Granell, R., Henderson, A. J., & Sterne, J. A. (2016). Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: A population-based birth cohort. *Journal of Allergy and Clinical Immunology, 138*(4), 1060-1070.e11. https://doi.org/10.1016/j.jaci.2016.01.046
Associations of wheezing phenotypes with late asthma outcomes in ALSPAC: a population-based birth cohort

Raquel Granell*, Jonathan A.C. Sterne & John Henderson

*Online Data Supplement*
Participants

ALSPAC recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. 14,541 is the initial number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a “Children in Focus” clinic by 19/07/99. Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above.

The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper1. The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 were alive at 1 year of age.

A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.

Please note that the study website contains details of all the data that is available through a fully searchable data dictionary" and reference the following webpage: <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>
**Skin Prick Test**

Atopy was measured at a research clinic at age 7½ years, as previously described (1). A positive response was defined as a mean weal diameter of >2 mm with an absent response to negative control solution, and atopy was defined as a positive response to one or more of house dust mite, cat or grass pollen.

**FeNO at 14-15 years**

Fractional exhaled nitric oxide (FeNO) was measured online at a constant flow of 50mL/s according to European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines using a Sievers NOA-280i nitric oxide analyser (GE Analytical Instruments, Boulder, CO.). Additionally, 758 children with less stringent criteria (individual blows >5% deviation but at least 1 within acceptable range of 10-200 ppb) were included. FeNO measurements were done before spirometry measurements. Children were requested to omit their inhaled corticosteroids if applicable 48 hours before their visit to the clinic. At the time of measurements, 14 children (0.3%) received oral steroids, 221 (5.2%) had a chest infection and/or fever with a cold in the preceding three weeks, and 39 (0.9%) and 89 (2.1%) had used short acting or long acting bronchodilators 6 or 24 hours, respectively, prior to the respiratory assessments. These children, and those with less stringent criteria of FeNO values, were included in our analyses since we observed no differences in results when they were included or excluded.

**Asthma status 0 to 14 years**

Using ever-reported doctor-diagnosed asthma at 91 and 166 months and maternal report of asthma at 166 months, we derived the following asthma status variable: "no asthma" if negative at both 91 and 166 months, "remittent asthma" if positive at 91 months but negative at 166 months or positive at both 91 and 166 months but negative maternal report of asthma in the last 12 months at 166 months, "incident asthma" if negative at 91 months but positive at 166 months and
“persistent asthma” if positive at both 91 and 166 months and positive maternal report of asthma in the last 12 months at 166 months.

Potential Confounders

We obtained details of maternal educational attainment (lower level defined as educated to school leaving certificate at 16 years or lower), smoking history and personal history of asthma or allergy from questionnaires sent to the mother during pregnancy. Sex of the child was obtained from delivery health care records. Postnatal maternal questionnaires from 3-15 months after birth were used to ascertain environmental tobacco smoke exposure.

Statistical analysis

In order to minimise the risk of bias due to misclassification, associations of wheezing phenotypes with late asthma outcomes (physician-diagnosed asthma and objective measurements of lung function and FeNO) were examined using logistic or linear regression models weighted for the probability of each individual of belonging to each phenotype. These probabilities were estimated previously and referred to as the posterior probabilities (2). Crude and adjusted odds ratios (for binary outcomes) and mean differences (for continuous outcomes) were derived in relation to the never/infrequent wheezing phenotype (reference group). Adjustment was done for potential confounders (gender, maternal lower education level, having at least one sibling (parity), maternal history of asthma or allergy, maternal smoking during pregnancy, maternal anxiety during pregnancy (as being in the 4th quantile of the Crown-Crisp Experiential Index (3)), low birth weight (<2.5kg), preterm delivery (<37 weeks) and daycare attendance during the first year.

Table E1

A total of 6330 (51.5%) participants were males, 5139 (46.2%) had an asthmatic or allergic mother, 2934 (26.1%) were exposed to maternal smoking during pregnancy and 6148 (54.9%) had at least one sibling. 575 (5.0%) had low birth weight and 682 (5.8%) were born preterm.
were exposed to maternal smoking during the first year and 641 (6.0%) attended day care during the first year. 2874 (26.1%) participants had wheezing reported at 6 months: the proportion of participants with reported wheezing decreased to 1756 (17.6%) by 3½ years, 1050 (12.9%) by 8½ years and 592 (10.5%) by 16½ years. Of 6691 participants with data available on skin prick tests at 7½ years, 1403 (21.0%) were atopic.

Comparing the samples of children with complete (n=3,170) and incomplete data (at least 2 observations of wheeze, n=9,133) on wheezing, we observed that incomplete data are associated with markers of social deprivation: increased exposure to tobacco smoke (p=), maternal anxiety (p=), maternal lower education (p=), parity (p=), low birthweight (p=) and pre-term delivery (p=), in those subsequently lost to follow up. Also, the proportion of wheezing differs between 6 and 69 months (p<) but its similar thereafter which is consistent with less wheezing reported among children with complete data, compared to those subsequently lost to follow up. Our analyses included children with incomplete data on wheeze, avoiding bias that could be introduced in complete case analyses.

Table E2

Male gender (adjusted multinomial odds ratios [mOR] range from 1.32 to 1.80) was associated with a similar higher risk of each phenotype (heterogeneity p-value=0.13). Maternal lower education level was associated with a higher risk of mid-childhood onset remitting wheeze (mOR 1.22, 1.02 to 1.45 with little evidence of heterogeneity p-value=0.11). Having at least one sibling was associated with pre-school and mid-childhood onset remitting and continuous wheezing phenotypes and there was little evidence for association with the other phenotypes (heterogeneity p-value=0.0012). Maternal history of asthma or allergy was associated with a higher risk of each wheezing phenotype (mOR 1.27 to 2.30, heterogeneity p-value<0.0001), strongest associations were with mid-childhood onset remitting (mOR 1.65 95%CI 1.40 to 1.93) and continuous wheezing (mOR 2.30 95%CI 1.88 to 2.81). Maternal smoking during pregnancy was associated with a higher risk of pre-school and mid-childhood onset remitting and continuous wheeze
phenotypes (mOR 1.33 to 1.46, heterogeneity p-value=0.71). Prenatal maternal anxiety was
associated with a higher risk of each wheezing phenotype (mOR 1.12 to 1.29, heterogeneity p-
value=0.08). Low birth weight was associated with continuous wheeze (mOR 1.63 95%CI 1.00 to
2.64, heterogeneity p-value=0.26). Preterm delivery was associated with higher risk of pre-school
and mid-childhood onset remitting and continuous wheezing (mOR 1.35 to 1.63, heterogeneity p-
value=0.30). Day care attendance during the first year was associated with a higher risk of pre-
school onset remitting wheeze phenotype, although we found small evidence of heterogeneity p-
value=0.16. We found small evidence for an association between maternal smoking during the
first year and any of the wheezing phenotypes.

REFERENCES
1. Roberts G, Peckitt C, Northstone K, Strachan D, Lack G, Henderson J, Golding J. Relationship
between aeroallergen and food allergen sensitization in childhood. ClinExpAllergy 2005;
35: 933-940.
2. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock AA, Strachan DP, Shaheen
SO, Sterne JA. Associations of wheezing phenotypes in the first six years of life with
atopy, lung function and airway responsiveness in mid childhood. Thorax 2008.
3. Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a
useful and valid measure of psychoneurotic pathology. Br J Med Psychol 1988;61:255-66
Table E1 Characteristics of children with at least 2 observations of wheeze (study population, N=12,303) who did and did not have complete data on wheezing.

| Potential confounders | Children with complete data on wheezing (n=3,170) | Children with 2–13 observations of wheezing (n=9,133) | Two-sample test of proportions |
|----------------------|-----------------------------------------------|-------------------------------------------------|--------------------------------|
|                      | n/total | %      | n/total | %      | P-value |
| Gender (Male)        | 1560/3170 | 49.2   | 4770/9133 | 52.2   | <0.003  |
| Lower maternal education* | 1547/3151 | 49.1   | 5614/8184 | 68.6   | <0.0001 |
| Having at least 1 sibling (parity) | 1597/3118 | 51.2   | 4551/8072 | 56.4   | <0.0001 |
| Maternal history of asthma or allergy | 1510/3107 | 48.6   | 3629/8025 | 45.2   | 0.001   |
| Maternal smoking during pregnancy | 439/3127 | 14.0   | 2495/8096 | 30.8   | <0.0001 |
| Maternal anxiety during pregnancy† | 479/3020 | 15.9   | 1831/7520 | 24.3   | <0.0001 |
| Low birth weight (<2.5Kg) | 134/3134 | 4.3    | 441/8397  | 5.3    | 0.032   |
| Preterm delivery (<37 weeks) | 153/3170 | 4.8    | 529/8504  | 6.2    | 0.004   |
| Maternal smoking during first year | 411/3122 | 13.2   | 2118/7690 | 27.5   | <0.0001 |
| Day care attendance during 1st year | 242/3124 | 7.7    | 399/7505  | 5.3    | <0.0001 |

Variables used in the Latent Class model

Reported wheezing at

|  |  |  |  |  |  |
|---|---|---|---|---|
| 6 months | 709/3170 | 22.4 | 2165/7834 | 27.6 | <0.0001 |
| 18 months | 780/3170 | 24.6 | 2205/7691 | 28.7 | <0.0001 |
| 30 months | 612/3170 | 19.3 | 1632/6775 | 24.1 | <0.0001 |
| 42 months (3½ years) | 487/3170 | 15.4 | 1269/6803 | 18.7 | <0.0001 |
| 54 months | 505/3170 | 15.9 | 1269/6221 | 20.4 | <0.0001 |
| 69 months | 435/3170 | 13.7 | 893/5426 | 16.5 | .0007 |
| 81 months | 393/3170 | 12.4 | 734/5225 | 14.0 | 0.70 |
| 91 months | 334/3170 | 10.5 | 544/5032 | 10.8 | 0.14 |
| 103 months (8½ years) | 386/3170 | 12.2 | 664/4990 | 13.3 | 0.41 |
| 128 months | 376/3170 | 11.9 | 559/4475 | 12.5 | 0.37 |
| 140 months | 360/3170 | 11.4 | 509/4229 | 12.0 | 0.83 |
| 157 months | 338/3170 | 10.7 | 402/3828 | 10.5 | 0.44 |
| 166 months | 339/3170 | 10.7 | 424/3760 | 11.3 | 0.86 |
| 198 months (16½ years) | 335/3170 | 10.6 | 257/2465 | 10.4 | 0.39 |
| Atopy at 7½ years (skin prick testing) | 524/2433 | 21.5 | 879/4258 | 20.6 | 0.70 |

*Educated to GCE level (school leaving certificate) or lower
† Defined as being in the 4th quantile of the Crown-Crisp Experiential Index
Table E2 Associations of possible confounders with wheezing phenotypes 0 to 16½ years and asthma at 14 years (Based on 12,303 children with at least 2 observations of wheezing)

| Demographic, maternal, pregnancy & child characteristics (adjusted by each other) | Pre-school onset remitting\(^*\) N=1,605 | Mid-childhood onset remitting\(^*\) N=620 | School-age onset persisting\(^*\) N=346 | Late-childhood onset persisting\(^*\) N=324 | Continuous wheeze\(^*\) N=420 | Heterogeneity p-value\(^+\) | Adjusted OR (95% CI) for Doctor ever diagnosed-asthma at 14 years N=5,838 |
|---|---|---|---|---|---|---|---|
| Gender (Male) | 1.39 (1.25, 1.55) | 1.41 (1.21, 1.66) | 1.54 (1.26, 1.89) | 1.32 (1.09, 1.60) | 1.80 (1.48, 2.19) | 0.13 | 1.26 (1.11, 1.42) |
| Maternal lower education level ± | 0.96 (0.86, 1.08) | 1.22 (1.02, 1.45) | 0.92 (0.74, 1.13) | 0.94 (0.77, 1.14) | 0.95 (0.77, 1.16) | 0.11 | 1.13 (1.00, 1.28) |
| Parity | 1.24 (1.11, 1.38) | 1.38 (1.17, 1.62) | 0.88 (0.72, 1.07) | 1.02 (0.85, 1.24) | 1.37 (1.12, 1.67) | 1.2E-03 | 0.95 (0.84, 1.07) |
| Maternal history of asthma or allergy | 1.27 (1.14, 1.42) | 1.65 (1.40, 1.93) | 1.47 (1.20, 1.80) | 1.42 (1.17, 1.72) | 2.30 (1.88, 2.81) | 1.9E-06 | 1.53 (1.35, 1.73) |
| Maternal smoking during pregnancy | 1.33 (1.17, 1.51) | 1.46 (1.22, 1.75) | 1.23 (0.97, 1.56) | 1.24 (0.99, 1.56) | 1.38 (1.10, 1.72) | 0.71 | 1.19 (1.01, 1.39) |
| Maternal anxiety during pregnancy | 1.20 (1.14, 1.26) | 1.25 (1.16, 1.35) | 1.12 (1.02, 1.23) | 1.14 (1.04, 1.24) | 1.29 (1.18, 1.41) | 0.08 | 1.13 (1.07, 1.20) |

| Perinatal characteristics adjusted by demographic, maternal, pregnancy and child characteristics | | | | | | | |
|---|---|---|---|---|---|---|---|
| Low birthweight (<2.5Kg) ‡ | 1.00 (0.73, 1.37) | 1.14 (0.73, 1.78) | 1.47 (0.86, 2.52) | 1.56 (0.93, 2.60) | 1.63 (1.00, 2.64) | 0.26 | 1.11 (0.77, 1.61) |
| Preterm delivery (<37 weeks) ‡ | 1.35 (1.07, 1.70) | 1.43 (1.03, 2.00) | 1.04 (0.65, 1.67) | 0.94 (0.59, 1.50) | 1.63 (1.11, 2.39) | 0.30 | 1.16 (0.87, 1.56) |

| Postnatal characteristics adjusted by demographic, maternal, pregnancy, child, perinatal & other postnatal characteristics | | | | | | | |
|---|---|---|---|---|---|---|---|
| Maternal smoking during first year | 1.22 (0.98, 1.51) | 1.15 (0.84, 1.58) | 0.96 (0.64, 1.44) | 1.01 (0.69, 1.49) | 1.09 (0.74, 1.61) | 0.80 | 1.06 (0.82, 1.37) |
| Day care attendance during 1\(^{st}\) year | 1.28 (1.02, 1.60) | 0.97 (0.66, 1.41) | 0.72 (0.44, 1.18) | 0.92 (0.59, 1.42) | 1.07 (0.70, 1.63) | 0.16 | 0.90 (0.70, 1.17) |

* compared with never/infrequent wheezing (N=6,305) and using each child’s phenotype probability as weights.
\+ Educated to school leaving certificate at 16 years (GCE level) or lower
\(+\) Chi-squared test across phenotypes
\(\‡\) Low birthweight was also adjusted by preterm delivery but preterm delivery was not adjusted for low birth weight (since birth weight does not influence gestational age)
Table E3 Crude associations of wheezing phenotypes 0 to 16½ years with doctor-diagnosed asthma ever, FeNO and BDR>12% at 14-15 years (based on in 12,303 children with at least 2 observations of wheeze)

| Wheezing phenotype 0 to 16½ years | Doctor-diagnosed asthma ever at 14 years | FeNO ≥35 ppb at 14-15 years | BDR >12% at 15 years |
|-----------------------------------|------------------------------------------|-----------------------------|----------------------|
|                                   | Number of asthmatic/total* | OR (95% CI) | n1/total* | OR (95% CI) | n2/total* | OR (95% CI) |
| Never/Infrequent                  | 272/3661                  | 1 (ref)      | 290/1157 | 1 (ref)     | 139/2003 | 1 (ref)     |
| Pre-school onset remitting        | 173/870                   | 2.74 (2.23, 3.36) | 61/243   | 1.06 (0.79, 1.44) | 33/472   | 1.10 (0.76, 1.59) |
| Mid-childhood onset remitting     | 231/337                   | 25.0 (19.4, 32.2) | 42/102   | 1.93 (1.28, 2.90) | 21/204   | 1.66 (1.04, 2.63) |
| School-age onset persisting       | 187/223                   | 49.9 (35.3, 70.7) | 57/82    | 6.39 (3.95, 10.34) | 27/127   | 3.28 (2.06, 5.22) |
| Late-childhood onset persisting   | 161/250                   | 19.8 (15.0, 26.1) | 38/66    | 3.67 (2.30, 5.85) | 19/131   | 2.10 (1.26, 3.48) |
| Continuous wheeze                | 246/254                   | 363 (179, 735)   | 49/71    | 6.95 (4.13, 11.72) | 19/126   | 2.36 (1.40, 3.98) |

* Number of children with data available (approximated from modal assignment)

n1: Number of children with FeNO ≥20 ppb
n2: Number of children with BDR>12%
Table E4 Crude association of wheezing phenotypes 0 to 16½ years with lung function measures at 15 years (z-scores) based on 12,303 children with at least two observations of wheezing

| Wheezing phenotype 0 to 16½ years | N   | Mean diff. (95% CI) | N   | Mean diff. (95% CI) | N   | Mean diff. (95% CI) | N   | Mean diff. (95% CI) |
|----------------------------------|-----|---------------------|-----|---------------------|-----|---------------------|-----|---------------------|
| Never/Infrequent                 | 1997| 0 (ref)             | 2094| 0 (ref)             | 1997| 0 (ref)             | 2094| 0 (ref)             |
| Pre-school onset remitting       | 463 | -0.02 (-0.12, 0.07) | 477 | 0.05 (-0.04, 0.14)  | 463 | -0.15 (-0.24, -0.05)| 477 | -0.13 (-0.22, -0.03)|
| Mid-childhood onset remitting   | 203 | 0.09 (-0.05, 0.23)  | 209 | 0.21 (0.07, 0.35)   | 203 | -0.23 (-0.37, -0.08)| 209 | -0.14 (-0.28, -0.00)|
| School-age onset persisting     | 127 | 0.08 (-0.10, 0.26)  | 131 | 0.18 (0.00, 0.35)   | 127 | -0.21 (-0.39, -0.04)| 131 | -0.14 (-0.32, 0.03)|
| Late-childhood onset persisting | 130 | -0.02 (-0.19, 0.15) | 135 | 0.02 (-0.14, 0.19)  | 130 | -0.08 (-0.25, 0.08) | 135 | -0.21 (-0.37, -0.04)|
| Continuous wheeze               | 126 | -0.08 (-0.26, 0.10) | 131 | 0.04 (-0.14, 0.22)  | 126 | -0.26 (-0.44, -0.08)| 131 | -0.30 (-0.48, -0.12)|

N: Number of children with data available (approximated from modal assignment)
Table E5 Adjusted associations of wheezing phenotypes 0 to 16½ years with lung function measures at 8 years (z-scores), in participants with at least 2 observations of wheeze.

| Wheezing phenotype 0 to 16½ years | FEV₁ (SDU) at 8 years | FVC (SDU) at 8 years | FEV₁/FVC (SDU) at 8 years | FEF₂₅-₇₅ (SDU) at 8 years |
|----------------------------------|-----------------------|----------------------|---------------------------|--------------------------|
|                                  | N         | Adjusted Mean diff. (95% CI) * | N       | Adjusted Mean diff. (95% CI) * | N       | Adjusted Mean diff. (95% CI) * | N         | Adjusted Mean diff. (95% CI) * |
| Never/Infrequent                 | 3394     | 0 (ref)                        | 3452    | 0 (ref)                         | 3295    | 0 (ref)                         | 3452     | 0 (ref)                         |
| Pre-school onset remitting       | 872      | -0.20 (-0.28, -0.13)          | 884     | -0.06 (-0.13, 0.02)            | 851     | -0.24 (-0.31, -0.17)           | 884      | -0.28 (-0.35, -0.21)           |
| Mid-childhood onset remitting    | 336      | -0.23 (-0.34, -0.12)          | 341     | -0.01 (-0.11, 0.10)            | 329     | -0.37 (-0.48, -0.26)           | 341      | -0.41 (-0.51, -0.30)           |
| School-age onset persisting      | 219      | -0.30 (-0.43, -0.16)          | 222     | -0.01 (-0.14, 0.12)            | 215     | -0.44 (-0.58, -0.31)           | 222      | -0.48 (-0.62, -0.35)           |
| Late-childhood onset persisting  | 212      | -0.23 (-0.36, -0.11)          | 215     | -0.08 (-0.21, 0.05)            | 207     | -0.21 (-0.34, -0.08)           | 215      | -0.30 (-0.43, -0.18)           |
| Continuous wheeze               | 245      | -0.40 (-0.53, -0.27)          | 249     | 0.10 (-0.03, 0.23)             | 236     | -0.78 (-0.91, -0.65)           | 249      | -0.75 (-0.88, -0.62)           |

* Adjusted for gender, parity, maternal history of asthma or allergy, maternal smoking and anxiety during pregnancy, preterm delivery, low birth weight and daycare attendance during first year.

N: Number of participants with data available (approximated from modal assignment)
Table E6 Adjusted associations of wheezing phenotypes 0 to 16½ years with pre-salbutamol lung function measures at 15 years (z-scores), in participants with at least 2 observations of wheeze.

| Wheezing phenotype 0 to 16½ years | FEV₁ (SDU) at 15 years | FVC (SDU) at 15 years | FEV₁/FVC (SDU) at 15 years | FEF₂₅-₇₅ (SDU) at 15 years |
|-----------------------------------|------------------------|-----------------------|-----------------------------|-----------------------------|
| N                                 | Adjusted Mean diff. (95% CI) * | N | Adjusted Mean diff. (95% CI) * | N | Adjusted Mean diff. (95% CI) * | N | Adjusted Mean diff. (95% CI) * |
| Never/Infrequent                  | 2064 0 (ref)            | 2092 0 (ref)          | 2064 0 (ref)                | 2091 0 (ref)                |
| Pre-school onset remitting        | 473 -0.06 (-0.16, 0.03) | 477 0.05 (-0.05, 0.14)| 473 -0.21 (-0.31, -0.12)  | 476 -0.16 (-0.25, -0.06)  |
| Mid-childhood onset remitting     | 207 -0.03 (-0.17, 0.11) | 209 0.16 (0.02, 0.30)| 207 -0.35 (-0.49, -0.22)  | 209 -0.25 (-0.39, -0.11)  |
| School-age onset persisting       | 129 -0.16 (-0.33, 0.02) | 131 0.08 (-0.10, 0.25)| 129 -0.45 (-0.62, -0.28)  | 131 -0.40 (-0.57, -0.22)  |
| Late-childhood onset persisting   | 135 -0.20 (-0.36, -0.03) | 135 -0.04 (-0.21, 0.13)| 135 -0.29 (-0.45, -0.13)  | 135 -0.33 (-0.50, -0.17)  |
| Continuous wheeze                | 128 -0.23 (-0.41, -0.04) | 130 0.04 (-0.14, 0.22)| 128 -0.54 (-0.72, -0.37)  | 130 -0.53 (-0.71, -0.35)  |

* Adjusted for gender, parity, maternal history of asthma or allergy, maternal smoking and anxiety during pregnancy, preterm delivery, low birth weight and daycare attendance during first year.

N: Number of participants with data available (approximated from modal assignment)
Table E7  Adjusted associations of wheezing phenotypes 0 to 16½ years with lung function measures at 15 years (pre-salbutamol z-scores) further adjusted by lung function measures at 8 years (pre-salbutamol z-scores), in participants with at least 2 observations of wheeze.

| Wheezing phenotype 0 to 16½ years | \( \text{FEV}_1 \) (SDU) at 15 years | \( \text{FVC} \) (SDU) at 15 years | \( \text{FEV}_1 / \text{FVC} \) (SDU) at 15 years | \( \text{FEF}_{25-75} \) (SDU) at 15 years |
|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Never/Infrequent                 | \( N \) 1784                      | \( N \) 1826                      | \( N \) 1743                      | \( N \) 1825                      |
| \( \text{Adjusted Mean diff.} \) \( (95\% \text{ CI}) \) *  | 0 (ref)                           | 0 (ref)                           | 0 (ref)                           | 0 (ref)                           |
| Pre-school onset remitting       | \( N \) 415                       | \( N \) 422                       | \( N \) 407                       | \( N \) 421                       |
| \( \text{Adjusted Mean diff.} \) \( (95\% \text{ CI}) \) *  | 0.02 (-0.08, 0.11)                | 0.08 (-0.01, 0.17)                | -0.16 (-0.25, -0.07)              | -0.03 (-0.12, 0.06)               |
| Mid-childhood onset remitting    | \( N \) 183                       | \( N \) 187                       | \( N \) 179                       | \( N \) 187                       |
| \( \text{Adjusted Mean diff.} \) \( (95\% \text{ CI}) \) *  | 0.08 (-0.05, 0.22)                | 0.17 (0.04, 0.31)                 | -0.22 (-0.36, -0.09)              | -0.02 (-0.15, 0.11)               |
| School-age onset persisting      | \( N \) 110                       | \( N \) 113                       | \( N \) 110                       | \( N \) 113                       |
| \( \text{Adjusted Mean diff.} \) \( (95\% \text{ CI}) \) *  | -0.05 (-0.22, 0.13)               | 0.11 (-0.06, 0.28)                | -0.33 (-0.50, -0.16)              | -0.19 (-0.36, -0.03)              |
| Late-childhood onset persisting  | \( N \) 117                       | \( N \) 118                       | \( N \) 117                       | \( N \) 118                       |
| \( \text{Adjusted Mean diff.} \) \( (95\% \text{ CI}) \) *  | -0.07 (-0.24, 0.09)               | 0.02 (-0.14, 0.18)                | -0.21 (-0.37, -0.05)              | -0.17 (-0.32, -0.01)              |
| Continuous wheeze               | \( N \) 106                       | \( N \) 110                       | \( N \) 103                       | \( N \) 110                       |
| \( \text{Adjusted Mean diff.} \) \( (95\% \text{ CI}) \) *  | -0.04 (-0.22, 0.14)               | 0.06 (-0.12, 0.23)                | -0.25 (-0.42, -0.07)              | -0.14 (-0.31, 0.03)               |

* Adjusted for gender, parity, maternal history of asthma or allergy, maternal smoking and anxiety during pregnancy, preterm delivery, low birth weight, daycare attendance during first year and additionally for lung function at 8 years.

\( N \): Number of participants with data available (approximated from modal assignment)
**Figure E1** Distribution of 12,303 children with 2 to 14 (complete data) observations of wheeze

**Figure E2** Estimated prevalence of wheezing at each time point from birth to 16½ years for each of the six wheezing phenotypes identified by latent class analysis in 12,303 children with at least 2 observations of wheeze including atopic status as a covariate in the model.