

## Supplementary tables and figures

### **A population-based prospective cohort study examining the influence of early-life respiratory tract infections on school-age lung function and asthma.**

Evelien R. van Meel, MD<sup>1,2,3</sup>, Herman T. den Dekker, MD<sup>1,2,3</sup>, Niels J. Elbert, MD<sup>1,4</sup>, Pauline W. Jansen, PhD<sup>5,6</sup>, Henriëtte A. Moll, MD, PhD<sup>7</sup>, Irwin K. Reiss, MD, PhD<sup>8</sup>, Johan C. de Jongste, MD PhD<sup>2</sup>, Vincent W.V. Jaddoe, MD PhD<sup>1,3,7</sup> Liesbeth Duijts, MD PhD<sup>2,3,8</sup>

<sup>1</sup>The Generation R Study Group; Erasmus MC, University Medical Center Rotterdam, <sup>2</sup>Department of Pediatrics, Division of Respiratory Medicine; Erasmus MC, University Medical Center Rotterdam, <sup>3</sup>Department of Epidemiology; Erasmus MC, University Medical Center Rotterdam, <sup>4</sup>Department of Dermatology; Erasmus MC, University Medical Center Rotterdam, <sup>5</sup>Department of Child and Adolescent Psychiatry/Psychology; Erasmus MC, University Medical Center Rotterdam, <sup>6</sup>Institute of Psychology; Erasmus University Rotterdam, Rotterdam, The Netherlands, <sup>7</sup>Department of Pediatrics; Erasmus MC, University Medical Center Rotterdam, and <sup>8</sup>Department of Pediatrics, Division of Neonatology; Erasmus MC, University Medical Center Rotterdam.

**Supplementary Table S1.** Characteristics of those included and not included in the study.

	Included subjects n = 5,197	Not included subjects n = 4,704	Test for difference p-value
<b>Maternal characteristics</b>			
Education, higher (%)	53.2 (2,603)	39.4 (368)	0.000
Body mass index at intake (kg/m <sup>2</sup> )	24.5 (4.2)	25.3 (4.9)	0.000
Parity, nullipara	56.4 (2,935)	48.4 (554)	0.000
Smoking during pregnancy, yes (%)	13.7 (637)	20.5 (184)	0.000
Psychiatric symptoms during pregnancy (GSI) <sup>1</sup>	0.15 (0.00, 0.88)	0.19 (0.00, 1.30)	0.000
Pet keeping, yes (%)	34.4 (1,425)	29.4 (233)	0.006
History of asthma or atopy, yes (%)	37.1 (1,694)	37.4 (331)	N.S.
Mode of delivery, caesarian section (%)	12.9 (602)	13.0 (494)	N.S.
<b>Children's characteristics</b>			
Female sex (%)	50.5 (2,626)	48.0 (2,183)	0.015
Gestational age at birth (weeks) <sup>1</sup>	40.1 (37.0, 42.0)	39.9 (35.9, 42.0)	0.000
Birth weight (grams)	3,445 (549)	3,316 (620)	0.000
Breastfeeding ever, no (%)	7.3 (319)	9.9 (69)	0.015
Day care attendance 1 <sup>st</sup> year, yes (%)	62.9 (2,123)	53.9 (216)	0.000

Values are means (SD), valid percentages (absolute numbers) or <sup>1</sup>medians (5-95% range). Differences between groups were evaluated using t-tests for continuous variables, chi-square tests for categorical variables or Mann-Whitney U tests for non-normal distributed variables. Non-significant (N.S.)

**Supplementary Table S2.** Unadjusted associations of any upper and lower respiratory tract infections with lung function and asthma at age 10 years

		<b>FEV<sub>1</sub></b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FVC</b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FEV<sub>1</sub>/FVC</b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FEF<sub>75</sub></b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>Current asthma</b> <b>OR (95% CI)</b> <b>n = 4,556</b>
<b>Any URTI</b>						
Age 6 months	n = 2,930	-0.01 (-0.12, 0.10)	-0.03 (-0.14, 0.07)	0.04 (-0.08, 0.15)	0.02 (-0.08, 0.13)	<b>1.67 (1.08, 2.58)*</b>
Age 1 year	n = 3,601	-0.05 (-0.12, 0.03)	-0.04 (-0.11, 0.03)	-0.01 (-0.08, 0.07)	-0.04 (-0.11, 0.03)	1.37 (0.99, 1.89)
Age 2 years	n = 3,768	0.01 (-0.06, 0.08)	-0.01 (-0.07, 0.06)	0.03 (-0.04, 0.10)	0.02 (-0.05, 0.09)	<b>1.87 (1.38, 2.53)**</b>
Age 3 years	n = 3,645	-0.01 (-0.09, 0.07)	0.02 (-0.05, 0.09)	-0.06 (-0.13, 0.02)	-0.03 (-0.10, 0.04)	<b>1.49 (1.08, 2.06)*</b>
Age 4 years	n = 3,658	-0.01 (-0.09, 0.07)	-0.01 (-0.08, 0.07)	-0.01 (-0.08, 0.07)	-0.00 (-0.08, 0.07)	1.20 (0.83, 1.73)
Age 6 years	n = 4,681	0.03 (-0.04, 0.10)	0.03 (-0.04, 0.10)	0.00 (-0.07, 0.07)	0.04 (-0.03, 0.11)	1.20 (0.87, 1.65)
<b>Any LRTI</b>						
Age 6 months	n = 2,996	<b>-0.21 (-0.35, -0.07)**</b>	-0.13 (-0.26, 0.01)	-0.12 (-0.26, 0.02)	-0.11 (-0.24, 0.03)	<b>1.82 (1.09, 3.04)*</b>
Age 1 year	n = 3,623	<b>-0.33 (-0.46, -0.20)**</b>	<b>-0.24 (-0.37, -0.11)**</b>	-0.12 (-0.25, 0.01)	<b>-0.21 (-0.34, -0.09)**</b>	<b>1.99 (1.25, 3.17)**</b>
Age 2 years	n = 3,828	<b>-0.21 (-0.30, -0.10)**</b>	-0.08 (-0.18, 0.02)	<b>-0.18 (-0.28, -0.08)**</b>	<b>-0.21 (-0.31, -0.12)**</b>	<b>3.93 (2.80, 5.52)**</b>
Age 3 years	n = 3,678	<b>-0.26 (-0.40, -0.13)*</b>	-0.10 (-0.22, 0.03)	<b>-0.25 (-0.38, -0.12)**</b>	<b>-0.23 (-0.36, -0.10)**</b>	<b>6.22 (4.31, 8.98)**</b>
Age 4 years	n = 3,649	<b>-0.21 (-0.37, -0.04)*</b>	-0.04 (-0.20, 0.12)	<b>-0.25 (-0.42, -0.09)**</b>	<b>-0.26 (-0.41, -0.10)**</b>	<b>11.75 (7.84, 17.62)**</b>
Age 6 years	n = 4,649	-0.07 (-0.21, 0.07)	0.11 (-0.02, 0.24)	<b>-0.30 (-0.43, -0.16)*</b>	<b>-0.18 (-0.31, -0.05)**</b>	<b>12.50 (8.85, 17.66)**</b>

Values are Z-scores or odds ratios (OR) with 95% confidence interval (95% CI), derived from linear or binomial logistic regression models. \* p-value <0.05, \*\* p-value <0.01. Models are unadjusted. Upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), Forced Expiratory Flow in 1 second (FEV<sub>1</sub>), Forced Vital Capacity (FVC), Forced Expiratory Flow when 75% of the FVC is exhaled (FEF<sub>75</sub>).

**Supplementary Table S3.** Associations of any upper and lower respiratory tract infections with lung function and asthma at age 10 years, in complete cases only

		<b>FEV<sub>1</sub></b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FVC</b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FEV<sub>1</sub>/FVC</b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FEF<sub>75</sub></b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>Current asthma</b> <b>OR (95% CI)</b> <b>n = 4,556</b>
<b>Any URTI</b>						
Age 6 months	n = 2,930	-0.02 (-0.18, 0.14)	-0.09 (-0.24, 0.07)	0.11 (-0.05, 0.27)	0.05 (-0.10, 0.20)	1.32 (0.69, 2.56)
Age 1 year	n = 3,601	-0.30 (-0.15, 0.09)	-0.05 (-0.16, 0.07)	0.01 (-0.11, 0.13)	-0.00 (-0.12, 0.11)	1.33 (0.79, 2.23)
Age 2 years	n = 3,768	0.10 (-0.01, 0.22)	0.04 (-0.07, 0.15)	0.11 (-0.00, 0.23)	0.09 (-0.02, 0.20)	1.75 (1.04, 2.93)
Age 3 years	n = 3,645	-0.01 (-0.14, 0.13)	-0.00 (-0.13, 0.13)	-0.02 (-0.15, 0.11)	-0.01 (-0.14, 0.11)	0.86 (0.46, 1.59)
Age 4 years	n = 3,658	-0.06 (-0.21, 0.10)	-0.06 (-0.20, 0.09)	-0.00 (-0.16, 0.15)	-0.02 (-0.17, 0.12)	0.82 (0.38, 1.73)
Age 6 years	n = 4,681	-0.06 (-0.22, 0.10)	-0.04 (-0.19, 0.12)	-0.03 (-0.19, 0.13)	-0.05 (-0.20, 0.10)	1.25 (0.61, 2.55)
<b>Any LRTI</b>						
Age 6 months	n = 2,996	-0.15 (-0.35, 0.04)	-0.13 (-0.32, 0.06)	0.02 (-0.18, 0.21)	0.04 (-0.15, 0.22)	<b>2.45 (1.23, 4.91)*</b>
Age 1 year	n = 3,623	<b>-0.34 (-0.55, -0.13)**</b>	<b>-0.32 (-0.52, -0.11)**</b>	-0.01 (-0.21, 0.20)	-0.15 (-0.35, 0.05)	1.17 (0.49, 2.81)
Age 2 years	n = 3,828	-0.10 (-0.27, 0.08)	0.05 (-0.12, 0.22)	<b>-0.23 (-0.41, -0.06)**</b>	<b>-0.26 (-0.43, -0.10)**</b>	<b>2.49 (1.33, 4.67)**</b>
Age 3 years	n = 3,678	<b>-0.29 (-0.55, -0.03)*</b>	-0.17 (-0.42, 0.08)	-0.21 (-0.47, 0.05)	-0.23 (-0.48, 0.01)	<b>4.01 (1.84, 8.76)**</b>
Age 4 years	n = 3,649	-0.05 (-0.36, 0.26)	0.00 (-0.30, 0.30)	-0.08 (-0.39, 0.23)	0.02 (-0.28, 0.31)	<b>6.58 (2.86, 15.12)**</b>
Age 6 years	n = 4,649	-0.17 (-0.47, 0.13)	-0.02 (-0.31, 0.27)	-0.23 (-0.53, 0.07)	-0.21 (-0.49, 0.08)	<b>12.99 (5.66, 29.82)**</b>

Values are Z-scores or odds ratios (OR) with 95% confidence interval (95% CI), derived from linear or binomial logistic regression models. \* p-value <0.05, \*\* p-value <0.01. Models are adjusted for maternal education, body mass index, parity, smoking during pregnancy, psychiatric symptoms during pregnancy, pet keeping, history of asthma or atopy, mode of delivery, and child's sex, gestational age at birth, birth weight corrected for gestational age at birth, breastfeeding and day care attendance. Additionally, upper

respiratory tract infections were adjusted for any preceding upper respiratory tract infections. Upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), Forced Expiratory Flow in 1 second ( $FEV_1$ ), Forced Vital Capacity (FVC), Forced Expiratory Flow when 75% of the FVC is exhaled ( $FEF_{75}$ ).

**Supplementary Table S4.** Associations of individual upper respiratory tract infections with lung function and asthma at age 10 years

		FEV <sub>1</sub> Z-score (95% CI) n = 4,672	FVC Z-score (95% CI) n = 4,672	FEV <sub>1</sub> /FVC Z-score (95% CI) n = 4,672	FEF <sub>75</sub> Z-score (95% CI) n = 4,672	Current asthma OR (95% CI) n = 4,556
<b>Age 6 months</b>						
Ear infection	n = 2,958	-0.04 (-0.17, 0.09)	-0.07 (-0.19, 0.05)	0.04 (-0.09, 0.16)	0.01 (-0.11, 0.13)	1.25 (0.74, 2.09)
Throat infection	n = 2,963	-0.01 (-0.23, 0.21)	-0.03 (-0.24, 0.17)	0.01 (-0.21, 0.22)	-0.01 (-0.22, 0.19)	<b>2.19 (1.05, 4.53)*</b>
False croup	n = 2,970	0.19 (-0.20, 0.58)	0.20 (-0.17, 0.56)	0.02 (-0.36, 0.40)	0.03 (-0.33, 0.40)	1.17 (0.27, 5.08)
Whooping cough	n = 2,967	-0.17 (-0.62, 0.27)	-0.04 (-0.46, 0.38)	-0.17 (-0.61, 0.27)	-0.11 (-0.53, 0.32)	0.58 (0.06, 5.68)
<b>Age 1 years</b>						
Ear infection	n = 3,573	-0.03 (-0.13, 0.07)	-0.04 (-0.14, 0.05)	0.01 (-0.08, 0.11)	-0.02 (-0.11, 0.08)	1.37 (0.90, 2.08)
Throat infection	n = 3,565	-0.04 (-0.18, 0.10)	0.05 (-0.08, 0.18)	-0.12 (-0.26, 0.02)	-0.11 (-0.24, 0.02)	<b>1.86 (1.09, 3.15)*</b>
False croup	n = 3,582	-0.00 (-0.30, 0.30)	-0.08 (-0.37, 0.20)	0.14 (-0.16, 0.43)	0.02 (-0.27, 0.30)	1.39 (0.84, 2.30)
Whooping cough	n = 3,574	-0.44 (-0.92, 0.04)	-0.42 (-0.88, 0.03)	0.03 (-0.45, 0.50)	-0.22 (-0.67, 0.24)	1.28 (0.22, 7.56)
<b>Age 2 years</b>						
Ear infection	n = 3,756	0.08 (-0.02, 0.18)	0.04 (-0.05, 0.14)	0.07 (-0.03, 0.16)	0.09 (-0.01, 0.18)	1.25 (0.81, 1.93)
Throat infection	n = 3,774	0.05 (-0.08, 0.18)	0.02 (-0.10, 0.14)	0.05 (-0.07, 0.18)	0.03 (-0.09, 0.15)	1.34 (0.81, 2.23)
False croup	n = 3,777	0.01 (-0.19, 0.22)	0.06 (-0.14, 0.25)	-0.08 (-0.28, 0.12)	-0.04 (-0.23, 0.16)	1.69 (0.78, 3.68)
Whooping cough	n = 3,775	-0.11 (-0.45, 0.24)	-0.12 (-0.44, 0.21)	0.01 (-0.33, 0.35)	-0.11 (-0.43, 0.22)	2.06 (0.59, 7.22)
<b>Age 3 years</b>						
Ear infection	n = 3,622	0.03 (-0.09, 0.15)	0.05 (-0.06, 0.16)	-0.06 (-0.17, 0.06)	-0.06 (-0.17, 0.05)	1.07 (0.65, 1.78)
Throat infection	n = 3,616	0.10 (-0.05, 0.26)	0.12 (-0.02, 0.27)	-0.04 (-0.19, 0.12)	0.01 (-0.13, 0.16)	1.17 (0.63, 2.17)

False croup	n = 3,608	-0.15 (-0.43, 0.14)	0.01 (-0.26, 0.28)	<b>-0.28 (-0.56, -0.00)*</b>	-0.13 (-0.40, 0.14)	0.64 (0.15, 2.80)
Whooping cough	n = 3,612	0.12 (-0.56, 0.79)	0.21 (-0.43, 0.85)	-0.19 (-0.85, 0.48)	-0.27 (-0.91, 0.37)	n.a.
<b>Age 4 years</b>						
Ear infection	n = 3,599	0.05 (-0.09, 0.18)	0.01 (-0.12, 0.13)	0.08 (-0.05, 0.21)	0.07 (-0.05, 0.20)	1.20 (0.67, 2.13)
Throat infection	n = 3,601	-0.02 (-0.21, 0.17)	-0.03 (-0.21, 0.15)	0.02 (-0.16, 0.21)	0.07 (-0.12, 0.25)	0.51 (0.18, 1.47)
False croup	n = 3,576	-0.21 (-0.58, 0.17)	-0.32 (-0.67, 0.03)	0.20 (-0.17, 0.56)	0.09 (-0.26, 0.44)	n.a.
<b>Age 6 years</b>						
Ear infection	n = 4,600	-0.01 (-0.14, 0.13)	-0.02 (-0.15, 0.10)	0.05 (-0.09, 0.18)	0.04 (-0.08, 0.17)	0.98 (0.53, 1.82)
Throat infection	n = 4,618	<b>0.26 (0.04, 0.47)*</b>	<b>0.24 (0.05, 0.44)**</b>	0.00 (-0.21, 0.21)	0.04 (-0.16, 0.24)	1.15 (0.50, 2.65)
False croup	n = 4,557	0.04 (-0.43, 0.51)	0.20 (-0.24, 0.64)	-0.29 (-0.75, 0.18)	-0.29 (-0.73, 0.16)	3.05 (0.89, 10.44)

Values are Z-scores or odds ratios (OR) with 95% confidence interval (95% CI), derived from linear or binomial logistic regression models. \* p-value <0.05, \*\* p-value <0.01. Not available (n.a.). Models are adjusted for maternal education, body mass index, parity, smoking during pregnancy, psychiatric symptoms during pregnancy, pet keeping, history of asthma or atopy, mode of delivery, and child's sex, gestational age at birth, birth weight corrected for gestational age at birth, breastfeeding and day care attendance. Additionally, upper respiratory tract infections were adjusted for any preceding upper respiratory tract infections. Upper respiratory tract infections (URTI), Forced Expiratory Flow in 1 second (FEV<sub>1</sub>), Forced Vital Capacity (FVC), Forced Expiratory Flow when 75% of the FVC is exhaled (FEF<sub>75</sub>).

**Supplementary Table S5.** Associations of individual lower respiratory tract infections (LRTI) with lung function and asthma at age 10 years

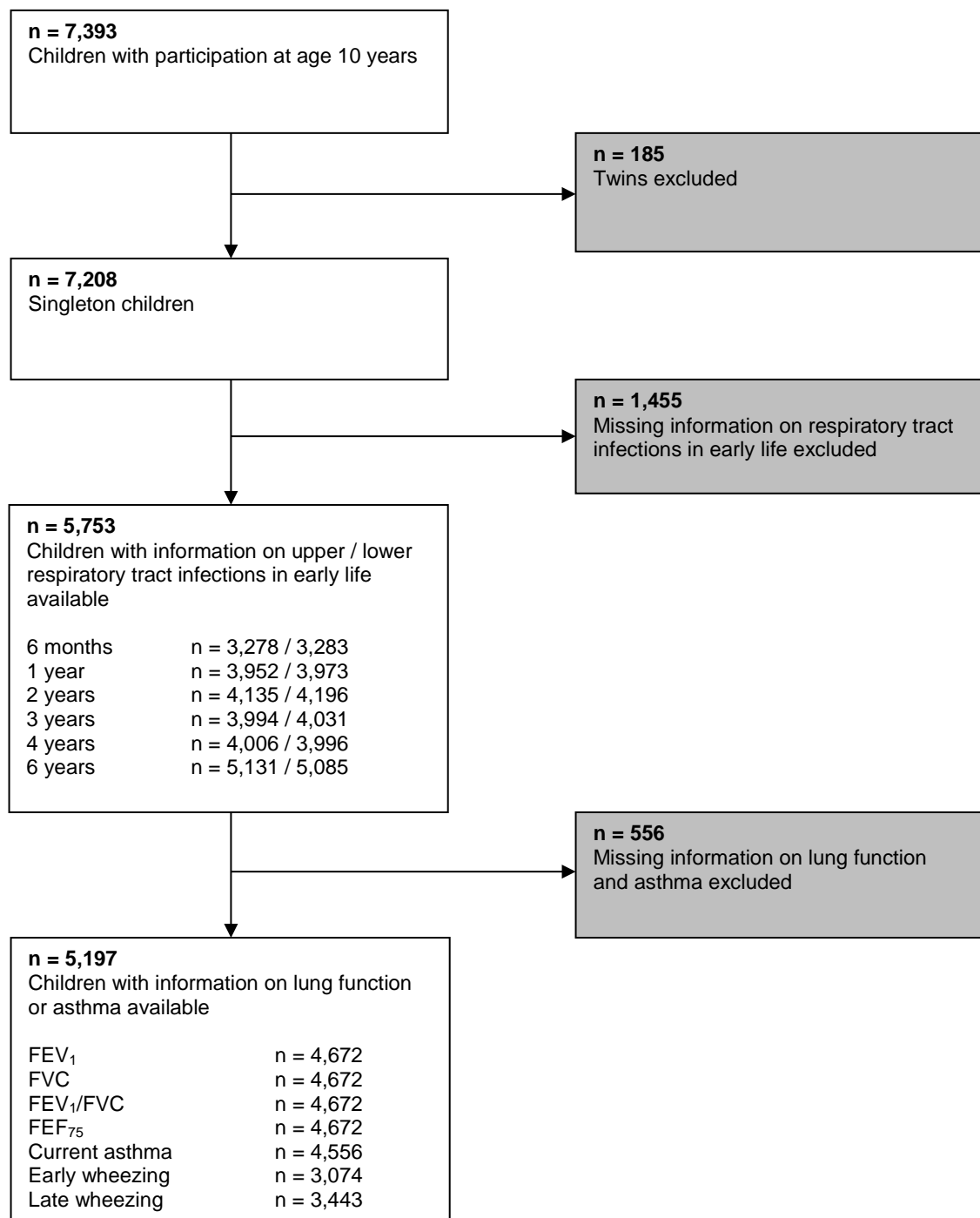
		<b>FEV<sub>1</sub></b> <b>Z-score (95% CI)</b> <b>n = 4672</b>	<b>FVC</b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FEV<sub>1</sub>/FVC</b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>FEF<sub>75</sub></b> <b>Z-score (95% CI)</b> <b>n = 4,672</b>	<b>Current asthma</b> <b>OR (95% CI)</b> <b>n = 4,556</b>
<b>Age 6 months</b>						
Bronchitis	n = 2,963	<b>-0.22 (-0.39, -0.05)*</b>	-0.12 (-0.29, 0.04)	-0.15 (-0.32, 0.02)	-0.14 (-0.30, 0.03)	<b>1.91 (1.05, 3.48)*</b>
Pneumonia	n = 2,961	-0.04 (-0.42, 0.33)	0.01 (-0.35, 0.36)	-0.07 (-0.43, 0.30)	-0.04 (-0.39, 0.31)	2.00 (0.57, 7.00)
Bronchiolitis	n = 2,959	-0.24 (-0.50, 0.01)	-0.22 (-0.46, 0.02)	-0.02 (-0.27, 0.23)	-0.10 (-0.34, 0.13)	1.23 (0.43, 3.52)
<b>Age 1 year</b>						
Bronchiolitis	n = 3,560	<b>-0.34 (-0.50, -0.18)**</b>	<b>-0.25 (-0.40, -0.10)**</b>	-0.14 (-0.29, 0.02)	<b>-0.25 (-0.40, -0.10)**</b>	1.57 (0.86, 2.87)
<b>Age 2 years</b>						
Bronchitis	n = 3,777	<b>-0.18 (-0.33, -0.03)**</b>	-0.00 (-0.15, 0.14)	<b>-0.28 (-0.42, -0.13)**</b>	<b>-0.30 (-0.44, -0.16)**</b>	<b>4.37 (2.68, 7.12)**</b>
Pneumonia	n = 3,767	-0.26 (-0.55, 0.03)	<b>-0.32 (-0.59, -0.04)*</b>	0.13 (-0.15, 0.42)	0.01 (-0.26, 0.29)	1.25 (0.37, 4.24)
Bronchiolitis	n = 3,776	-0.00 (-0.28, 0.28)	0.07 (-0.20, 0.33)	-0.13 (-0.40, 0.15)	-0.17 (-0.43, 0.09)	<b>2.63 (1.07, 6.46)*</b>
<b>Age 3 years</b>						
Bronchitis	n = 3,615	-0.10 (-0.33, 0.13)	0.02 (-0.20, 0.23)	-0.17 (-0.39, 0.05)	-0.11 (-0.32, 0.11)	<b>4.91 (2.63, 9.15)**</b>
Pneumonia	n = 3,620	<b>-0.33 (-0.64, -0.02)*</b>	-0.18 (-0.48, 0.11)	-0.26 (-0.57, 0.04)	-0.25 (-0.55, 0.04)	<b>5.21 (2.33, 11.65)**</b>
<b>Age 4 years</b>						
Bronchitis	n = 3,584	-0.15 (-0.42, 0.11)	-0.05 (-0.30, 0.19)	-0.16 (-0.42, 0.10)	-0.15 (-0.40, 0.09)	<b>9.20 (4.67, 18.11)**</b>
Pneumonia	n = 3,579	0.27 (-0.23, 0.76)	0.37 (-0.09, 0.84)	-0.17 (-0.66, 0.32)	0.04 (-0.43, 0.51)	2.83 (0.73, 11.04)
<b>Age 6 years</b>						
Bronchitis	n = 4,592	0.12 (-0.13, 0.37)	0.26 (0.02, 0.49)	<b>-0.25 (-0.49, -0.00)*</b>	-0.09 (-0.32, 0.15)	<b>13.34 (6.74, 26.42)**</b>
Pneumonia	n = 4,568	0.18 (-0.22, 0.57)	<b>0.40 (0.03, 0.77)*</b>	-0.36 (-0.74, 0.03)	-0.22 (-0.59, 0.15)	<b>10.55 (3.91, 28.44)**</b>



Values are Z-scores or odds ratios (OR) with 95% confidence interval (95% CI), derived from linear or binomial logistic regression models. \* p-value <0.05, \*\* p-value <0.01. Models are adjusted for maternal education, body mass index, parity, smoking during pregnancy, psychiatric symptoms during pregnancy, pet keeping, history of asthma or atopy, mode of delivery, and child's sex, gestational age at birth, birth weight corrected for gestational age at birth, breastfeeding and day care attendance. Additionally, lower respiratory tract infections were adjusted for any preceding lower respiratory tract infections. Lower respiratory tract infections (LRTI), Forced Expiratory Flow in 1 second (FEV<sub>1</sub>), Forced Vital Capacity (FVC), Forced Expiratory Flow when 75% of the FVC is exhaled (FEF<sub>75</sub>).

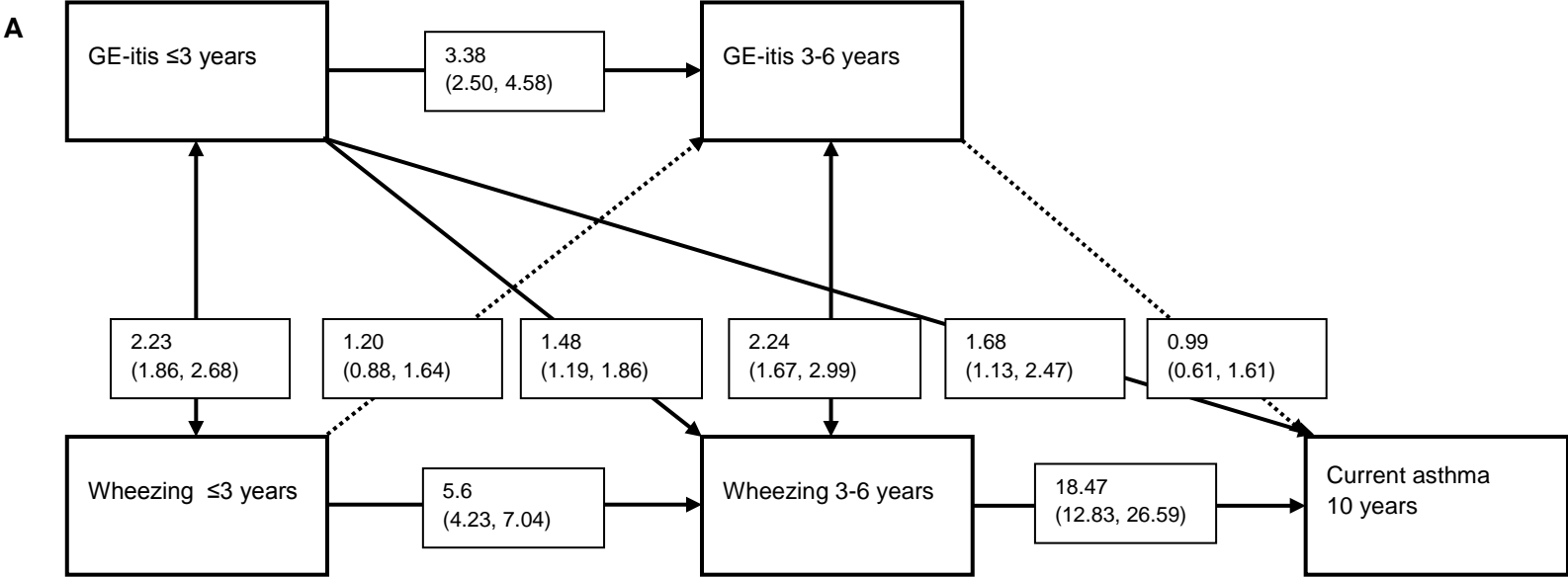
**Supplementary Figure S1.** Flow chart of participants included for analysis

Available numbers of upper and lower respiratory tract infections reflect the number of children with data available before excluding children with missing data on lung function and asthma.



**Supplementary Figure S2.** Direction of associations of gastro-enteritis (A) and urinary tract infections (B) with wheezing patterns and current asthma, at age 10 years.

Values are odds ratios (OR) with their corresponding 95% confidence interval (95% CI) derived from binomial logistic regression models, using cross-lagged modeling which takes bidirectional associations into account. Models are also adjusted for maternal education, body mass index, parity, smoking during pregnancy, psychiatric symptoms during pregnancy, pet keeping, history of asthma or atopy, mode of delivery, and child's sex, gestational age at birth, birth weight corrected for gestational age at birth, breastfeeding and day care attendance. Arrows indicate the direction of the associations and if they are significant (bold) or non-significant (dashed). Gastro-enteritis (GE-itis), urinary tract infection (UTI).



**B**

