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**Should lip dosing be reconsidered when performing open food challenges?**

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1 **Title:** Should lip dosing be reconsidered when performing open food challenges?

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9 **Running title:** "Should we revisit lip dosing again?"

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26 To the Editor,

27

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29 A lip dose or labial food challenge (LFC) is a simple, easy to perform method of diagnosis that  
30 could potentially be a convenient alternative to conducting an oral food challenge in children (1).  
31 Rance and Dutau (1) published a paper on LFC in 1997 demonstrating their clinical utility, according  
32 to the technique described by Moneret-Vautrin et al. (2). This involved a drop of the allergen being  
33 placed on the lower lip and left for 10 seconds to two minutes, with the mouth slightly opened.  
34 However, in the study by Rance et al. (1), children with positive LFC did not continue to have an  
35 oral food challenge (OFC). A subsequent study by Cantani et al.(3) concluded that the LFC should  
36 not replace the OFC, but be used at the first step in a food challenge, particularly where there is a  
37 risk of anaphylaxis (4). LFCs are not currently included in international food challenge guidelines  
38 (5) (7). Here we present data from lip dose reactions in the Food Allergy and Intolerance (FAIR)  
39 study from the Isle of Wight in the United Kingdom (UK), with the aim of demonstrating the  
40 predictive value of LFCs for diagnosis of food allergy, compared to OFCs.

#### 41 **Methodology**

42 The FAIR study comprised of two different types of cohorts: The FAIR birth cohort (n = 969) which  
43 was seen and challenged at 1, 2, 3, and 10/11 years of age (7–9). The FAIR school cohorts included  
44 3 cohorts of children aged 6, 11 and 15 years (n = 798, 775 and 757 respectively) (8,11). In the  
45 FAIR birth cohort, 900 (92.9%), 858 (88.5%), 891 (92.0%) and 827 (85.4%) children were seen at  
46 1, 2, 3, and 10/11 years of age respectively. In the FAIR school cohorts, 798 (55.4%), 775 (47.4%)  
47 and 757 (50.2%) children were seen at 6, 11 and 15 years of age respectively. Recruitment of  
48 participants and data collection has been previously described in detail elsewhere (8,10).

49 Children were clinically examined and skin prick tests (SPT) were performed to common  
50 food allergens (milk, egg, cod, sesame, wheat and peanut) and invited for food challenges when  
51 indicated. A positive SPT was defined by a mean wheal diameter of 3 mm or greater than the  
52 negative control (saline). SPT was conducted using standardised allergen reagents and  
53 methodology (ALK-Abello, Hørsholm, Denmark). Eczema was measured using the question “Has  
54 your child ever been diagnosed with eczema”.

55 The labial dose was performed by rubbing the inner lower lip five times with a cooked  
56 sample of the allergenic food. In order to prevent irritant reactions, only plain foods were used (e.g.  
57 unsalted rather than salted peanuts). The challenge outcomes were graded according to the Isle  
58 of Wight David Hide Asthma and Allergy Research Centre protocols and later those of the  
59 PRACTALL guidelines (6), which were very similar.

60 For the 10 year follow-up of the FAIR birth cohort, ethical approval for the study was  
61 obtained from the NRES South Central – Southampton B Research Ethics Committee (ref:  
62 10/H0504/11). For all other cohorts, ethical approval was obtained from the Isle of Wight,  
63 Portsmouth, and South East Hampshire Local Research Ethics Committee (ref: 09/01).

64 **Results**

65 **Initial analyses**

66 The demographic data for the full cohorts has previously been published in a number of prevalence  
67 papers from the Isle of Wight (7–10). A total of 112 LFCs took place. This included four cases of  
68 children with positive LFCs, who did not proceed to an OFC, as parents declined to continue with  
69 the process. Therefore a total of 108 LFCs, followed up by an open food challenge, were included  
70 in the primary analysis, as indicated in Figure 1.

71 Of these 108 LFCs, a positive labial reaction was noted in nine challenges. All nine positive  
72 labial reactions resulted in a positive oral food challenge. Looking overall at the 108 food  
73 challenges, of which nine were preceded by a positive LFC, we have calculated a positive predictive  
74 value of 100% (95% CI 66.4-100%), a negative predictive value of 72.7% (95% CI 68.8-76.3), with  
75 100% specificity (95% CI 94.9-100) and 25.0% sensitivity (95% CI 12.1-42.2).

76 The nine positive labial reactions, summarised in Table 1, were to sesame (n=1), peanut  
77 (n=3), prawn (n=1) and egg (n=4). The most common reaction to the labial dose was urticaria (n =  
78 3), followed by lip angioedema (n =2). Other symptoms reported were rash and rhinorrhea. The  
79 dose reacted to during OFC varied from 250mg for peanut and egg (equating to 62.5 mg peanut  
80 and 32.5mg egg protein respectively) to a maximum eliciting dose of 40g prawn (equating to  
81 1000mg prawn protein). The majority of participants reacted within the first 3 challenge doses  
82 (250mg, 500mg and 1g), apart from the participant who reacted to 40g of prawn.

83 Overall 44 children (40.7%) reported a history of eczema. 55.6% (n = 5) of those with a  
84 positive LFC had a history of eczema, compared to 39.8% (n = 39) of those with a negative LFC,  
85 however this difference was not statistically significant (Fisher's exact test p = 0.483). In terms of  
86 sensitization, 77.8% (n = 7) of those with a positive LFC had a positive SPT, compared to 47.6%  
87 (n = 39) of those with a negative LFC, however this difference was not significantly different  
88 (Fisher's exact test p = 0.158).

89

90 **Additional analyses**

91 We conducted additional analyses including the four cases of children with positive LFCs,  
92 who did not proceed to an OFC. Hypothetically if these four participants had a positive OFC result,  
93 the positive predictive value of the LFC would remain at 100% (95% CI 75.29-100), as would the  
94 negative predictive value of 72.7% (95% CI 68.8-76.3) and the specificity of 100% (95% CI 95.01-  
95 100). However the sensitivity would increase to 32.5% (95% CI 18.57-49.13). Conversely if these  
96 four participants had a negative OFC result, the positive predictive value would decrease to 69.2%  
97 (95% CI 42.6-87.2), the negative predictive value would remain stable at 72.7% (95% CI 68.8-  
98 76.3), as would the sensitivity remaining at 25% (95% CI 12.1-42.2). However the specificity would  
99 decrease to 94.7% (95% CI 87.1-98.6).

100

101 **Discussion**

102 This study aimed to investigate whether a lip dose challenge can be used as a feasible alternative  
103 to a complete oral food challenge protocol in children. The data shows that a positive LFC was  
104 highly indicative of a positive oral food challenge, but a negative LFC does not rule out a positive  
105 oral food challenge. Although proportionately more children with a positive LFC had both eczema  
106 and a positive SPT to the food, compared to children with a negative LFC, the difference was not  
107 statistically significant. Due to the small number of children with a positive labial challenge, our  
108 analysis may be underpowered, so results should be interpreted with caution.

109 Unlike the study of Rance et al.,(1) where 4.5% of cases experienced systemic reactions,  
110 none of the children in this study experienced systemic reactions. This suggests, using our limited  
111 data, that a lip dose challenge is both safe and feasible. In this dataset, there were four cases of  
112 positive LFCs that did not proceed to a full OFC due to lack of parental consent to proceed. It was  
113 not possible to include these four cases in the statistical analysis, as we could not compare them  
114 against a valid OFC outcome and it is not possible to predict whether a systemic reaction would  
115 have occurred. Unfortunately there is limited published research available to compare our findings  
116 to. The only other study we could find referring to the usefulness of the labial challenge is that of  
117 Cantani et al. (3), who conducted 113 OFCs in children, the majority to cows' milk.

118 As ours was an observational birth cohort study, rather than a sample recruited from a  
119 clinical setting, we could not determine a priori which food allergens to investigate. We observed  
120 positive LFCs to only four different foods: sesame, peanut, shellfish and egg. Although cows' milk  
121 is the most common food allergen in young children in the United Kingdom (8,11), the sample  
122 included in this study did not include any positive LFCs to cows' milk. This is probably because  
123 most CMA in the UK is non-IgE mediated as indicated in the UK cohort of the FAIR study in 2006  
124 (12) and then confirmed by the of the EUROPREVALL study (13). Rance et al. (1) included LFCs  
125 to a wider variety of foods (mustard, cod, kiwi, snails, fennel and duck); which is reflective of the  
126 differing prevalence of food allergies between the UK and France.

127 The strengths of this study are that it included children of varied ages, using standardized  
128 protocols. The main limitation of the study is the small sample size of children with a positive LFC,  
129 which included only four food allergens. In conclusion our data, despite a very limited dataset,  
130 indicates that LFCs are feasible and safe. A positive LFC is highly indicative of a positive OFC, but  
131 a negative LFC does not rule out a positive OFC. This may have implications for implementation of  
132 food challenges in clinics with limited resources, particularly in terms of indicating which children  
133 are more likely to have a positive OFC.

134

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138

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141

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146

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148

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Table 1 Summary of challenges undertaken at different ages

Age	Sex	Foods challenged	Number participants with eczema	Number of positive SPTs	Number of LFCs	Number of positive LFCs	Number of positive OFC following positive LFC	Number of negative LFCs	OFC outcome following negative LFC
1 year	27 male 13 female	Milk, egg, cod, wheat, corn, tomato, citrus fruit, strawberry	16	13	40	3 (egg)	3	37	10 positive 27 negative
2 years	6 male 4 female	Milk, egg, wheat, citrus fruit	9	4	10	1 (egg)	1	9	2 positive 7 negative
3 years	14 male 8 female	Egg, cod, corn, peanut, sesame, kiwi, pineapple	11	10	22	1 (peanut)	1	21	4 positive 17 negative
6 years	5 male 4 female	Sesame, banana, peanut, cod, almond	3	9	9	0	0	9	2 positive 7 negative
10 years	6 male 2 female	Peanut, egg, brazil nut	3	6	8	0	0	8	4 positive 4 negative
11 years	4 male 7 female	Peanut, almond, sesame, soy, cheese	1	8	11	2 (peanut)	2	9	2 positive 7 negative
15 years	5 male 3 female	Milk, fruit, soya, hazelnut, prawn, sesame, raisin	1	3	8	2 (1 child sesame & 1 child prawn)	2	6	3 positive 3 negative
<b>Total</b>	<b>67 male 41 female</b>		<b>71</b>	<b>53</b>	<b>108</b>	<b>9</b>	<b>9</b>	<b>99</b>	<b>27 positive 72 negative</b>

SPT: Skin prick test OFC: Oral food challenge. LFC: Labial food challenge.

Figure 1. Flowchart outlining number of participants with positive and negative results

