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1 **Filaggrin gene defects are associated with eczema, wheeze and nasal disease during**
2 **infancy: prospective study**

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15

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24

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26 child, infant.

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30 **Capsule Summary**

31 This prospective cohort study describes associations between the presence of filaggrin gene
32 mutations and eczema, rhinitis and wheeze from as early as age six months, raising new
33 questions regarding underlying mechanisms and timing of interventions.

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37 **Filaggrin gene defects are associated with eczema, wheeze and nasal disease during**
38 **infancy: prospective study**

39 *To the Editor:*

40 The protein filaggrin (FLG) is present in the skin and nasal epithelium and helps maintain the
41 skin barrier while performing other functional roles¹⁻³. Many studies have related the
42 presence of common, loss-of-function filaggrin gene (*FLG*) defects to the incidence and
43 severity of eczema³ and the severity of asthma^{4,5} during childhood.

44 As allergy-related diseases, such as eczema or wheeze, often start from early infancy, it is
45 important to explore whether the presence of *FLG* gene defects influences symptoms during
46 infancy (6 and 12-month time points) and how these relate to progression of symptoms
47 beyond infancy. If filaggrin does influence allergy-related symptom status during infancy,
48 there may be justification for trialling interventions starting soon after birth, targeted towards
49 infants with adverse *FLG* genotype, in order to explore beneficial effects on eczema, wheeze
50 and other clinical outcomes as early as 6 and 12 months. It is known that *FLG* defects are
51 associated with impaired skin barrier function, while skin barrier function defects are
52 potentially correctable through the use of regular treatments⁶.

53 A systematic review (December 2018) identified only two studies^{7,8}, both retrospective, that
54 have explored the link between filaggrin gene defects and allergy-related symptoms below 12
55 months. Repeated measurements analyses in the Isle of Wight cohort showed that *FLG*
56 defects were associated with an almost 3-fold increased risk of eczema during the first 12
57 months of life. Nine out of nine infants with eczema at 3 months continued to have eczema at
58 6 months of age⁶. This supported our retrospective analyses showing that presence of *FLG*
59 mutations in two cohorts of modest size (Copenhagen n=379; Manchester n=503) was
60 associated with a significant increase in eczema risk before the age of 12 months⁷. There was
61 a significant enhancement of this risk with cat ownership at birth, thus adding further strength
62 to the hypothesis that the genetically driven skin barrier defect may be playing a causal role
63 through allergen entry⁷. We designed a prospective study to define the role of *FLG* gene
64 defects on allergy-related outcomes during infancy.

65 2312 pregnant women were recruited to the GO-CHILD study between 2009 and 2015 from
66 8 National Health Service (NHS) Trusts in England and Scotland. The study was approved by
67 the Tayside Committee on Medical Research and Ethics. Expectant mothers were invited
68 during antenatal visits and a cord blood sample at birth or saliva in the postnatal period was

69 collected for genotyping. (See Online Methods for details) The cord blood samples were
70 stored at -80°C. Cord blood and saliva samples were transported to the University of Dundee
71 for genotyping. Infants with severe perinatal problems or congenital anomalies were
72 excluded from the subsequent follow-up. The children were followed up for symptoms
73 related to atopy at the ages of 6, 12 and 24 months by postal questionnaires sent to the carers
74 (online Methods). Online Figure 1 shows the methodology and Online Table 1 describes the
75 demographic characteristics of the cohort. Questions related to dry skin, eczema, wheeze,
76 upper respiratory conditions and food allergies, and how these symptoms affected the child's
77 life, including any visits to primary or secondary care and the prescribing of medication. For
78 simplicity and greater accuracy through recall, responses for any of the three options - yes,
79 no, don't know - were used for analysis. 'Wheeze' was defined as 'breathing that makes a
80 high-pitched whistling or squeaking sound from the chest, not the throat' and 'rhinitis' was
81 defined as "a problem with sneezing, or a runny, or blocked nose when he/she did not have a
82 cold or the flu".

83 All genetic analyses were anonymised. Genotyping for *FLG* R501X, 2282del4, S3247X and
84 R2447X was performed as described in earlier papers³⁻⁵. AA refers to the wild- type *FLG*
85 genotype, Aa refers to heterozygous genotype with one of the mutations, and aa refers to
86 homozygous genotype. The homozygous, heterozygous and compound heterozygous
87 genotypes were considered together as Aa/aa. Data analyses were conducted using the IBM
88 SPSS Statistics 146 software, Version 23 (IBM Corp., Armonk, and New York, USA), Stata
89 version 15.2(College Station, TX: StataCorp LLC) and InStat for Macintosh programmes.
90 Binary logistic regression was used to estimate e odds ratios for dry or itchy skin for
91 comparing the effects of the mutations. For atopic outcomes i.e. eczema, wheeze and rhinitis,
92 log-binomial regression was used to estimate relative risks.. Attendance at day-care and
93 exposure to animals were included in all models as covariates after stepwise removal
94 procedures (covariates with $p < 0.05$ were retained). Exposure to smoke, another potential
95 covariate, did not contribute significantly to the model and was not associated with genotype
96 in any subgroup tested and hence was excluded from the final analysis.

97 The presence of dry or itchy skin, and a parent-reported diagnosis of eczema were found to
98 be significantly increased in children with any *FLG* mutation at all the three time-points (6
99 months, 1 year, 2 years following birth). At 6 months of age, the heterozygous and
100 homozygous genotypes for any of the *FLG* mutations were associated with higher risk of

101 eczema (RR 1.82, 95%CI 1.39-2.39), dry or itchy skin (OR 2.71, 95%CI 1.61-4.55), wheeze
102 (RR 1.63, 95%CI 1.00-2.65) and rhinitis (RR 1.46, 95%CI 1.06-2.01), compared to the wild
103 type (Online Table 2). At age 1 year, the presence of one or more *FLG* mutations continued
104 to be associated with higher risk of increased eczema (RR 1.80, 95%CI 1.39-2.32) and odds
105 of dry or itchy skin (OR 2.28, 95%CI 1.32-3.92) compared to wild type, however, the
106 association with wheeze and rhinitis were not significant (Online Table3). At age 2 years, the
107 presence of one or more *FLG* mutations was associated with significantly higher risk of
108 eczema (RR 1.40, 95%CI 1.00-1.97) and odds of dry or itchy skin (OR 1.83, 95%CI 1.02-
109 3.28), The associations with wheeze and rhinitis were not significant (Online Table 4). We
110 report the results of the repeated measurements analysis in Table 5.

111

112 Three-hundred thirty-one families returned completed questionnaires for their children at all
113 three time-points, 6 months, 1 year and 2 years. This allowed us to explore whether there are
114 differences in the time-course of allergy-related events in filaggrin-sufficient versus filaggrin-
115 deficient infants and children over the first two years of life. Infants and young children with
116 *FLG*-deficient status were more likely to suffer from eczema; estimated difference in
117 proportions (d) 0.12(95% CI, 0.01 to 0.24) and rhinitis; $d=0.10$ (95% CI, 0.02 to 0.19) over 6-
118 24 months in comparison to those with *FLG*-sufficient status; however, there were no
119 observed differences for wheeze; $d=0.04$ (95% CI, -0.05 to 0.14). The bar charts show that,
120 for those with a filaggrin mutation, prevalence (red portion of bar) of wheeze, eczema and
121 rhinitis are all greater in the past 6, 12 and 24 months compared to those without a mutation.
122 This pattern is less pronounced for wheeze and no difference was observed at 24 months.
123 (online Figure 2)

124 This is the first prospective study exploring the role of *FLG* gene defects on allergy-related
125 disease outcomes at age 6 months. It indicates that the presence of one or more *FLG* gene
126 defects from birth influences multiple aspects of allergy-related disease, including eczema,
127 wheeze and nasal disease, at early infancy. The increased risk of filaggrin-associated nasal
128 symptoms in 6-month olds may involve interactions between filaggrin deficiency states and
129 allergen exposures to the nose occurring very early in life. The presence of *FLG* defects may

130 also define a sub-phenotype of allergy-related disease that manifests over the first 2 years of
131 life, with implications for allergy-related disease phenotype over later childhood. There are
132 some limitations of this study. We did not plan and perform a formal *a priori* calculation of
133 sample size and this is a weakness of our study. However, the rationale underlying our choice
134 of sample size⁹ is presented in Online Methods. The sample size for all the analyses reported
135 in this paper is at least twice the figure of 150 recommended by the paper⁹. We thus feel there
136 is a high expectation that these results are valid and can be replicated in future meta-
137 analyses⁹. In addition, the recommendations⁹ refer to case-control studies, whereas this is a
138 longitudinal cohort study, which has a more robust design. Findings of association studies
139 must be supported by independent replication, with associations combining family- based and
140 population- based analysis, with an odds ratio/relative risk and/or attributable risk that is
141 high⁹. However, we have not found any published data to compare to and thus replicate our
142 findings. Being a prospective birth cohort study, there is a fair amount of work for new
143 mothers in terms of completing the questionnaires and hence there was a relatively low return
144 rate and complete data comprising all three questionnaires. We are also unable to comment
145 on any possible effect of ethnicity variations as the majority of the participants were
146 Caucasian. Future interventional studies directed at *FLG*-deficient populations from birth
147 may show improvements in clinical outcomes beyond eczema from as early as 6 months of
148 age.

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200

201 **Figure Legends**

202

203 **Figure 1: Study design**

204

205 **Figure 2: Incidence (%) of atopy-related clinical outcomes during the first 2 years of** 206 **life in children where 6-month, 12-month and 24-month follow-up data are available** 207 **(n=331)**

208 Any filaggrin mutation No/Yes: history of eczema

209 *KEY:*

210 Blue bar: No

211 Red bar: Yes

212

213 Any filaggrin mutation No/Yes: history of dry of itchy skin

214 *KEY:*

215 Blue bar: No

216 Red bar: Yes

217

218 Any filaggrin mutation No/Yes: history of wheeze

219 *KEY:*

220 Blue bar: No

221 Red bar: Yes

222

223 Any filaggrin mutation No/Yes: history of rhinitis

224 *KEY:*

225 Blue bar: No

226 Red bar: Yes

227

228

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The Influence of genetic and environmental factors on childhood diseases

Postal questionnaire to assess asthma/allergy and infection

Thank you for agreeing to participate in our study. Please fill out this questionnaire with the information about the first 6 months of your child’s life and return this in the pre-paid envelope that has been supplied.

Name of Child:

Bar Code Sticker

CHI / NHS Number:

Date of Birth:

- Person completing questionnaire (tick box please):
Mother Father Other

- Date questionnaire completed:
day ____ month _____ year _____
(please fill in today’s date)

Bar code sticker

Questions on wheezing

By “wheezing” we mean breathing that makes a high-pitched whistling or squeaking sound from the chest, not the throat

1. Has your child had wheezing or whistling in the chest in the last 6 months? Yes/ No

If you answered “no” please skip to question 11.

2. How old was your child when he/she first began to wheeze?

_____ years _____ months

3. In the first 6 months, has your child had wheezing or whistling in the chest during or soon after a cold or flu? Yes/ No

4. In the first 6 months, has your child had wheezing or whistling in the chest even without having a cold or flu? Yes/ No

5. How many attacks of wheezing has your child had during the first 6 months?

None 1 to 3 4 to 12 more than 12

6. Do these attacks cause him/her to be short of breath?

yes, always most of the time occasionally no, never

7. Which of these two descriptions fits best your child’s wheeze? (tick one only)

a) My child has only short attacks of wheeze, for example with colds. In between these attacks, he/she does not normally wheeze.

b) My child wheezes always or a lot of the time. With colds he/she has attacks with more severe wheeze.

8. In the first 6 months, how often, on average, has your child’s sleep been disturbed due to wheezing?

never woken with wheezing less than one night per week
 one or more nights per week

9. In the first 6 months, how much did wheezing interfere with your child’s daily activities?

not at all a little a moderate amount a lot

10. In the first 6 months did the following things cause wheezing in your child?

- exercise (playing) yes no don't know
- laughing, crying or excitement yes no don't know
- contact with pets or other animals yes no don't know
- food or drinks yes no don't know

11. In the first 6 months, did your child suffer from rattly breathing (rattles)?

- never only with a cold
- sometimes even without a cold almost always

12. Does your child attend day care or nursery? Yes/ No

13. Was your child breastfed? Yes/ No

If yes, how long: less than a month 1-3 months 4-6 months

14. During the first 6 months of life, did your child posit or vomit?

- not at all a little a lot

15. Has your child had an itchy rash at any time in the first 6 months? Yes/ No

Has your child had this itchy skin condition in the last week? Yes/ No

How old was your child when this condition began.....

Has this skin condition ever affected the skin creases in the past – by skin creases we mean fronts of elbows, behind the knees, front of ankles, around the neck or around the eyes?

Yes/ No

16. In the first 6 months, has your child suffered from a dry skin in general? Yes/ No

Has your child suffered from any of the following skin complaints (Please tick one or more)

- Eczema Cradle cap Nappy rash Facial spots Heat rash

17. If your child had a rash did you think at the time that this was related to your washing powder?

Yes/ No

What type of washing powder were you using at the time of the rash?

- Biological Non-biological Not sure

Questions on ears, nose and throat

18. In the first 6 months, how many times has your child had a cold or flu?

- Never 1 - 3 times 4 - 6 times
7 -10 times more than 10 times

19. How long does a cold usually last in your child?

- less than 1 week 1 to 2 weeks
2 to 4 weeks more than 4 weeks

20. In the first 6 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did NOT have a cold or the flu? Yes / No

21. In the first 6 months, how much did this nose problem interfere with your child's daily activities?

- Not at all a little a moderate amount a lot

22. Over the first 6 months, has your child snored or had a blocked nose at night?

Yes/ No

- If yes, how often: only with a cold sometimes even without a cold
almost always

23. Did the snoring/blocked nose disturb your child's sleep?

- not at all a little a moderate amount a lot

Questions on coughing

24. Does your child usually have a cough with colds?

Yes/ No

25. Does your child have a cough even without having a cold?

- No, never yes, sometimes yes, always

26. Do you think that your child coughs more than other children?

Yes/ No

27. In the first 6 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?

Yes/ No

28. In the first 6 months, did the following things cause coughing in your child?

- exercise (playing) yes no don't know
- laughing, crying or excitement yes no don't know
- contact with pets or other animals yes no don't know
- food or drinks yes no don't know

Questions on your household

29. Do you keep any household pets? Yes/No

If yes, do you keep any of these pets? (tick as many as apply)

- Dog Cat Other furry pets Bird

30. Is the child exposed to smoking? Yes/No

31. Does the child's mother smoke cigarettes? Yes/No

- If yes, how many per day? 1 to 10 11 to 20 more than 20

32. Do any other household members smoke cigarettes? Yes/No

If yes, how many per day (total of cigarettes)?

- 1 to 10 11 to 20 more than 20

33. How would you describe the location of your house?

- In a street with very dense traffic (main road)
- In a street with moderate traffic (residential road)
- In a quiet street with little or no traffic

Questions about Infection

Hospital Admissions

Was your baby admitted to the Special Care Baby Unit? Yes/No

- If YES why?

Premature

Breathing problems

Suspected infection

Confirmed infection

- If infection what kind? Chest Meningitis Blood Other?

.....

- Has your child had any/other admissions to hospital? Yes/No

If YES, How many times?

Please fill this table for further information about your child hospital admission

Name of hospital and Date of admission	Age	Diagnosis	Treatment
1 st Admission Name of hospital Date of Admission:		Meningitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Blood infection (sepsis) <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Other.....	Antibiotics through the vein <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Nebuliser <input type="checkbox"/> Fluids through the vein <input type="checkbox"/> Other.....
2 nd Admission Name of hospital Date of Admission:		Meningitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Blood infection (sepsis) <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Other.....	Antibiotics through the vein <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Nebuliser <input type="checkbox"/> Fluids through the vein <input type="checkbox"/> Other.....
3 rd Admission Name of hospital Date of Admission:		Meningitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Blood infection (sepsis) <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Other.....	Antibiotics through the vein <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Nebuliser <input type="checkbox"/> Fluids through the vein <input type="checkbox"/> Other.....

(Please find the attached tables if needed for more admission)

GP Visit

1. Has your child ever visited the GP when unwell? Yes/No

- If YES, How many times

(Please fill this table for further information about your child's GP visit)

Date/age of visit	Symptoms	Diagnosis	Treatment
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....

(Please find the attached tables if needed for more GP visit)

Child's Health at Home

2. Are your child's vaccinations up to date?

Yes

No

Partly

• Has your child been unwell at home but not needed to go to the GP's? Yes/ No

If Yes, Please tell us more about it.

Date or age of illness	Symptoms	Treatment
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....

(Please find the attached tables if needed for more Child's Health at Home)

Did you have problems understanding this questionnaire? Yes no

Please write any comments you have about your child's health or about the questionnaire in the space below:

.....
.....
.....

Thank you for completing the questionnaire. It will cost you nothing to return it if you use the pre-paid envelope provided (FREEPOST). No stamp required.

For any queries please do not hesitate to contact us:

Dr Kaninika Basu

01273 696955, ext 2404

Questions about Infection

Hospital Admissions

Was your baby admitted to the Special Care Baby Unit? Yes/No

- If YES why?

Premature

Breathing problems

Suspected infection

Confirmed infection

- If infection what kind? Chest Meningitis Blood Other?

.....

- Has your child had any/other admissions to hospital? Yes/No

If YES, How many times?

Please fill this table for further information about your child hospital admission

Name of hospital and Date of admission	Age	Diagnosis	Treatment
1 st Admission Name of hospital Date of Admission:		Meningitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Blood infection (sepsis) <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Other.....	Antibiotics through the vein <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Nebuliser <input type="checkbox"/> Fluids through the vein <input type="checkbox"/> Other.....
2 nd Admission Name of hospital Date of Admission:		Meningitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Blood infection (sepsis) <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Other.....	Antibiotics through the vein <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Nebuliser <input type="checkbox"/> Fluids through the vein <input type="checkbox"/> Other.....
3 rd Admission Name of hospital Date of Admission:		Meningitis <input type="checkbox"/> Pneumonia <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Blood infection (sepsis) <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Other.....	Antibiotics through the vein <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Nebuliser <input type="checkbox"/> Fluids through the vein <input type="checkbox"/> Other.....

(Please find the attached tables if needed for more admission)

GP Visit

3. Has your child ever visited the GP when unwell? Yes/No

- If YES, How many times

(Please fill this table for further information about your child's GP visit)

Date/age of visit	Symptoms	Diagnosis	Treatment
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Other.....	Viral cold <input type="checkbox"/> Chest infection <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Wheeze <input type="checkbox"/> Feeding problems <input type="checkbox"/> Urinary tract infection <input type="checkbox"/> Ear infection <input type="checkbox"/> Other.....	Advice only <input type="checkbox"/> Oral antibiotics <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol/Calpol <input type="checkbox"/> Ibuprofen/Nurofen <input type="checkbox"/> Other.....

(Please find the attached tables if needed for more GP visit)

Child's Health at Home

4. Are your child's vaccinations up to date?

Yes

No

Partly

• Has your child been unwell at home but not needed to go to the GP's? Yes/ No

If Yes, Please tell us more about it.

Date or age of illness	Symptoms	Treatment
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....
	Cough <input type="checkbox"/> Runny/blocked nose <input type="checkbox"/> Rash <input type="checkbox"/> Temperature <input type="checkbox"/> Diarrhoea/vomiting <input type="checkbox"/> Other.....	Observe only <input type="checkbox"/> Inhalers <input type="checkbox"/> Paracetamol (Calpol) <input type="checkbox"/> And/or Ibuprofen (Nurofen) <input type="checkbox"/> Other.....

(Please find the attached tables if needed for more Child's Health at Home)



The Influence of genetic and environmental factors on childhood diseases

Postal questionnaire to assess asthma/allergy: Year 1

Thank you for agreeing to participate in our study. Please fill out this questionnaire with the information about the first 1 year of your child's life and return it in the pre-paid envelope that has been supplied.

How to complete the questionnaire: Please tick the appropriate box

Example: Person completing questionnaire (tick box please):

Mother Father Other

Name of Child:

Bar Code Sticker

Date of Birth:

- Person completing questionnaire (tick box please):

Mother Father Other

- Date questionnaire completed: day ____ month ____ year ____
(please fill in today's date)

1. In the last year, has your child had an **ITCHY** skin condition - by *itchy* we mean scratching or rubbing the skin)?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 2

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

1b.	Was this ITCHY skin condition coming and going for at least six months?	Yes	<input type="checkbox"/>
		No	<input type="checkbox"/>
1c.	Has your child had this ITCHY skin condition in the last week?	Yes	<input type="checkbox"/>
		No	<input type="checkbox"/>
1d.	How old was your child when this skin condition began?	<input type="text"/>	months old
1e.	Has this skin condition ever affected the skin creases in the past – by skin creases we mean fronts of elbows, behind the knees, front of ankles, around the neck or around the eyes?	Yes	<input type="checkbox"/>
		No	<input type="checkbox"/>

2. In the first year, has your child suffered from a dry skin in general?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

3. In the first year, has your child suffered from any of the following skin complaints: (PLEASE TICK ALL THAT APPLY).

Eczema	<input type="checkbox"/>
Facial spots	<input type="checkbox"/>
Nappy rash	<input type="checkbox"/>

4. In the first year, has your child ever had wheezing or whistling in the chest? By "wheezing" we mean breathing that makes a high-pitched whistling or squeaking sound from the chest, not the throat

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 12

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

4a. How old was your child when he/she first began to wheeze? months

5. In the first year, has your child had wheezing or whistling in the chest during or soon after a cold or flu? Yes
No

6. How many attacks of wheezing has your child had in the first year? None
1 to 3
4 to 12
More than 12

7. Do these attacks cause him/her to be short of breath? Yes, always
Most of the time
Occasionally
No, never

8. Which of these two descriptions fits best your child's wheeze? (TICK ONE ONLY)

My child has only short attacks of wheeze, for example with colds. In between these attacks, he/she does not normally wheeze
My child wheezes always or a lot of the time. With colds he/she has attacks with more severe wheeze

9. In the first year, how often, on average, has your child's sleep been disturbed due to wheezing? never woken with wheezing
less than one night per week
one or more nights per week

10. In the first year, did any of the following things cause wheezing in your child?

Feeding; playing; exercise?

Yes
No
Don't know

laughing, crying or excitement?

Yes
No
Don't know

Contact with pets or other animals?

Yes
No
Don't know

Food or drinks?

Yes
No
Don't know

11. Looking back on the first year, do you think that your child had asthma?

Yes
No

12. Does your child usually have a cough with colds?

Yes
No

13. Does your child have a cough even without having a cold?

Yes, always
Yes, sometimes
No, never

14. Do you think that your child coughs more than other children?

Yes
No

15. In the first year, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?

Yes
No

16. In the first year, did the following things cause coughing in your child?

Feeding, playing or exercise?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

laughing, crying or excitement?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

contact with pets or other animals?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

food or drinks?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

17. How often did your child see the GP for coughing or wheezing during the first 12 months?

Never	<input type="checkbox"/>
Once	<input type="checkbox"/>
2-3 times	<input type="checkbox"/>
4-6 times	<input type="checkbox"/>
7 or more times	<input type="checkbox"/>

18. In the first 12 months, has wheezing or asthma resulted in your child:

being referred to a consultant in hospital

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

being admitted to hospital

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

attending the casualty (A and E) department

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

attending (or calling) the GP in an emergency

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

19. Did your child take any of the following drugs in the first 12 months?
 Salbutamol, Ventolin, Bricanyl or other blue inhaler

No
 Don't know

Pulmicort, Flixotide, Becotide or other brown inhaler

Yes
 No
 Don't know

Steroid tablets (prednisolone) for asthma attacks

Yes
 No
 Don't know

20. In the first year, did your child suffer from rattly breathing (rattles)?

Never
 Only with a cold
 Sometimes even without a cold
 Almost always

21. In the first year, how many times has your child had a cold or flu?

Never
 1-3 times
 4-6 times
 7-10 times
 More than 10 times

22. How long does a cold usually last in your child?

Less than 1 week
 1 to 2 weeks
 2 to 4 weeks
 More than 4 weeks

23. In the first year, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did NOT have a cold or the flu?

Yes
 No

24. In the first year, how much did this nose problem interfere with your child's feeding, playing or other activities?

Not at all
 A little
 A moderate amount
 A lot

25. Over the first 12months, has your child snored at night?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 26

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

25.a. If yes, has he/she snored:	Only with a cold	<input type="checkbox"/>
	Sometimes even without a cold	<input type="checkbox"/>
	Almost always	<input type="checkbox"/>
25.b Did the snoring disturb your child's sleep?	Not at all	<input type="checkbox"/>
	A little	<input type="checkbox"/>
	A moderate amount	<input type="checkbox"/>
	A lot	<input type="checkbox"/>

26. In the first 12months, has your child had any ear infections?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

27. Has your child ever suffered from any of the following conditions?

pneumonia?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

whooping cough?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

bronchiolitis?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

croup?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

28. Does your child attend day care, childminder, nursery school or play school? Yes
No

29. Was your child breastfed? Yes
No

If yes, how long: less than a month
1-3 months
4-6 months
more than 6 months

30. During the first year of life, did your child posit or vomit? Not at all
A little
A lot

31. Do you think your child has a reaction to any food items? Yes
No

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 32

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

<p>31a. Does your child have a reaction to any of these foods? (PLEASE TICK ALL THAT APPLY)</p> <p>If you have ticked 'other', please describe the type of food that causes the reaction:.....</p>	Peanuts	<input type="checkbox"/>
	Cows milk	<input type="checkbox"/>
	Egg	<input type="checkbox"/>
	Gluten (eg wheat, oats)	<input type="checkbox"/>
	Fruit	<input type="checkbox"/>
	Other (please describe)	<input type="checkbox"/>
<p>31b. What type of reaction does the food cause? (PLEASE TICK ALL THAT APPLY)</p> <p>If you have ticked 'other', please describe the type of reaction:.....</p>	Breathing problems	<input type="checkbox"/>
	Vomit	<input type="checkbox"/>
	Diarrhea	<input type="checkbox"/>
	Stomach pain	<input type="checkbox"/>
	Rashes	<input type="checkbox"/>
	Irritability	<input type="checkbox"/>
Other (please describe)	<input type="checkbox"/>	

31c. Has your child been treated by a doctor for allergies to any of these foods? (PLEASE TICK ALL THAT APPLY)

If you have ticked 'other', please describe the type of food allergy that has been treated:.....
.....

Peanuts	<input type="checkbox"/>
Cows milk	<input type="checkbox"/>
Egg	<input type="checkbox"/>
Gluten (eg wheat, oats)	<input type="checkbox"/>
Fruit	<input type="checkbox"/>
Other (please describe)	<input type="checkbox"/>

32. Does your child have brothers and sisters who have the same mother and father as him/her?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If yes, how many? (please fill in number)

If yes, how many have: -

Asthma or wheezing? (please fill in number)	<input type="text"/>
Hay fever? (please fill in number)	<input type="text"/>
Eczema? (please fill in number)	<input type="text"/>

33. How many children under 16 live in your household?

(PLEASE FILL IN NUMBER)

34. How many adults over 16 usually live in your household?

(PLEASE FILL IN NUMBER)

35. How many rooms are there in your house, not counting kitchens, bathrooms and toilets? (PLEASE FILL IN NUMBER)

36. At what age did the child's mother finish full-time education?

(PLEASE FILL IN AGE)

37. Which fuel is mainly used for cooking in your home?

Electricity	<input type="checkbox"/>
Gas	<input type="checkbox"/>
Other fuel	<input type="checkbox"/>

38. How do you heat your home? (PLEASE TICK AS MANY AS APPLY)

Electric central heating	<input type="checkbox"/>
Gas central heating	<input type="checkbox"/>
Central heating with other fuel, e.g. oil	<input type="checkbox"/>
Heaters in rooms	<input type="checkbox"/>
Coal or wood fire	<input type="checkbox"/>

39. Is there visible damp within the house?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If there is visible damp, which rooms is it in?
(PLEASE TICK ALL THAT APPLY)

Kitchen	<input type="checkbox"/>
Bathroom	<input type="checkbox"/>
Child's bedroom	<input type="checkbox"/>
Other living areas	<input type="checkbox"/>

40. What type of flooring does your child have in his/her bedroom?

Carpet	<input type="checkbox"/>
Laminate	<input type="checkbox"/>
Laminate with rug	<input type="checkbox"/>
Other hard flooring	<input type="checkbox"/>
Other	<input type="checkbox"/>

41. Is your child exposed to animals?

(By exposed we mean do they come into close contact with any animals on a regular basis)

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If yes, which of the following animals?

(PLEASE TICK ALL THAT APPLY)

If your child is exposed to other animals that are not on the list, please write which kind of animals in the space below:

.....

- Cat
- Dog
- Bird
- Fish
- Rat
- Gerbil
- Rabbit
- Hamster
- Guinea pig
- Sheep
- Pigs
- Cows
- Horses

42. Does the child's mother smoke cigarettes?

- Yes
- No

If yes, how many per day?

- 1 to 10
- 11 to 20
- More than 20

43. Do any other household members smoke cigarettes?

- Yes
- No

If yes, how many per day (total cigarettes smoked by household members other than mother)?

- 1 to 10
- 11 to 20
- More than 20

44. How would you best describe the location of your house?

(PLEASE TICK THE ONE THAT BEST APPLIES)

- In a street with very dense traffic (main road)
- In a street with moderate traffic (residential road)
- In a quiet street with little or no traffic

45. Did you have any problems understanding this questionnaire?

- Yes
- No

Please write any comments you have about your child's health or about the questionnaire in the space below:

.....
.....
.....

Thank you for completing the questionnaire. It will cost you nothing to return it if you use the pre-paid envelope provided.

For any queries please do not hesitate to contact us:

Ms Liz Lance, Dr Kaninika Basu; Contact: 01273 696955, ext 2404, 2353

Liz.Lance@bsuh.nhs.uk, k.basu@bsms.ac.uk



The Influence of genetic and environmental factors on childhood diseases

Postal questionnaire to assess asthma/allergy: Year 2

Thank you for agreeing to participate in our study. Please fill out this questionnaire with the information about the first 2 years of your child's life and return it in the pre-paid envelope that has been supplied.

How to complete the questionnaire: Please tick the appropriate box

Example: Person completing questionnaire (tick box please):

Mother Father Other

Name of Child:

Bar Code Sticker

Date of Birth:

- Person completing questionnaire (tick box please):

Mother Father Other

- Date questionnaire completed: day ____ month ____ year ____
(please fill in today's date)

1. In the last year, has your child had an **ITCHY** skin condition - by *itchy* we mean scratching or rubbing the skin)?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 2

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

1b.	Was this ITCHY skin condition coming and going for at least six months?	Yes	<input type="checkbox"/>
		No	<input type="checkbox"/>
1c.	Has your child had this ITCHY skin condition in the last week?	Yes	<input type="checkbox"/>
		No	<input type="checkbox"/>
1d.	How old was your child when this skin condition began?	<input type="text"/>	months old
1e.	Has this skin condition ever affected the skin creases in the past – by skin creases we mean fronts of elbows, behind the knees, front of ankles, around the neck or around the eyes?	Yes	<input type="checkbox"/>
		No	<input type="checkbox"/>

2. Between 12 and 24months, has your child suffered from a dry skin in general?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

3. Between 12 and 24months, has your child suffered from any of the following skin complaints: (PLEASE TICK ALL THAT APPLY).

Eczema	<input type="checkbox"/>
Facial spots	<input type="checkbox"/>
Nappy rash	<input type="checkbox"/>

4. Between 12 and 24months, has your child ever had wheezing or whistling in the chest? By "wheezing" we mean breathing that makes a high-pitched whistling or squeaking sound from the chest, not the throat

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 12

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

4a. How old was your child when he/she first began to wheeze? months

5. In the second year, has your child had wheezing or whistling in the chest during or soon after a cold or flu? Yes
No

6. How many attacks of wheezing has your child had between 12 and 24 months? None
1 to 3
4 to 12
More than 12

7. Do these attacks cause him/her to be short of breath? Yes, always
Most of the time
Occasionally
No, never

8. Which of these two descriptions fits best your child's wheeze? (TICK ONE ONLY)

My child has only short attacks of wheeze, for example with colds. In between these attacks, he/she does not normally wheeze
My child wheezes always or a lot of the time. With colds he/she has attacks with more severe wheeze

9. Between 12 and 24 months, how often, on average, has your child's sleep been disturbed due to wheezing? never woken with wheezing
less than one night per week
one or more nights per week

10. Between 12 and 24months, did any of the following things cause wheezing in your child?

Feeding; playing; exercise?

Yes

No

Don't know

laughing, crying or excitement?

Yes

No

Don't know

Contact with pets or other animals?

Yes

No

Don't know

Food or drinks?

Yes

No

Don't know

11. Looking back between 12 and 24months, do you think that your child had asthma?

Yes

No

12. Does your child usually have a cough with colds?

Yes

No

13. Does your child have a cough even without having a cold?

Yes, always

Yes, sometimes

No, never

14. Do you think that your child coughs more than other children?

Yes

No

15. Between 12 and 24months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?

Yes

No

16. Between 12 and 24months, did the following things cause coughing in your child?

Feeding, playing or exercise?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

laughing, crying or excitement?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

contact with pets or other animals?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

food or drinks?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Don't know	<input type="checkbox"/>

17. How often did your child see the GP for coughing or wheezing between 12 and 24months?

Never	<input type="checkbox"/>
Once	<input type="checkbox"/>
2-3 times	<input type="checkbox"/>
4-6 times	<input type="checkbox"/>
7 or more times	<input type="checkbox"/>

18. Between 12 and 24months, has wheezing or asthma resulted in your child:

being referred to a consultant in hospital

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

being admitted to hospital

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

attending the casualty (A and E) department

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

attending (or calling) the GP in an emergency

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

Yes	<input type="checkbox"/>
-----	--------------------------

19. Did your child take any of the following drugs between 12 and 24months?
 Salbutamol, Ventolin, Bricanyl or other blue inhaler

No
 Don't know

Pulmicort, Flixotide, Becotide or other brown inhaler

Yes
 No
 Don't know

Steroid tablets (prednisolone) for asthma attacks

Yes
 No
 Don't know

20. Between 12 and 24months, did your child suffer from rattly breathing (rattles)?

Never
 Only with a cold
 Sometimes even without a cold
 Almost always

21. In the second year, how many times has your child had a cold or flu?

Never
 1-3 times
 4-6 times
 7-10 times
 More than 10 times

22. How long does a cold usually last in your child?

Less than 1 week
 1 to 2 weeks
 2 to 4 weeks
 More than 4 weeks

23. Between 12 and 24months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did NOT have a cold or the flu?

Yes
 No

24. Between 12 and 24months, how much did this nose problem interfere with your child's feeding, playing or other activities?

Not at all
 A little
 A moderate amount
 A lot

25. Between 12 and 24months, has your child snored at night?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 26

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

25.a. If yes, has he/she snored:	Only with a cold	<input type="checkbox"/>
	Sometimes even without a cold	<input type="checkbox"/>
	Almost always	<input type="checkbox"/>
25.b Did the snoring disturb your child's sleep?	Not at all	<input type="checkbox"/>
	A little	<input type="checkbox"/>
	A moderate amount	<input type="checkbox"/>
	A lot	<input type="checkbox"/>

26. Between 12 and 24months, has your child had any ear infections?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

27. Has your child ever suffered from any of the following conditions?

pneumonia?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

whooping cough?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

bronchiolitis?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

croup?

No, never	<input type="checkbox"/>
Yes, once	<input type="checkbox"/>
Yes, more than once	<input type="checkbox"/>

28. Does your child attend day care, childminder, nursery school or play school? Yes
No

29. Was your child breastfed? Yes
No

If yes, how long: less than a month
1-3 months
4-6 months
more than 6 months

30. Between 12 and 24 months, did your child posit or vomit? Not at all
A little
A lot

31. Do you think your child has a reaction to any food items? Yes
No

IF YOU HAVE ANSWERED 'NO' PLEASE SKIP TO QUESTION 32

IF YOU HAVE ANSWERED 'YES' PLEASE ANSWER THE QUESTIONS IN THE SHADED BOX BELOW:

<p>31a. Does your child have a reaction to any of these foods? (PLEASE TICK ALL THAT APPLY)</p> <p>If you have ticked 'other', please describe the type of food that causes the reaction:.....</p>	Peanuts	<input type="checkbox"/>
	Cows milk	<input type="checkbox"/>
	Egg	<input type="checkbox"/>
	Gluten (eg wheat, oats)	<input type="checkbox"/>
	Fruit	<input type="checkbox"/>
	Other (please describe)	<input type="checkbox"/>
<p>31b. What type of reaction does the food cause? (PLEASE TICK ALL THAT APPLY)</p> <p>If you have ticked 'other', please describe the type of reaction:.....</p>	Breathing problems	<input type="checkbox"/>
	Vomit	<input type="checkbox"/>
	Diarrhea	<input type="checkbox"/>
	Stomach pain	<input type="checkbox"/>
	Rashes	<input type="checkbox"/>
	Irritability	<input type="checkbox"/>
Other (please describe)	<input type="checkbox"/>	

31c. Has your child been treated by a doctor for allergies to any of these foods? (PLEASE TICK ALL THAT APPLY)

If you have ticked 'other', please describe the type of food allergy that has been treated:.....
.....

Peanuts	<input type="checkbox"/>
Cows milk	<input type="checkbox"/>
Egg	<input type="checkbox"/>
Gluten (eg wheat, oats)	<input type="checkbox"/>
Fruit	<input type="checkbox"/>
Other (please describe)	<input type="checkbox"/>

32. Does your child have brothers and sisters who have the same mother and father as him/her?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If yes, how many? (please fill in number)

If yes, how many have: -

Asthma or wheezing? (please fill in number)	<input type="text"/>
Hay fever? (please fill in number)	<input type="text"/>
Eczema? (please fill in number)	<input type="text"/>

33. How many children under 16 live in your household?

(PLEASE FILL IN NUMBER)

34. How many adults over 16 usually live in your household?

(PLEASE FILL IN NUMBER)

35. How many rooms are there in your house, not counting kitchens, bathrooms and toilets? (PLEASE FILL IN NUMBER)

36. At what age did the child's mother finish full-time education?

(PLEASE FILL IN AGE)

37. Which fuel is mainly used for cooking in your home?

Electricity	<input type="checkbox"/>
Gas	<input type="checkbox"/>
Other fuel	<input type="checkbox"/>

38. How do you heat your home? (PLEASE TICK AS MANY AS APPLY)

Electric central heating	<input type="checkbox"/>
Gas central heating	<input type="checkbox"/>
Central heating with other fuel, e.g. oil	<input type="checkbox"/>
Heaters in rooms	<input type="checkbox"/>
Coal or wood fire	<input type="checkbox"/>

39. Is there visible damp within the house?

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If there is visible damp, which rooms is it in?
(PLEASE TICK ALL THAT APPLY)

Kitchen	<input type="checkbox"/>
Bathroom	<input type="checkbox"/>
Child's bedroom	<input type="checkbox"/>
Other living areas	<input type="checkbox"/>

40. What type of flooring does your child have in his/her bedroom?

Carpet	<input type="checkbox"/>
Laminate	<input type="checkbox"/>
Laminate with rug	<input type="checkbox"/>
Other hard flooring	<input type="checkbox"/>
Other	<input type="checkbox"/>

41. Is your child exposed to animals?

(By exposed we mean do they come into close contact with any animals on a regular basis)

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

If yes, which of the following animals?

(PLEASE TICK ALL THAT APPLY)

If your child is exposed to other animals that are not on the list, please write which kind of animals in the space below:

.....

- Cat
- Dog
- Bird
- Fish
- Rat
- Gerbil
- Rabbit
- Hamster
- Guinea pig
- Sheep
- Pigs
- Cows
- Horses

42. Does the child's mother smoke cigarettes?

- Yes
- No

If yes, how many per day?

- 1 to 10
- 11 to 20
- More than 20

43. Do any other household members smoke cigarettes?

- Yes
- No

If yes, how many per day (total cigarettes smoked by household members other than mother)?

- 1 to 10
- 11 to 20
- More than 20

44. How would you best describe the location of your house?

(PLEASE TICK THE ONE THAT BEST APPLIES)

- In a street with very dense traffic (main road)
- In a street with moderate traffic (residential road)
- In a quiet street with little or no traffic

45. Did you have any problems understanding this questionnaire?

- Yes
- No

Please write any comments you have about your child's health or about the questionnaire in the space below:

.....
.....
.....

Thank you for completing the questionnaire. It will cost you nothing to return it if you use the pre-paid envelope provided.

For any queries please do not hesitate to contact us:

Ms Liz Lance, Dr Kaninika Basu; Contact: 01273 696955, ext 2404, 2353

Liz.Lance@bsuh.nhs.uk, k.basu@bsms.ac.uk

1 **Filaggrin gene defects are associated with eczema, wheeze and nasal disease during**
2 **infancy: prospective study**

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20 **Declaration of financial interest:** None

21 **None of the authors disclose any conflict of interest statement.**

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28 **Methods**

29 The GO-CHILD study is a longitudinal study of a birth-cohort of 2312 infants born to
30 mothers recruited from antenatal clinics in 8 different National Health Service (NHS) trusts
31 in England and Scotland, between March 2009 and July 2015. The quality control procedures
32 followed 'Good Clinical Practice' guidelines¹. The study is reported in accordance with the
33 STROBE checklist.² The study was approved by the Tayside Committee on Medical
34 Research and Ethics.

35

36 At all the sites, an information leaflet about the study was given to all expecting mothers at
37 their 12-week scan appointment and at any other antenatal visit from 12 weeks gestation
38 onwards. Informed written consent was obtained prior to recruitment. The children were
39 followed-up until the age of 2 years. All neonates born at term were eligible for inclusion in
40 the study; and infants with any perinatal insult such as perinatal asphyxia, significant
41 respiratory difficulty, or congenital anomalies were excluded.

42 We estimated the required sample size based on the findings reported in a letter in Nature
43 Genetics published a few years before we designed this study³. This study showed that a
44 small sample size of the first publication and a large number of studies were independent
45 predictors of discrepancies identified on subsequent meta-analyses of genetic association
46 studies. The authors noted statistically significant discrepancies in 5 of 7 cases in which the
47 first publications had a sample size of less than 150, compared with 3 of 29 when the sample
48 size of the first study or studies was more than 150. We allowed for a relatively high level of
49 attrition and aimed for an antenatal cohort size exceeding n=2000, aiming to achieve a
50 sample size over 150 for all the analyses.

51

52

53 Detailed study design is described in online figure 1. The antenatal questionnaire collected
54 information on family history of atopic conditions, environmental exposure to the child and
55 parental smoking. The children were followed up for symptoms related to atopy, at the ages
56 of 6, 12 and 24 months by postal questionnaires. These questionnaires were used to collect
57 comprehensive information on respiratory, nasal and dermatological outcomes, precipitating
58 environmental factors such as exposure to smoking and animals, and the effects of these
59 conditions in relation to daily activities. These questions related to dry skin, eczema, wheeze,
60 upper respiratory conditions and food allergies, and how these symptoms affected the child's
61 life, including any visits to primary or secondary care and the prescribing of medication. For
62 simplicity and greater accuracy through recall, only yes/no responses for any of the three
63 options (yes, no, don't know) were used for analysis. The questionnaires were developed
64 based on the Leicestershire questionnaire⁴ and were modified to make them relevant for
65 younger children and also for the general population and not targeted towards children with
66 asthma or wheeze.

67

68 'Wheeze' was defined as 'breathing that makes a high-pitched whistling or squeaking sound
69 from the chest, not the throat' and 'rhinitis' was defined as 'a problem with sneezing, or a
70 runny, or blocked nose when he/she did NOT have a cold or the flu'. 'Dry and itchy skin' was
71 the parental report of generally dry and itchy skin but not including affected skin creases,
72 'respiratory impairment' was defined as any respiratory symptom affecting day-to-day life
73 such as shortness of breath, disturbed sleep, dry nocturnal cough, and the nasal symptoms
74 affecting day-to-day life comprised either or all of decreased daily activity due to rhinitis,
75 snoring and sleep disturbance due to nasal symptoms.

76

77 Cord blood samples were collected at the time of delivery for genotyping. In absence of cord
78 blood, a sample of saliva was collected in the postnatal period. Expecting mothers were
79 invited through posters and leaflets to join the study at the time of their antenatal visits. Cord
80 blood samples were collected at the time of delivery for genotyping. If this was unsuccessful,
81 a sample of saliva (Oragene Neonatal Saliva Collection Kit, DNA Genotek, Ottawa, Canada
82 K2G5W6) was collected in the postnatal period. The sample was collected by the researchers
83 either at home or in the hospital, or posted to the researchers after collection at home by the
84 family. The cord blood samples were stored at -80°C at the individual sites and later
85 transported in batches to the Biomedical Research Institute, Dundee, for genotyping. The
86 saliva was obtained from the infant using the Oragene Neonatal saliva sample collection kit
87 (DNA Genotek, 29 Camelot Drive, Ottawa, Ontario, Canada K2G5W6). The sample was
88 collected by the researchers either at home or in the hospital, or by the mother at home and
89 posted to the researchers. All the genetic analyses are anonymised.

90
91 Genotyping for FLG R501X and 2282del4 was performed as described in our earlier
92 publication⁵. AA refers to the wild- type FLG genotype for R501X, 2282del4, S3247X and
93 R2447X mutations, Aa refers to heterozygous genotype for either of R501X, 2282del4,
94 S3247X and R2447X, and aa refers to homozygous genotype for either of R501X, 2282del4,
95 S3247X or R2447X. The homozygous, heterozygous and compound heterozygous genotypes
96 were considered together as Aa/aa.

97
98 Data analyses were conducted using the IBM SPSS Statistics 146 software, Version 23 (IBM
99 Corp., Armonk, and New York, USA), Stata version 15.1 (College Station, TX: StataCorp
100 LLC) and Instat for Macintosh programmes. The chi-square test was used to compare the
101 effects of the mutations on the atopic outcomes such as eczema, wheeze, rhinitis and dry or

102 itchy skin. Significance was assessed at $P < 0.05$. We have fitted log-binomial models to
103 report relative risks and report estimates with 95% CIs; and we have additionally fitted log-
104 binomial models by generalised estimating equations with an unstructured correlation matrix
105 (to account for the lack of independence between repeated measurements, accepting that
106 there are insufficient repeated measurements to estimate an autoregressive correlation
107 structure). We report the results of the repeated measurements analysis in Table 5.
108 We also performed binary logistic regression for the 4 atopic outcomes individually at each
109 time point separately and subsequently log-binomial regressions for each outcome to obtain
110 estimates of relative risk.

111

112

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128
129

Figure 1: Study design

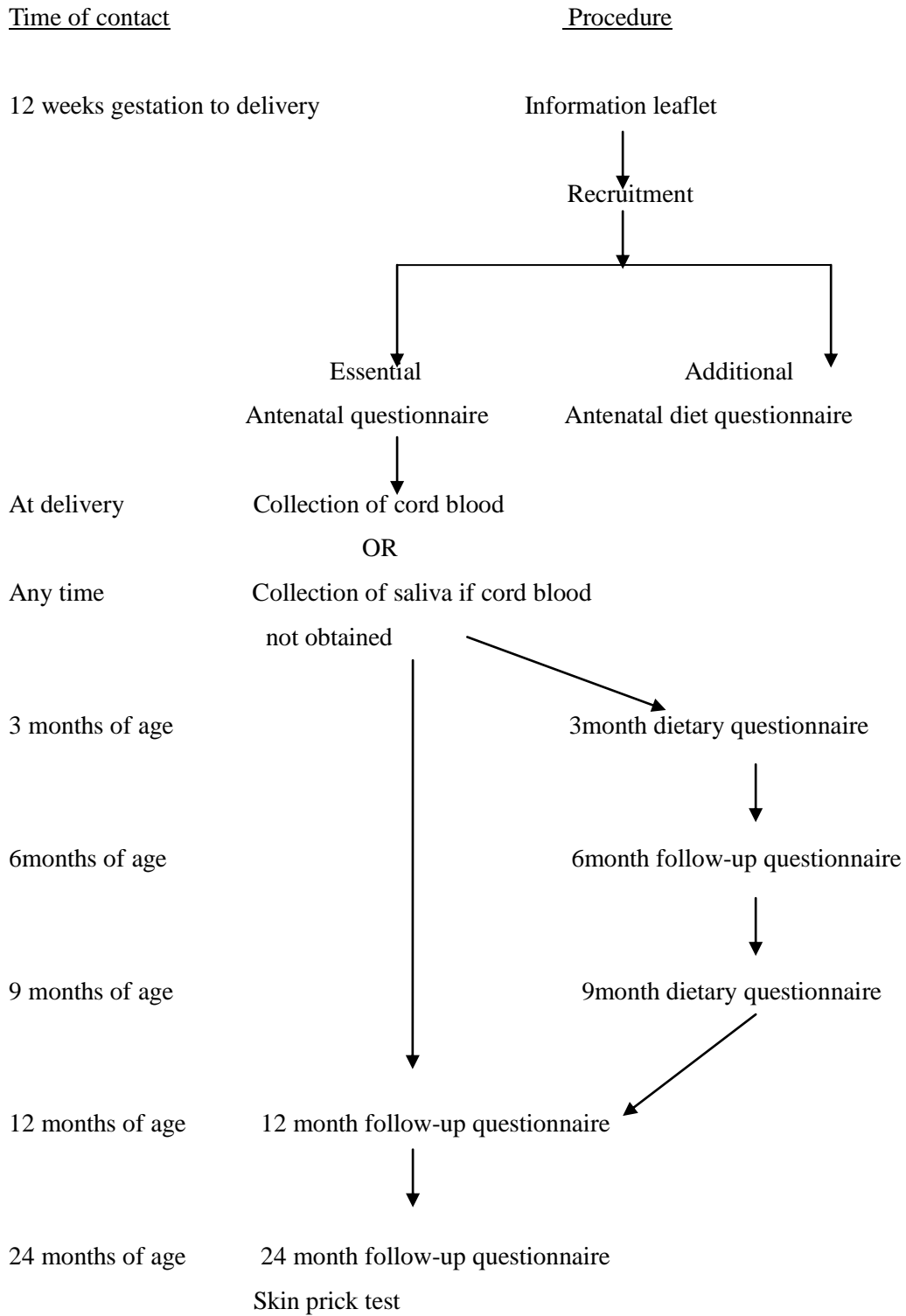
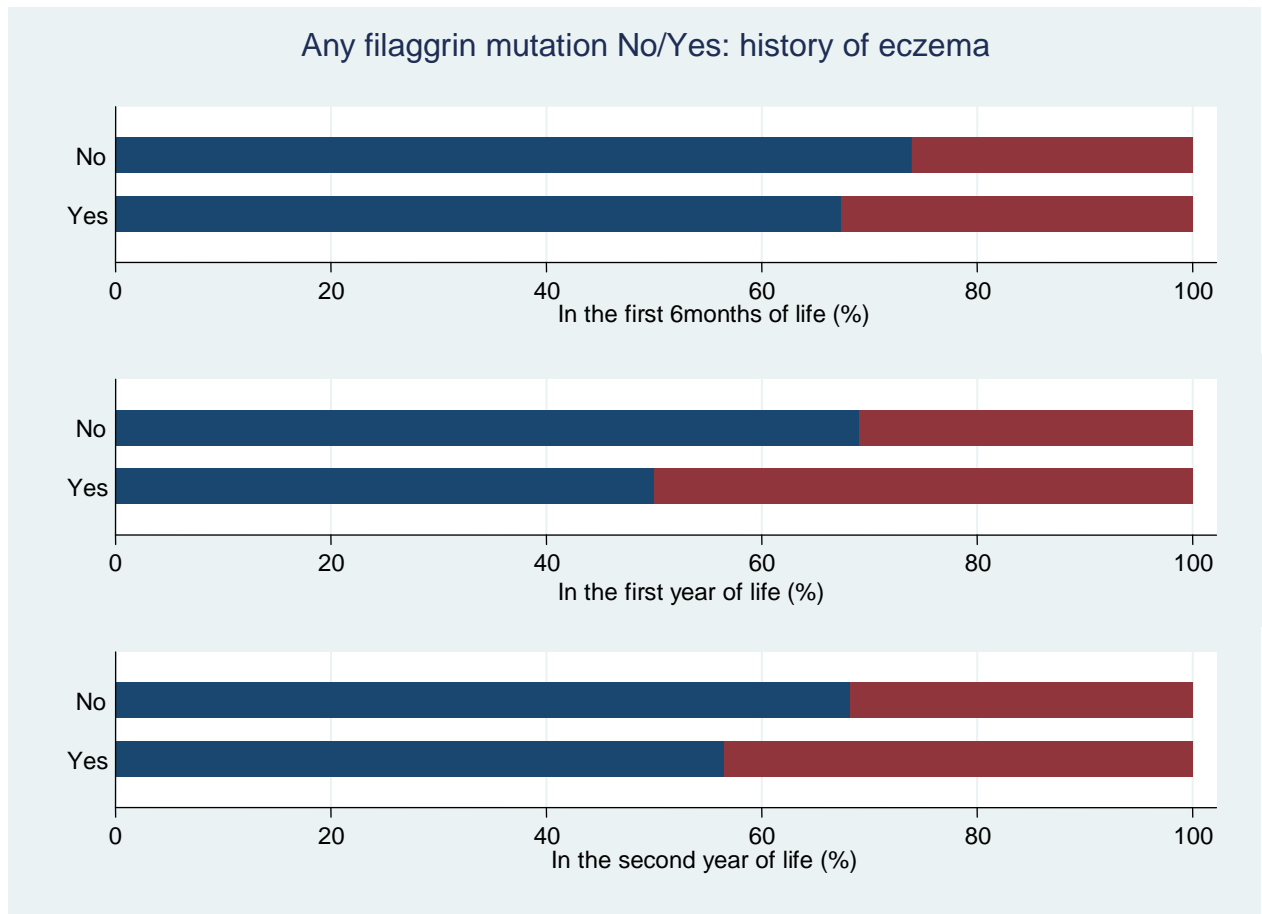


Figure 2: Incidence (%) of atopy-related clinical outcomes during the first 2 years of life in children where 6-month, 12-month and 24-month follow-up data are available (n=331)

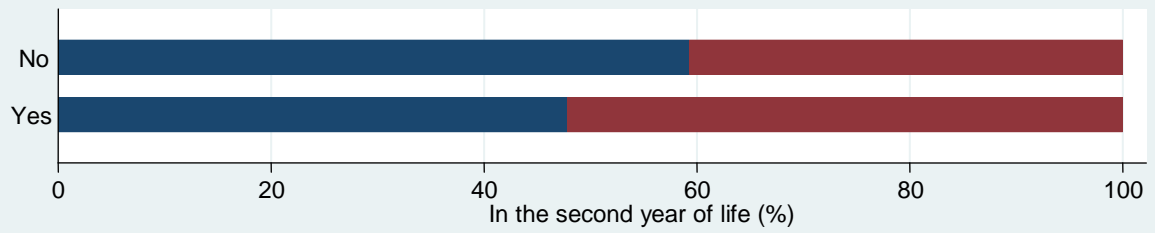
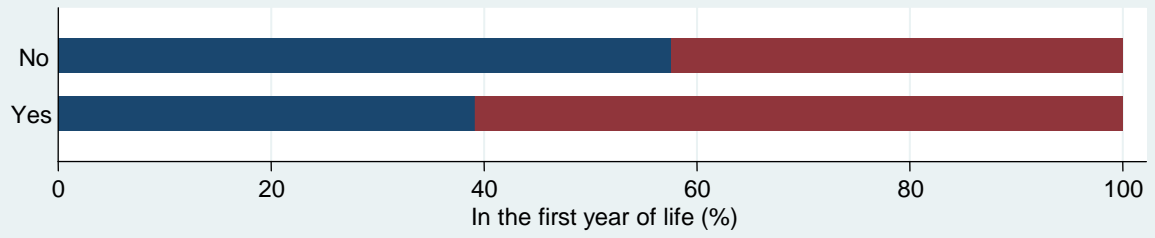
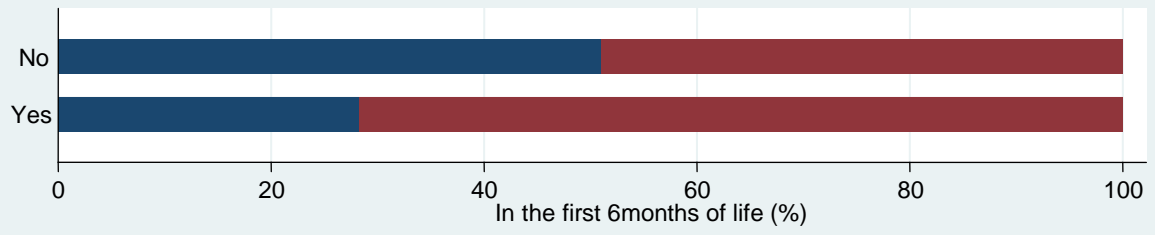


KEY:

Blue bar: No

Red bar: Yes

Any filaggrin mutation No/Yes: history of dry or itchy skin

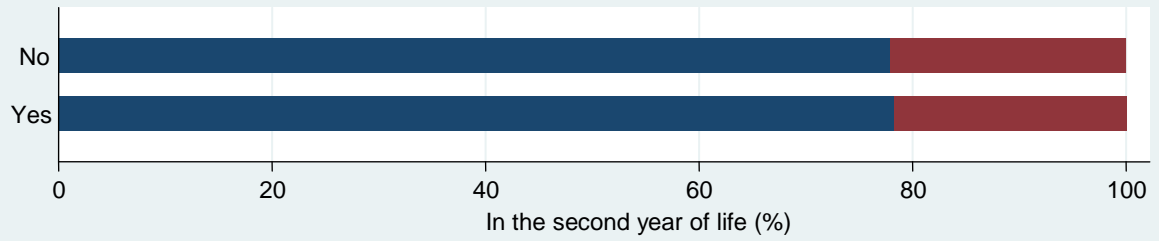
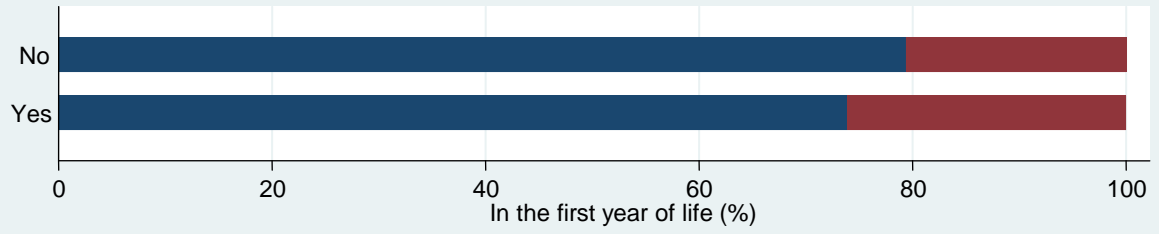
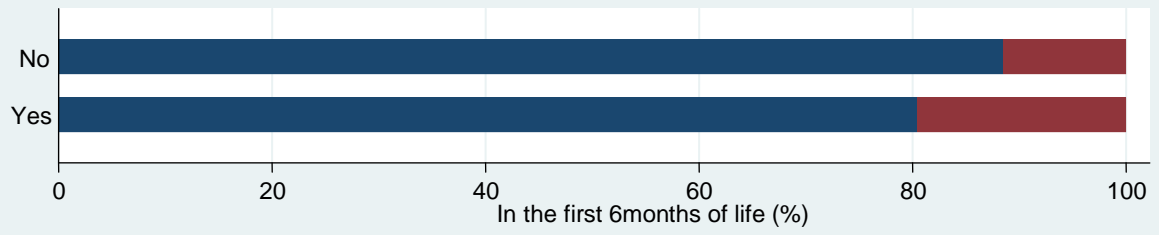


KEY:

Blue bar: No

Red bar: Yes

Any filaggrin mutation No/Yes: history of wheeze

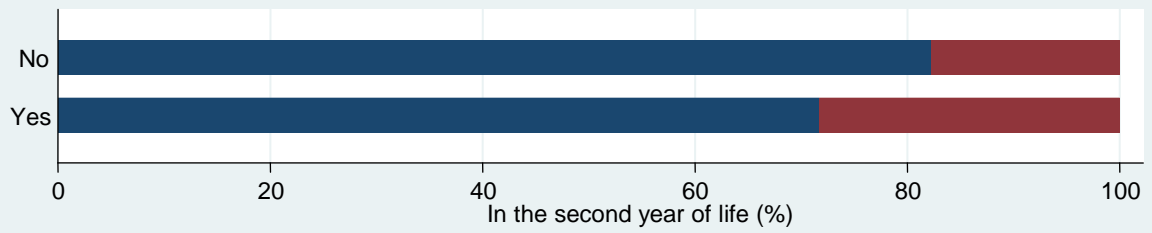
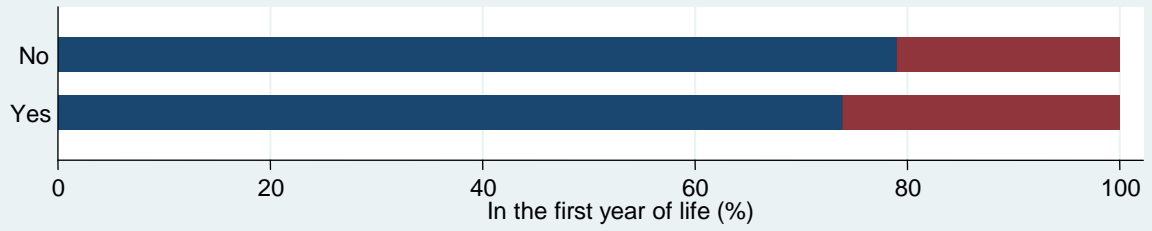
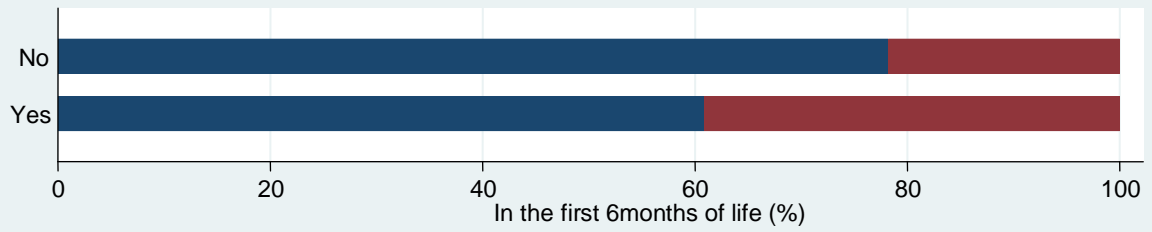


KEY:

Blue bar: No

Red bar: Yes

Any filaggrin mutation No/Yes: history of rhinitis



KEY:

Blue bar: No

Red bar: Yes

**Filaggrin gene defects are associated with eczema, wheeze and nasal disease during infancy:
prospective study**

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Declaration of financial interest: None

None of the authors disclose any conflict of interest statement.

Table 1a. Characteristics of the GO-CHILD antenatal cohort (n=2312)

<i>FLG</i> mutation	AA: 1263 (88%) Aa/aa: 168 (12%)
Exposure to animals ¹	311 (13%)
Exposure to smoke	92 (4%)
Family history of asthma	1143 (49%)
Family history of eczema	975 (42%)
Family history of rhinitis	1134 (49%)
Ethnicity (n=1489)	Caucasian: 1387 (93%) (including mixed Caucasian 18) (1.2%) Asian: 26 (1.7%) Black: 16 (1.1%) Other: 11 (0.7%)

Table 1b. Number (%) of parent reported skin, respiratory and nasal symptoms

Clinical outcomes	During first 6 months (n=910*)	During first year (n=1176*)	During second year (n=962*)
Eczema	257 (28%)	372 (32%)	311 (32%)
Dry or itchy skin ¹	480 (53%)	559 (47%)	439 (46%)
Wheeze	123 (13%)	268 (23%)	206 (21%)
Respiratory impairment ²	96 (10%)	242 (21%)	188 (19%)
Rhinitis ³	236 (26%)	263 (22%)	195 (20%)
Nasal symptoms affecting day-to-day life ⁴	521 (57%)	545 (46%)	435 (45%)
Parental report of asthma	Not applicable	56 (5%)	62 (6%)

*Number of returned questionnaires

¹Dry or itchy skin is parental report of generally dry or itchy skin but not including affected skin creases

²Respiratory impairment is any respiratory symptom affecting day-to-day life such as shortness of breath, disturbed sleep, dry nocturnal cough

³ A problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu

⁴Nasal symptoms affecting day-to-day life is either or all of decreased daily activity due to rhinitis, snoring and sleep disturbance due to nasal symptoms

Table 2. Associations between *FLG* genotype (co-dominant and mutant variants) and eczema, dry or itchy skin, wheeze and rhinitis during the first 6 months of life (n=677*)

	Filaggrin	AA	Aa/aa	Total	Adjusted Relative Risk** (95% CI)
Eczema	No	448	44	492	1.82 (1.39, 2.39)
	Yes	150	35	185	
	Total	598	79	677	
Dry or itchy skin	No	304	22	326	†2.71 (1.61, 4.55)
	Yes	294	57	351	
	Total	598	79	677	
Wheeze	No	525	63	588	1.63 (1.00, 2.65)
	Yes	73	16	89	
	Total	598	79	677	
Rhinitis	No	449	50	499	1.46 (1.06, 2.01)
	Yes	149	29	178	
	Total	598	79	677	

KEY:

† Adjusted odds ratio as log-binomial model non-convergent

*Number of participants with *FLG* genotyping and returned questionnaires at 6 month time-point

** Adjusted for exposure to day care and animals

aa: Homozygous R501X or 2282del4 genotype or compound heterozygous genotype

Aa: Heterozygous genotype for either R501X or 2282del4

AA: Wild- type/ wild- type *FLG* genotype for R501X and 2282del4 mutation

Table 3. Associations between *FLG* genotype (co-dominant and mutant variants) and eczema, dry or itchy skin, wheeze and rhinitis during the first year of life (n=809*)

	Filaggrin	AA	Aa/aa	Total	Adjusted relative risk** (95% CI)
Eczema	No	507	46	553	1.80 (1.39, 2.32)
	Yes	207	49	256	
	Total	714	95	809	
Dry or itchy skin	No	399	30	429	†2.28 (1.32, 3.92)
	Yes	315	65	380	
	Total	714	95	809	
Wheeze	No	552	66	618	1.45 (0.98, 2.13)
	Yes	162	29	191	
	Total	714	95	809	
Rhinitis	No	560	70	630	1.48 (0.99, 2.22)
	Yes	154	25	179	
	Total	714	95	809	

KEY:

† Adjusted odds ratio as log-binomial model non-convergent

*Number of participants with *FLG* genotyping and returned questionnaires at 12 month time-point

** Adjusted for exposure to day care and animals

aa: Homozygous R501X or 2282del4 genotype or compound heterozygous genotype

Aa: Heterozygous genotype for either R501X or 2282del4

AA: Wild- type/ wild- type *FLG* genotype for R501X and 2282del4 mutation

Table 4. Associations between FLG genotype (co-dominant and mutant variants) and eczema, dry or itchy skin, wheeze and rhinitis during the second year of life (n=664*)

	Filaggrin	AA	Aa/aa	Total	Adjusted relative risk** (95% CI)
Eczema	No	409	46	455	1.40 (1.00, 1.97)
	Yes	171	38	209	
	Total	580	84	664	
Dry or itchy skin	No	332	32	364	†1.83 (1.02, 3.28)
	Yes	248	52	300	
	Total	580	84	664	
Wheeze	No	460	66	526	0.84 (0.47, 1.51)
	Yes	120	18	138	
	Total	580	84	664	
Rhinitis	No	468	60	528	1.38 (0.84, 2.25)
	Yes	112	24	136	
	Total	580	84	664	

KEY:

† Adjusted odds ratio as log-binomial model non-convergent

*Number of participants with *FLG* genotyping and returned questionnaires at 24 month time-point

** Adjusted for exposure to day care and animals

aa: Homozygous R501X or 2282del4 genotype or compound heterozygous genotype

Aa: Heterozygous genotype for either R501X or 2282del4

AA: Wild- type/ wild- type *FLG* genotype for R501X and 2282del4 mutation

Table 5. Associations between FLG genotype (co-dominant and mutant variants) and eczema, dry and itchy skin, wheeze and rhinitis across 6, 12 and 24 months of life (n=677)

Outcome	Adjusted relative risk**	95% CI
Eczema	1.70	(1.38, 2.11)
Dry or itchy skin (n=559)	†2.02	(1.25, 3.26)
Wheeze	1.29	(0.92, 1.81)
Rhinitis	1.42	(1.11, 1.83)

† Adjusted odds ratio as log-binomial model non-convergent

** adjusted for exposure to day care and animals

aa: Homozygous R501X or 2282del4 genotype or compound heterozygous genotype

Aa: Heterozygous genotype for either R501X or 2282del4

AA: Wild- type/ wild- type *FLG* genotype for R501X and 2282del4 mutation