic dermatitis and constipation.

48 **Results:** Out of 4651 children, 12-17% had functional constipation between 24 and 48 months.
49 Symptoms of wheezing and atopic dermatitis decreased from 20% and 30% at 24 months to 10% and
50 18% at 48 months. Between the age of 24 and 48 months, wheezing symptoms were significantly
51 associated with functional constipation (OR: 1.17; 1.02 – 1.34) but these results were mainly
52 explained by the child's infections exposure and use of antibiotics (aOR: 1.08; 95%CI: 0.95 – 1.24).
53 No significant association was found between symptoms of atopic dermatitis and functional
54 constipation (OR: 1.08; 95%CI: 0.94, 1.23).

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

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3 59 **ARTICLE SUMMARY**
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7 61 **Article focus**

- 9 62 • Constipation, wheezing and atopic dermatitis are common symptoms in children.
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11 63 • Functional bowel disorders are linked with asthma and atopy in adults.
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13 64 • Functional bowel disorders, asthma and atopic disease may share common risk-factors that
14
15 65 may explain co-existence of these symptoms.
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19 67 **Key messages**

- 20
21 68 • Wheezing but not atopic dermatitis is associated with functional constipation in pre-school
22
23 69 children. The association is mainly explained by a history of infection exposure.
24
25 70 • Hence the association between wheezing and functional constipation is not independent.
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27 71 Further research is needed to explore whether this result also apply to the outcome of
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29 72 asthma.
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33 74 **Strengths**

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35 75 • Population-based study population. The study group were not selected according to medical
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37 76 care.
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39 77 • This study addresses a topical area that has not had sufficient study and can have a
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41 78 contribution on the discussion how asthma or atopy may be associated with functional bowel
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43 79 disorders.
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45 80 • This study took multiple shared risk-factors of wheezing and constipation into account that
46
47 81 sheds light on the suggested association in literature.
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51 83 **Limitations**

- 52
53 84 • Symptoms were available only from parental-reported questionnaires. This may led to
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55 85 misclassification of the symptoms.
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57 86 • Early wheezing in infancy is not a sufficient predictor of childhood asthma.
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3 87 • No data was available regarding parental concerns of the child's health status. Bias may
4 occur when parents with high concerns are more likely to report symptoms in their child as
5 88 wheezing, constipation and infectious disease.
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9 90 • No data was available on IgE sensitization, thus the study preclude conclusions on the
10 association between allergic disease and constipation.
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92 INTRODUCTION

93
94 Functional constipation and other functional bowel diseases account for the majority of
95 gastrointestinal symptoms worldwide and is increasing in the Western world (1-2). The prevalence of
96 atopic diseases such as asthma and atopic dermatitis is also increasing in Western Countries(3). In
97 adults, several studies have suggested that asthma or atopy may be linked with constipation(4) or
98 other functional gastro-intestinal disorders (5-8). In children, different results with regard to
99 constipation have been described (9-10). Some pathophysiological overlaps may explain the
100 proposed correlation between constipation and atopy. For example, atopic disease, which affects
101 approximately 30% of the population, include food allergies that may cause various organ dysfunction
102 implying that the link between constipation and atopy may be explained by food allergy(11). Likewise,
103 a shared risk-factor for both asthma and constipation is obesity. As reported in several studies,
104 asthma is highly prevalent in children with obesity(12) and obesity has been found to be more
105 common in subjects with functional constipation(13).

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

116 To better understand the mechanisms playing a role in these disorders, it is warranted to examine
117 which common risk-factors explain the association between atopy and constipation as described in
118 the literature. In addition, most of the exposures associated with disease start early in life and the
119 majority of adults with other functional bowel disorders experience symptoms of functional
120 constipation that are already present during childhood (20). The aim of our study, therefore, is to
121 examine whether wheezing and atopic dermatitis are associated with functional constipation in

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122 childhood. A second aim is to assess if and to what extent cow's milk allergy, overweight, indices of
123 infection exposure and parental stress contribute to the association between wheezing, atopic
124 dermatitis and functional constipation in young children.

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125 PATIENTS AND METHODS

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127 Participants and study design

128 This study was embedded in the Generation R study, a population-based prospective cohort study
129 from foetal life until young adulthood and has been described in detail previously (21-22). In total,
130 7893 mothers with a delivery date between April 2002 and January 2006 provided consent for follow-
131 up. The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre,
132 Rotterdam, The Netherlands.

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134 Functional constipation

135 At the age of 24, 36 and 48 months, stool pattern of the child was assessed by using a questionnaire
136 (response rates: 70%, 64% and 63% respectively). Accordingly, the outcome of functional
137 constipation was defined in this study if at least one of the following symptoms of ROME II(23) were
138 reported: 1) defecation frequency <3 times a week for at least 2 weeks or 2) predominantly hard
139 faeces for the majority of stools for at least 2 weeks.

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

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146 Wheezing and atopic dermatitis

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

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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 about 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, yoghurt, porridge, egg, bread or biscuits, peanuts, nuts and soy products. The reported introduction of these food products were 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 their infant's diet but at the infant's age of 6 months the parent filled in that the infant consumed porridge based on wheat for at least once, then the introduction of this gluten was considered to be before or equal to 6 months of age. 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 was 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 with 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 by 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 4-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).

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3 185 Other variables possibly related to functional constipation, wheezing and atopic dermatitis were
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5 186 obtained from prenatal and postnatal questionnaires filled in by the parents (ethnicity, mother's
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7 187 educational level, maternal and paternal history of atopic dermatitis, asthma, hay fever, allergy to
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9 188 house dust and prenatal smoking). From obstetric records assessed in mid-wife practices and from
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11 189 hospital registries data on gender, birth weight and gestational age were available as described
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13 190 previously(21-22).

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16 17 192 **Statistical analysis**

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19 193 Firstly, univariate analyses were performed by using Chi-square tests for categorical variables and the
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21 194 Mann-Whitney U test for continuous variables. Secondly, logistic regression analyses by using
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23 195 generalized estimating equations (GEE) were performed. Briefly, regression analysis by GEE
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25 196 assesses the association between two variables by correction for the within subject's dependence as
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27 197 a result of the repeated observations on wheezing, eczema and functional constipation since
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29 198 repeated measurements within one individual are frequently correlated (32). The within-subject
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31 199 correlation coefficient for wheezing, atopic dermatitis and functional constipation at the three time
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33 200 points were comparable ($r=0.3-0.4$). Therefore, an exchangeable working correlation structure was
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35 201 used in the GEE analyses as adjustment for the dependency between the repeated measurements .
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37 202 Logistic regression analysis with GEE was performed with functional constipation compared to no
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39 203 constipation as dependent variables and the presence of any wheezing or atopic dermatitis in the past
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41 204 year as independent variable. In addition, model 1 was adjusted for time (i.e. age), and major child
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43 205 characteristics as gender, mother's educational level, ethnicity (western versus non-western), birth
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45 206 weight, gestational age, maternal smoking and family history of atopic disorders on the basis factors
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47 207 associated with asthma-like symptoms and constipation in literature(28, 33) . Subsequently, to assess
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49 208 whether the association between functional constipation and atopy was dependent on BMI, infection
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51 209 exposure, food allergy and infant nutrition, or parental stress; the following variables were added
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53 210 separately to model 1: BMI (model 2), daycare attendance, use of antibiotics in previous year, and
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55 211 history of respiratory or gastrointestinal infections in the previous year (model 3), history of food
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57 212 allergy, breast-feeding duration, and introduction of food allergens ≤ 6 months (model 4), and parental
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59 213 stress score (NOSIK) (model 5). To test whether the associations between wheezing, atopic
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214 dermatitis and functional constipation were different at the age of 24, 36 and 48 months, effect

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3 215 modification by time was evaluated by adding the product-term of wheezing/atopic dermatitis and time
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5 216 (e.g. wheezing*time) as independent variable to the crude GEE model.
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7 217 To reduce potential bias associated with missing data, missing values (approximately 0.1% - 40%)
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9 218 were multiple imputed ($n=5$ imputed datasets). The multiple imputation was based on the correlation
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11 219 between each variable with missing values with the other subject characteristics as described
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13 220 previously by Sterne et al(34). Data were analyzed in each data set separately to obtain desired effect
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15 221 sizes and standard errors. Finally, the results of the 5 imputed analyses were pooled and reported in
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17 222 this paper. In addition, the pooled odds ratio (OR) was calculated by taking the average of the OR's of
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19 223 the 5 imputed datasets. The pooled standard error to assess the 95% confidence intervals (95%CI)
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21 224 was then calculated by using Ruben's rule(35): $\sqrt{[W+(1+1/m)*B]}$ with W = mean variance of the effect
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23 225 size within the imputed datasets; B =variance of the effect sizes between the imputed datasets; m =
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25 226 number of imputed datasets ($n=5$).A P -value <0.05 was considered as statistically significant.
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27 227 Statistical analyses were carried out by using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL).
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228 RESULTS

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230 Characteristics of the study population are presented in table 1.

231 Non-response analysis at 48 months showed that non-responders slightly reported more often
232 wheezing at 36 months (17.1% vs. 11.9%, $P<0.01$), functional constipation at 24 and 36 months (18%
233 vs. 11.3% and 23.2 and 16.2% respectively, $P<0.01$), had more often mothers with a lower social
234 economic background (16.6% vs. 5.8% $P<0.01$) and a non-western ethnicity (54.5% vs. 25.2%,
235 $P<0.01$) and smoked more often during pregnancy (77.4% vs. 65.5%, $P<0.01$).

236 Prevalence of functional constipation remained relatively stable between 12% and 14% at the age of
237 24, 36 and 48 months. The highest prevalence of wheezing symptoms during childhood was at the
238 age of 24 months (20%) and this decreased to a prevalence of 12% at 36 and 48 months. The
239 prevalence of atopic dermatitis decreased from 30% at the age of 24 months to 20% and 18% at the
240 age of 36 and 48 months respectively. Out of 4651 children, 3-4% had persistent symptoms of
241 functional constipation, atopic dermatitis or wheezing at all time points (i.e. at 24, 36 and 48 months).

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

248 The distribution of wheezing and atopic dermatitis in children with and without functional constipation
249 between 24 and 48 months is shown in figure 1. Wheezing symptoms were significantly associated
250 with symptoms of functional constipation in childhood but no significant association was found
251 between atopic dermatitis and functional constipation in univariate analyses (Table 2). After
252 adjustment for age, gender, birth weight, gestational age, maternal smoking, maternal educational
253 background, ethnicity and parental history of atopy, wheezing remained significantly associated with
254 functional constipation (Table 2; model 1), which was also the case after stepwise adjustment for BMI,
255 history of food allergy and infant nutrition and parental stress (Table 2; model 2, 4 and 5). The
256 greatest alteration in the effect estimate in the analyses of wheezing and functional constipation was
257 found after adjustment for infection exposure and use of antibiotics of the child, which mainly

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3 258 explained the association between wheezing and constipation (Table 2; model 3). Adjustment in
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5 259 addition to model 1 for other potential shared risk-factors did not explain the association between
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7 260 wheezing and functional constipation (Table 2).
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9 261 The results between wheezing and constipation did not significantly differ by the different time points
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11 262 of 24, 36 and 48 months ($P=0.57$ for statistical interaction between wheezing and age and $P=0.43$ for
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13 263 statistical interaction between eczema and age).

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3 264 **DISCUSSION**

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7 266 This study shows that wheezing symptoms and functional constipation frequently coexist in pre-school
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9 267 children but this relationship was markedly influenced by infection exposure of the child. Other
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11 268 potential shared-risk factors as BMI, history of food allergy, infant nutrition, and parental stress did not
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13 269 explain the association between wheezing and constipation.

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15 270 Several studies in adults showed a link between functional bowel disorders and asthma (5-8), but
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17 271 different results in children are described so far. In addition, Caffarelli et al. demonstrated no
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19 272 difference in constipation in allergic children compared to controls(36) but reported that other
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21 273 gastrointestinal symptoms as diarrhoea and vomiting are more prevalent in children with atopic
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23 274 eczema than in controls(10). Also, Simeone et al. showed no association between constipation and
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25 275 atopy in young children(9) whereas a small increase in the prevalence irritable bowel syndrome over
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27 276 time was observed in subjects with asthma aged 5-65 years(7). Yet, Leander et al(4) showed recently
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29 277 that constipation was associated with asthma independently of age (9)

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31 278 The strength of our study lays in the large study population who were not selected according to
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33 279 medical care, thereby diminishing selection bias. Earlier studies have been carried out in selected
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35 280 populations of patients seeking medical care. This could lead to selection towards for instance
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37 281 children at high risk for atopic constitution that may have a higher proportion of functional bowel
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39 282 disorders than in the general population. Also, most studies did not take account for potential shared
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41 283 risk-factors that may improperly suggest that the relationship is independent. The broad range of
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43 284 available data of potential confounders in our study elucidates the contribution of shared risk-factors
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45 285 in the association between atopy and functional bowel disorders.

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47 286 Our study confirmed that the association between wheezing and functional constipation was
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49 287 influenced by infection exposure. This finding can be explained in several ways. First, respiratory
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51 288 infections are risk-factors for wheezing and asthma (26) but gastro-intestinal infections are also
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53 289 associated with constipation (37). During for example an influenza-like illnesses, both respiratory and
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55 290 gastrointestinal symptoms may co-exist (38-39) and may clarify that our association wheezing and
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57 291 constipation is explained by history of infections as defined by fever accompanied with diarrhoea or
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59 292 respiratory symptoms. Second, from animal studies it is known that very early exposure to micro-
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293 organisms, for example by crowding or infections earlier in life, is required to have a proper maturation

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3 294 of the immune system in and outside the gut which may have a protective effect on allergic disease
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5 295 (40). Also, it is speculated that frequent exposure to childhood infections is responsible for the low
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7 296 prevalence of functional bowel disorders in developing countries and that early colonization may
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9 297 enable the intestinal epithelium to respond efficiently to antigenic challenge that may result in a
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11 298 pronounced amelioration of gastro-intestinal symptoms after infections (41). However, if the latter was
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13 299 the case in our study, we would expect that adjustment for infection exposure would make the
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15 300 association between wheezing and constipation even stronger instead of weaker. Further in-depth
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17 301 research exploring the process of colonization may elucidate the contribution of infections and
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19 302 exposure to microorganisms in the association between wheezing and constipation.
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21 303 Underlying mechanisms as altered contractility of smooth muscles cells and dysfunction of the
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23 304 autonomic nervous system that can be triggered by emotional stress is suggested to play a common
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25 305 role in asthma and constipation (17-18). Since parental stress was demonstrated to be an important
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27 306 predictor of somatic symptoms in children in a previous study (31) we expected a certain explanatory
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29 307 effect of parental stress on the association between wheezing and constipation. However, adjustment
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31 308 for parental stress only slightly weakened the association between wheezing and functional
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33 309 constipation. Nevertheless, it may well be that stress operates at the spectrum of infection exposure
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35 310 of the child since prenatal and postnatal stress can be associated with an increased risk of infectious
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37 311 disease in the offspring (42-43) which itself was thus of major importance in explaining the association
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39 312 between wheezing and constipation.
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41 313 To appreciate the results some limitations of this study should be considered. We had data on
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43 314 functional constipation by the use of parental derived questionnaires and no additional information
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45 315 from medical records or physical examinations was available. Therefore, some subjects may be
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47 316 misclassified concerning the diagnosis of functional constipation. However, only if this
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49 317 misclassification is also related to wheezing, this misclassification has overestimated our results.
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51 318 Loss to follow-up is a common phenomenon in large birth-cohort studies. Relative to other birth cohort
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53 319 studies, the participation rate of our study was high (60-70% in our study group versus 30-40% in
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55 320 other studies)(44). As in most other studies, the non-response analyses showed that the participation
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57 321 in our study was selective. Nevertheless, this would only have influenced our results when the
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59 322 association between wheezing and constipation would be completely different among participants of
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323 this study relative to those who did not participate(44). It has been suggested that food allergy in early

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3 324 infancy may be a risk factor for wheezing attacks(45). The limited clarifying effect of food allergy on
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5 325 our study results might be explained by the fact that not all food-sensitized children have manifest
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7 326 food allergy(46). Consequently, sensitization to food allergens, as demonstrated by tests of specific
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9 327 serum IgE, might be a better explanation rather than report of food allergy or timing of introduction of
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11 328 food allergens in the association between atopic disorders and functional constipation. We did not
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13 329 have other evidence of food allergy in the first year available than the parental report of doctor-
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15 330 diagnosed food allergy. It is known that self-report of food allergy overestimates the true prevalence of
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17 331 food allergy. On the other hand, we expect that this information bias may have led to over-adjusted
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19 332 odds ratios and thereby an underestimation of the final results because parents who believe that their
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21 333 child had food allergy may also have reported symptoms related to atopic diseases or constipation
22
23 334 more frequently. Nevertheless, bias may occur when parents with high concerns are more likely to
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25 335 report symptoms in their child as wheezing, constipation and infectious disease. Adjustment for
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27 336 NOSIK score may slightly reduce this effect. However, it only consisted of information on parental
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29 337 stress due to parent factors but not stress due to the child's health status.

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31 338 **At last, previous studies on functional bowel disorders focused on the link with asthma and allergic**
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33 339 **disease. Early wheezing in infancy is not a major predictor of childhood asthma (26) and we did not**
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35 340 **have data on allergic sensitization as measured by IgE. Hence, our results do not allow for**
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37 341 **conclusions regarding functional constipation and childhood asthma and allergic disease.** Although
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39 342 we took several shared-risk factors into account when analyzing the association between wheezing
40
41 343 and constipation, other determinants may also explain the association between asthma and functional
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43 344 bowel disorders in other studies. Recently it has been demonstrated that consumption of fruit and
44
45 345 vegetables is associated with a lower prevalence of asthma (47) but also with constipation in
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47 346 children(48). Another symptom that may overlap wheezing with constipation is gastro-oesophageal
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49 347 reflux disease. Gastro-oesophageal reflux disease is a relatively common disorder in infants and
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51 348 children which has been demonstrated to be associated with respiratory symptoms(49) and functional
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53 349 bowel disorders(50). Therefore, explaining the association between other respiratory symptoms and
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55 350 asthma, and functional constipation in both children and adults needs further clarification.

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3 354 **Conclusion**
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5 355 In a population-based setting, functional constipation and wheezing symptoms may coexist in pre-
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7 356 school children. However, this association is not independent and can be mainly explained by
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9 357 infection exposure of the child and antibiotic use. Other potential shared risk-factors as BMI, food
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11 358 allergy, infant nutrition and parental stress do not explain this association. Further research should
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13 359 elucidate whether colonization plays a role in the explanatory effect of infectious disease in the
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15 360 association between wheezing and constipation and if these results do also apply to the adult
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17 361 population and to secondary care patients.
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6
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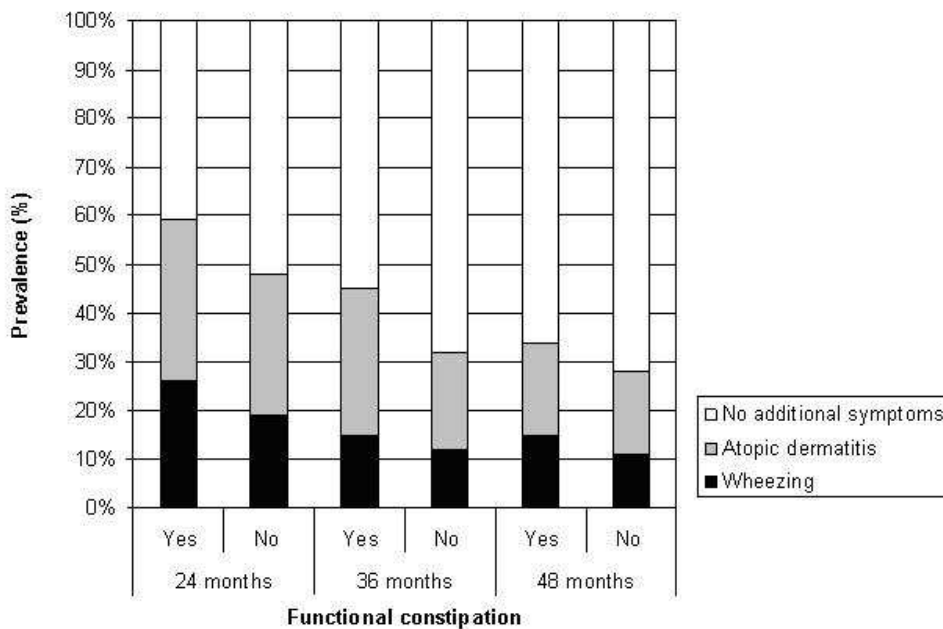
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Figure 1: Distribution of wheezing and atopic dermatitis symptoms in children with and without functional constipation (N=4651)



54x43mm (300 x 300 DPI)

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1 STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	X
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	X
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	X
Objectives	3	State specific objectives, including any prespecified hypotheses	X
Methods			
Study design	4	Present key elements of study design early in the paper	X
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X
Bias	9	Describe any efforts to address potential sources of bias	X
Study size	10	Explain how the study size was arrived at	X
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	X X X
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	X X (non-response Analyse described) X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	X X

		(c) Summarise follow-up time (eg, average and total amount)	X
Outcome data	15*	Report numbers of outcome events or summary measures over time	X
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X
		(b) Report category boundaries when continuous variables were categorized	X
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	X
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	X
Discussion			
Key results	18	Summarise key results with reference to study objectives	X
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X
Generalisability	21	Discuss the generalisability (external validity) of the study results	X
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.