**Supplementary material for the Barrier Enhancement for Eczema Prevention randomised trial 5-year results**

**Methods**

*Wording of questions for outcomes*

| **Outcome measures** | **Question on questionnaire**  |
| --- | --- |
| ***AD related*** |  |
| Presence of AD in the previous year at 3, 4 and 5 years based on parental report of a clinical diagnosis of AD. | “In the last year, has your child been diagnosed with eczema by a doctor or a nurse?” (36, 48 and 60 months) |
| Any parental report that in their opinion their child has eczema at 3, 6, 12, 18 months, 2, 3, 4 and 5 years | “In the last xx months/year, has your child suffered from any of the following skin problems?” (last xx months/year is time period since last questionnaire) with response options of Impetigo, Eczema, Chicken pox, Facial spots, Cradle cap or None of these. (3, 6, 12, 18, 24, 36, 48 and 60 months) |
| ***Other atopic diseases*** |  |
| Parental reported wheezing at 3, 4 and 5 years | “In the last year, has your child had any wheezing or whistling in the chest?” (36, 48 and 60 months) |
| Parental reported allergic rhinitis at 3, 4 and 5 years | “In the last 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?” (36, 48 and 60 months) |
| Parental reported food allergy symptoms at 3, 4 and 5 years | At 36, 48 and 60 months, parents were asked whether in the their child has had a reaction to any food containing (i) cow’s milk, (ii) egg, (iii) nuts or (iv) any other food in the last year. For cow’s milk, egg and nuts there was also a question on the time from eating the food to the reaction with response options of: within 30 minutes, 30-60 minutes later, 1-2 hours later and more than 2 hours later.  |
| Parental report of a clinical diagnosis of asthma or allergic rhinitis by 5 years. | On the 60 month questionnaire, “Has your child ever been diagnosed with asthma by a doctor or nurse?” and “Has your child ever been diagnosed with hayfever by a doctor or nurse?” |
| Parental report of a clinical diagnosis of food allergy at 3, 4 and 5 years | “In the last year has your child been diagnosed with any food allergy by a doctor?” (36, 48 and 60 months) |

*Further details of statistical methods*

Multiple imputation using chained equations was used to impute missing outcomes collected at 5 years on parental report of a clinical diagnosis of asthma and parental report of a clinical diagnosis of allergic rhinitis and the derived outcomes of parental report of a clinical diagnosis of AD from the age of 12 months to 60 months and parental report of a clinical diagnosis of food allergy by 5 years. The following variables were used in the imputation model: allocated group, randomisation stratification variables (centre, number of immediate family members with atopic disease) and baseline variables identified as predictive of drop-out (by examination only): mothers age at randomisation, number of other children in the household at randomisation and decile of index of multiple deprivation. Fifty datasets were imputed.

To explore the robustness of the results to the missing at random (MAR) assumption, sensitivity analysis were conducted for the outcomes of parental report of clinical diagnosis of AD from the age of 12 months to 60 months and parental report of clinical diagnosis of food allergy by 60 months under a missing not at random assumption using controlled multiple imputation (S1). Delta () based multiple imputation was used to modify the value imputed under a missing at random assumption by a fixed amount to explore how the results would change if participants with missing outcomes were more likely to have a worse outcome than predicted (based on the MAR assumption). A range of  values were used in the sensitivity analysis.

**Summary of parental reported outcomes at 2 years**

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Emollient  | Control  | Adjusted relative risk(95% CI) | Adjusteddifference in risk(95% CI) |
|   |  |  |  |  |
| Parental report of a clinical diagnosis of AD between birth and age 2 years  | 266/610 (44%) | 282/616 (46%) | 0.96(0.85 to 1.08) | -2.0%(-7.5% to 3.6%) |
|   |  |  |  |  |
| Presence of AD based on completion by parents of UK Working Party Diagnostic Criteria for AD (questionnaire version1) | 187/599 (31%) | 195/612 (32%) | 0.98(0.83 to 1.16) | -0.5%(-5.7% to 4.8%) |
|   |  |  |  |  |
| Moderate, severe, or very severe AD according to POEM  | 58/576 (10%) | 51/595 (9%) | 1.18(0.82 to 1.68) | 1.7%(-1.6% to 5.0%) |
|   |  |  |  |  |
| Parental report of reaction to any food between birth and age 2 years | 208/574 (36%) | 197/597 (33%) | 1.10(0.94 to 1.28) | 3.3% (-2.1% to 8.8%) |
|   |  |  |  |  |
| Parental report of immediate allergy to cow’s milk, egg or peanut between birth and age 2 years2 | 98/574 (17%) | 83/598 (14%) | 1.23(0.94 to 1.61) | 3.3% (-0.9% to 7.4%) |
|   |  |  |  |  |
| Parental report of clinical diagnosis of food allergy between birth and age 2 years3 | n = 575 | n = 599 |  |  |
| No | 421 (73%) | 436 (73%) |  |  |
| Yes | 72 (13%) | 66 (11%) | 1.12 (0.82 to 1.52) | 1.5% (-2.8% to 5.7%) |
| No diagnosis of food allergy reported between 1 & 2 years, not known between birth and 1 year | 82 (14%) | 97 (16%) |
|   |  |  |  |  |
| Parental report of wheezing or whistling in the chest between age 1 and 2 years | 197/572 (34%) | 191/598 (32%) | 1.07(0.91 to 1.26) | 2.5%(-2.9% to 7.9%) |
|   |  |  |  |  |
| Parental report of allergic rhinitis symptoms between age 1 and 2 years | 174/572 (30%) | 188/598 (31%) | 0.97 (0.82 to 1.15) | -0.8%(-6.2% to 4.5%) |
|   |   |   |  |  |

POEM = Parental reported eczema measure

1 – Parents not asked questions on visible flexural dermatitis at 2 years

2 – Immediate defined as defined as reaction within 2 hours of eating the food

3 – 995 participants included in analysis model for parent report of clinical diagnosis of food allergy at 24 months. Participants with no diagnosis of food allergy between 12 and 24 months and unknown information between birth and 12 months not included.

**Results**

*Table S1: Number of observations and participants included in each analysis*

|  | Emollient (n = 693) | Control(n = 701) |
| --- | --- | --- |
|  |  |  |
| *Table II* |  |  |
| Presence of AD in the previous year based on parental report of a clinical diagnosis of AD | 4052 observations632 participants | 4171 observations643 participants |
|  |  |  |
| Presence of AD based on completion by parents of UK Working Party Diagnostic Criteria for AD | 2507 observations619 participants | 2640 observations637 participants |
|  |  |  |
| Moderate, severe, or very severe AD according to POEM | 2463 observations612 participants | 2600 observations633 participants |
|  |  |  |
| *Table III* |  |  |
| Parental report of reaction to any food within the previous year | 1855 observations596 participants | 1983 observations622 participants |
|  |  |  |
| Parental report of immediate reaction to milk, egg or nuts within the previous year | 1872 observations596 participants | 2004 observations622 participants |
|  |  |  |
| Parental report of a clinical diagnosis of food allergy within the previous year | 2381 observations609 participants | 2514 observations632 participants |
|  |  |  |
| *Table IV* |  |  |
| Parental report of wheezing or whistling in the chest in previous year | 1936 observations596 participants | 2061 observations623 participants |
|  |  |  |
| Parental report of allergic rhinitis symptoms in previous year | 1937 observations595 participants | 2058 observations623 participants |
|  |  |  |

*Table S2: Any parental report that in their opinion their child had AD at 3, 6, 12, 18 months, 2, 3, 4 and 5 years*

|  | Emollient | Control | Adjusted relative risk(95% CI) | Adjusteddifference in risk(95% CI) |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| 3 months | 91/530 (17%) | 107/523 (20%) | 0.83 (0.65 to 1.06) | -3.5% (-8.0% to 1.0%) |
|  |  |  |  |  |
| 6 months | 160/523 (31%) | 155/517 (30%) | 1.01 (0.85 to 1.21) | 0.4% (-4.9% to 5.8%) |
|  |  |  |  |  |
| 12 months | 189/514 (37%) | 186/528 (35%) | 1.03 (0.88 to 1.20) | 0.9% (-4.7% to 6.6%) |
|  |  |  |  |  |
| 18 months | 173/489 (35%) | 183/506 (36%) | 0.99 (0.84 to 1.16) | -0.3% (-6.1% to 5.4%) |
|  |  |  |  |  |
| 2 years | 189/591 (32%) | 193/607 (32%) | 1.01 (0.86 to 1.19) | 0.2% (-5.0% to 5.4%) |
|  |  |  |  |  |
| 3 years | 169/474 (36%) | 168/493 (34%) | 1.03 (0.87 to 1.21) | 1.0% (-4.8% to 6.8%) |
|  |  |  |  |  |
| 4 years | 154/459 (34%) | 162/513 (32%) | 1.06 (0.89 to 1.26) | 1.9% (-3.8% to 7.5%) |
|  |  |  |  |  |
| 5 years | 168/460 (37%) | 151/499 (30%) | 1.18 (0.99 to 1.39) | 5.4% (-0.3% to 11.1%) |
|  |  |  |  |  |

Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data adjusting for randomisation stratification variables (using fixed effect for of number of immediate family members with atopic disease and a random effect for the recruiting centre) and including a random effect for participants with an exchangeable covariance structure. Model includes 8226 observations (4040 intervention, 4186 control) from 1278 participants (632 intervention, 646 control).

*Table S3: Sensitivity analysis for missing data using delta based multiple imputation*

1. parental report of clinical diagnosis of AD from the age of 12 months to 60 months

|  |  |  |
| --- | --- | --- |
|  | Adjusted relative risk(95% CI) | Adjusteddifference in risk(95% CI) |
|  |  |  |
| Main analysis assuming MAR  | 1.10 (0.93 to 1.30) | 2.8% (-2.3% to 7.8%) |
|  |  |  |
| Sensitivity analysis (exp(δ) = 1.2)1 | 1.11 (0.94 to 1.31) | 3.1% (-2.1% to 8.2%) |
|  |  |  |
| Sensitivity analysis (exp(δ) = 1.5) | 1.11 (0.94 to 1.31) | 3.2% (-2.0% to 8.4%) |
|  |  |  |
| Sensitivity analysis (exp(δ) = 2.0) | 1.11 (0.94 to 1.31) | 3.3% (-1.9% to 8.5%) |
|  |  |  |

 1 – Based on 49 imputed datasets, model failed to converge in 1 imputed dataset

δ represents the difference in the log-odds of the outcome for participants where the outcome is missing compared to participants where the outcome is non missing e.g. if exp(δ) = 1.2, odds ratio for AD in participants with missing data compared to non-missing data is 1.2.

1. parental report of clinical diagnosis of food allergy by 5 years

|  |  |  |
| --- | --- | --- |
|  | Adjusted relative risk(95% CI) | Adjusteddifference in risk(95% CI) |
|  |  |  |
| Main analysis assuming MAR  | 1.11 (0.84 to 1.45) | 1.5% (-2.5% to 5.6%) |
|  |  |  |
| Sensitivity analysis (exp(δ) = 1.2) | 1.12 (0.86 to 1.46) | 1.7% (-2.3% to 5.7%) |
|  |  |  |
| Sensitivity analysis (exp(δ) = 1.5) | 1.12 (0.86 to 1.46) | 1.8% (-2.3% to 5.9%) |
|  |  |  |
| Sensitivity analysis (exp(δ) = 2.0) | 1.13 (0.87 to 1.46) | 1.9% (-2.3% to 6.1%) |
|  |  |  |

*Table S4: Exploratory subgroup analysis for parental report of a clinical diagnosis of AD between 12 and 60 months according to FLG genotype (post hoc)*

|  | Emollient | Control | Adjusted interaction effect (relative risk)(95% CI) | Adjusted interaction effect (risk difference)(95% CI) |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |
| ***FLG genotype for children with mother and father of white ethnicity and children of other ethnicity with mutation*** | n = 402 | n = 414 |  |  |
|  +/+ (no mutations) | 104/339 (31%) | 100/352 (28%) |  |  |
|  +/- (one *FLG* null mutation) | 26/62 (42%) | 20/60 (33%) | 1.15(0.71 to 1.88) | 6.4%(-11.9% to 24.6%) |
|  -/- (two *FLG* null mutations) | 1/1 (100%) | 1/2 (50%) |
|  |  |  |  |  |
|  |  |  |  |  |

*FLG* genotype obtained from saliva samples at 24 months. Samples were tested for the four most prevalent *FLG* loss of-function mutations in the white European population (2282del4, R501X, S3247X, and R2447X). The *FLG* subgroup analysis (for both the primary outcome at 2 years and presented in the table above for long term follow-up) included children providing saliva samples whose mother and father reported being of white ethnicity (n = 810) and children with at least one mutation (regardless of ethnicity, n = 6).

Two groups for *FLG* genotype used in model including interaction effect: +/+ (no mutations) and +/- or -/- (one or two *FLG* null mutations) due to the small number of participants with two *FLG* null mutations. Adjusted interaction effect estimated using generalised estimating equations with the Binomial family and log/identity link respectively, with and number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate and an exchangeable correlation matrix to account for randomisation being stratified by centre.

**Supplementary material references**

S1. Cro S, Morris TP, Kenward MG, Carpenter JR. Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: A practical guide. Statistics in Medicine. 2020; 39: 2815– 2842. <https://doi.org/10.1002/sim.8569>

S2. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet (London, England). 2020;395(10228):962-72.