PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Establishing breast feeding in Infants with Down syndrome: the FADES cohort experience
AUTHORS	Williams, Georgina Murray Leary, Sam Leadbetter, Sofia Toms, Stu Mortimer, Georgina Scorrer, Tim Gillespie, Kathleen Shield, Julian PH

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Mrs. Coral Smith Institution and Country: University of Nottingham School of Medicine, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	25-Jun-2022

GENERAL COMMENTS	A well written and informative piece of work.. Please can you double check the numbers on page 14; table 5 (lines 21-23). Age at first given cow's milk [Median 44 (IQR 28, 36)]. Minor point On page 17 line 10 you have written "Other 'medical' reasons, were are all standard causes for any neonate to receive NG tube feeds including..... this does not read well.

REVIEWER	Reviewer name: Dr. Shanti Raman Institution and Country: South Western Sydney Local Health District, Australia Competing interests: None
REVIEW RETURNED	07-Jul-2022

GENERAL COMMENTS	General Firstly, I would amend the title to Down syndrome, rather than Down's syndrome, and I would use that terminology or Trisomy 21 throughout. However, I realise that the UK seems stuck on using Down's syndrome- mentioned in the Association, so I will leave the decision to the Editorial team. This is a very important topic and I congratulate the authors on undertaking this project. I think the authors need to do a better job of selling the paper- as an exploration of the breastfeeding practices of infants with DS and their mothers, in the first 6 months of life, and a comparison with what is known about breastfeeding with the general population in the UK. There is rich data available to analyse in the FADES cohort- even in the information collected and reported in this paper- not enough has actually been done to adequately explore that. In particular, since the NG tube feeding is a significant issue raised- is it possible to draw any conclusions from the data on NG feeding and association with breastfeeding duration? I think there are some great messages to come out of this study- including the fact that

any breastfeeding at 6 months is higher in the DS cohort than in the general population (need to explore whether this difference is significant). And that this paper provides critical understanding of the early breastfeeding practices and experiences of mothers with infants with DS.

Abstract
Not enough information provided on the Methods. I would say that "data was analysed from participants in the FADES (spell out) cohort, from September 2014 to August 2017, who were surveyed using a questionnaire based questions on the Infant Feeding Survey. Descriptive analysis done using STATA vs. 15

Background
1st para: spell "NG" tube- as first time used.
I would break up the 1st paragraph into 2. Lead the second paragraph, with some general evidence around the benefits of breastfeeding, then proceed to make the case for the particular benefits that breastfeeding would confer to infants with DS.
There is also no clear statement on what the aims of this project are. Please end the 3rd paragraph with: "Our aims were to describe breastfeeding prevalence and experiences among infants with Down Syndrome and their mothers, in the first six months of life. We used findings from the feeding data collected in the first three years of the FADES cohort, to explore this and compare to breastfeeding prevalence in the general population."

Methods
More information needs to be provided- where was the information about breastfeeding prevalence of general population from? Was there any attempt made to look at associations between any breastfeeding and any maternal or infant characteristics (eg maternal age or NG tube feeding). Some mention must be made also of the free text responses- did authors make an attempt to analyse these- or just report them verbatim with no particular reason behind why certain quotes were picked? This paper would be more powerful as a mixed methods study- with more rigorous analysis of the quantitative data as well as the qualitative data.

Results
There is a lot of descriptive information here- some of it very interesting- but it is not well presented. Tables have not been well formulated for ease of reading..it is usual practice to have number followed by percentage in parentheses- not as it presented here the percentage first in one column followed by the proportion. There is also no analysis of the possible associations of breastfeeding duration with any maternal of infant characteristics- which would make this more useful and compelling.
Presenting the breastfeeding rates of infants with DS compared to the general population is done without providing any sort of assessment of the significance of the difference..is it possible to do that?

Discussion
1st para: sell your study a bit better. If it is the first study to explore the early breastfeeding practices and experiences of mothers of infants with DS in the UK- state that.

Subsequent paragraphs should unpack the findings better- but I am hoping that the authors could do more to analyse their findings and contextualise them better.

Conclusions
State: It is clear that babies with DS can be exclusively breastfed for six months as per WHO guidelines. Our study shows that almost two-thirds of babies with DS were being breast fed at 6 months.

REVIEWER	Reviewer name: Dr. Karel Allegaert Institution and Country: KU Leuven, Belgium Competing interests: None
REVIEW RETURNED	24-Jun-2022

GENERAL COMMENTS	I have read this paper with great interest. The authors report on a (sub)analysis of the FADES cohort, with focus on aspects related to breast feeeding in a relevant cohort of babies (infants, is perhaps a better word choice) with Down syndrome. I value the paper, and only have minor comments the introduction (first alinea, second sentence) is wrong (as also illustrated by the cohort itself) as diagnosis prenatally is quite common (nip test, triple test, or ultrasound, nasal bone/nuchal tickness). beside this, i'm not sure if this journal uses 'three' boxes (3rd section on 'impact')

VERSION 1 – AUTHOR RESPONSE

Dear Professor Imti Choonara,

We are very grateful for all of the comments and the reviewers's time. We have responded to each of the individual points in the attached document and I have copied below. Responses are in Blue font in the attached document but hopefully are also clear below.

We looked forward to hearing the final decision for the paper and are grateful for your consideration

Best wishes

Dr Georgina Williams (Corresponding Author)

Formatting Amendments (where applicable):

Editor in Chief Comments to Author :

Please use numbers before % in your Results (text and tables) and in the abstract results

Be cautious in your conclusions - your numbers are small and you may have excluded those most disadvantaged.

Thank you for your recommendations, we have now altered the results to show numbers before percentages. We have kept the numbers as proportions as the denominator changes. We have removed a column in the tables which hopefully makes these easier to view. The general population data come from the infant feeding survey 2010 and we have only included percentages from their data.

We have already commented on the selection bias (page 18 lines 345 - 348: throughout, our lines and pages relate to unmarked revised text) however: to be clear on this important point, we have also added the following sentence in to our discussion on pages 17/18 lines 341-345:

Although the number of participants is relatively high compared to other cohorts of infants with DS, the small number in this paper means that caution needs to be used when drawing conclusions. Those infants born with a child protection plan, fostered, or adopted and parents who do not speak English did not meet the inclusion criteria, therefore we are likely to have excluded some of the most disadvantaged of our population.

Reviewer: 1

Dr. Karel Allegaert, KU Leuven, Erasmus MC Sophia

Comments to the Author

I have read this paper with great interest. The authors report on a (sub)analysis of the FADES cohort, with focus on aspects related to breast feeeding in a relevant cohort of babies (infants, is perhaps a better word choice) with Down syndrome.

Thank you for your very positive comments and we are glad you found the paper of interest. Throughout the paper we have changed the term babies to infants as recommended.

I value the paper, and only have minor comments

the introduction (first alinea, second sentence) is wrong (as also illustrated by the cohort itself) as diagnosis prenatally is quite common (nip test, triple test, or ultrasound, nasal bone/nuchal tickness).

Thank you for highlighting this: we have added the word antenatally - DS is usually diagnosed antenatally or in the first few days of life by recognition of salient features. (page 3 line 55 - 56)

Of note around 92% of prenatal diagnoses lead to a termination and therefore of those that are live births, a proportion will still be unexpected and diagnosed shortly after birth.

beside this, i'm not sure if this journal uses 'three' boxes (3rd section on 'impact')

We believe this journal does have a three section policy

Reviewer: 2

Mrs. Coral Smith, University of Nottingham School of Medicine

Comments to the Author

A well written and informative piece of work..

Please can you double check the numbers on page 14; table 5 (lines 21-23). Age at first given cow's milk [Median 44 (IQR 28, 36)].

Thanks you, we have corrected this, apologies this was a typographical error - Median 44 (IQR 28, 48) (page 14 Table 5)

Minor point On page 17 line 10 you have written "Other ‘medical’ reasons, were are all standard causes for any neonate to receive NG tube feeds including..... this does not read well

We have deleted the words “were all standard causes and instead have written - Other ‘medical’ reasons included prematurity, ventilation or surgical abdomen. Prevalence of NG tube feeding in the” (Page 17 line 322 - 324)

Reviewer: 3

Dr. Shanti Raman, South Western Sydney Local Health District, University of New South Wales

Comments to the Author

General

Firstly, I would amend the title to Down syndrome, rather than Down’s syndrome, and I would use that terminology or Trisomy 21 throughout. However, I realise that the UK seems stuck on using Down’s syndrome- mentioned in the Association, so I will leave the decision to the Editorial team.

Thank you for your comments on the paper. We have changed the terminology from “Down’s Syndrome” to “Down Syndrome” or “Trisomy 21” throughout.

This is a very important topic and I congratulate the authors on undertaking this project.

Thank you so much for your positive comments and recognition of this important topic. Overall, there is a lack of research for this population, but we hope this paper will help to address this.

I think the authors need to do a better job of selling the paper- as an exploration of the breastfeeding practices of infants with DS and their mothers, in the first 6 months of life, and a comparison with what is known about breastfeeding with the general population in the UK. There is rich data available to analyse in the FADES cohort- even in the information collected and reported in this paper- not enough has actually been done to adequately explore that.

The FADES cohort was initially established as a feasibility study to establish whether it was possible to recruit participants, collect samples and collect questionnaire data to explore associations between autoimmunity in babies with DS and feeding (part of a PhD). Numbers therefore are small, and the exploration of feeding practices was a sub-analysis. Even as a feasibility study, compared to other cohorts the number of participants recruited is comparatively large, but remains underpowered for a full statistical analysis investigating associations. The descriptive analysis and key findings are important and highlight areas for future research.

We have changed the Statistical Analysis section in Methods to represent this:

Statistical Analysis: As a feasibility study, analysis of the questionnaires is descriptive as there is not enough power to statistically test for associations. ….(page 5 line 109– 110)

In particular, since the NG tube feeding is a significant issue raised- is it possible to draw any conclusions from the data on NG feeding and association with breastfeeding duration?

This would be interesting to explore further, and this paper highlights the high proportion of infants who were NG tube fed. As described above the numbers are small so the study is not adequately powered to look at associations.

I think there are some great messages to come out of this study- including the fact that any breastfeeding at 6 months is higher in the DS cohort than in the general population (need to explore whether this difference is significant).

Thank you for your comments regarding study's findings and we hope these will lead to changes in the messages that families are given. We cannot comment on statistical significance due to small numbers.

And that this paper provides critical understanding of the early breastfeeding practices and experiences of mothers with infants with DS.

Thank you for this comment we have included this in the first line of our conclusion. (Page 19 line 384 - 385)

Abstract

Not enough information provided on the Methods. I would say that "data was analysed from participants in the FADES (spell out) cohort, from September 2014 to August 2017, who were surveyed using a questionnaire based questions on the Infant Feeding Survey. Descriptive analysis done using STATA vs. 15

Within the abstract we found that we were rather constrained by the journals abstract heading titles which do not include a 'methods' section and the limited word count. This detail is provided in the methods section of the paper. We have included under the abstract heading 'Subjects' the following

Infants under the age of 8 months with Down syndrome (DS) recruited to the FADES (Feeding and Autoimmunity in Down Syndrome Evaluation Study) between….. (Page 2 line 34 - 35)

Background

1st para: spell "NG" tube- as first time used.

This has been changed as recommended (Page 3 line 74)

I would break up the 1st paragraph into 2. Lead the second paragraph, with some general evidence around the benefits of breastfeeding, then proceed to make the case for the particular benefits that breastfeeding would confer to infants with DS.

We have split and moved these paragraphs as recommended so that the recommendations for breastfeeding are presented ahead of specific information regarding breastfeeding for those with Down Syndrome. (Page 3 lines 60 – 75).

There is also no clear statement on what the aims of this project are. Please end the 3rd paragraph with: “Our aims were to describe breastfeeding prevalence and experiences among infants with Down Syndrome and their mothers, in the first six months of life. We used findings from the feeding data collected in the first three years of the FADES cohort, to explore this and compare to breastfeeding prevalence in the general population.”

Thank you for highlighting this and we have now changed this final paragraph to include the following:

The aim of this paper is to describe breastfeeding prevalence and experiences among infants with DS and their mothers, in the first six months of life. This paper describes findings from the analysis of the feeding data collected between September 2014 and August 2017, to explore this and compare to breastfeeding prevalence in the general population. (Page 4 line 85 – 88)

Methods

More information needs to be provided- where was the information about breastfeeding prevalence of general population from?

We have now included the following information within the statistical analysis section of the Methods:

….. were approximately normal, and medians and interquartile ranges (IQRs) for non-normal data. Analysis used STATA vs. 15. Comparisons are made with the general population from the results reported by the IFS 2010 (15). Page 5 line 112- 114

Was there any attempt made to look at associations between any breastfeeding and any maternal or infant characteristics (eg maternal age or NG tube feeding).

As described above the numbers are small and not adequately powered to look at associations.

Some mention must be made also of the free text responses- did authors make an attempt to analyse these- or just report them verbatim with no particular reason behind why certain quotes were picked? This paper would be more powerful as a mixed methods study- with more rigorous analysis of the quantitative data as well as the qualitative data.

Free text responses were selected and reported verbatim to illustrate important findings but a full qualitative analysis was not completed as part of this feasibility study. We acknowledge that a full qualitative study and analysis of the free text should be included in any further study.

We have edited the methods section to include the following statement:

Mothers were able to provide free text answers to some questions and quotes from these have been used to illustrate key points. A full qualitative study and analysis has not been completed as part of this feasibility study. Page 5 line 103 - 105

Results

There is a lot of descriptive information here- some of it very interesting- but it is not well presented. Tables have not been well formulated for ease of reading..it is usual practice to have number followed by percentage in parentheses- not as it presented here the percentage first in one column followed by the proportion.

The data were collected across a number of questionnaires at different time points (initial questionnaire, 7 month and 12month), presenting the results was therefore challenging particularly as the denominators vary depending on the variable. We recognise that the tables contain a large amount of information, but we are keen not to constrain this too much. We have now altered the results as recommended to show numbers before percentages within the tables (where we have now removed a column) and in the text. We have kept the numbers as proportions as the denominator changes.

There is also no analysis of the possible associations of breastfeeding duration with any maternal of infant characteristics- which would make this more useful and compelling.

Presenting the breastfeeding rates of infants with DS compared to the general population is done without providing any sort of assessment of the significance of the difference.is it possible to do that?

This paper reports key findings with respect to the prevalence of breastfeeding in infants with DS and a descriptive analysis on background maternal and infant characteristics. Due to the small numbers, we are unable to do a statistical analysis to investigate associations.

Discussion

Subsequent paragraphs should unpack the findings better- but I am hoping that the authors could do more to analyse their findings and contextualise them better.

The aim of this paper was to describe breastfeeding prevalence and experiences of mothers feeding their babies in the first six months of life. FADES is a feasibility study and therefore was not adequately powered for full statistical analysis. However as one of the largest cohorts of infants with DS and the only one looking at early feeding practices the key messages are impactful.

Conclusions

State: It is clear that babies with DS can be exclusively breastfed for six months as per WHO guidelines. Our study shows that almost two-thirds of babies with DS were being breast fed at 6 months.

Thank you, our conclusion has been changed to reflect this, we have said that ‘many’ can breastfeed as not all infants will be able to.

This paper provides critical understanding of the early breastfeeding practices and experiences of mothers with infants. It is clear that many infants with DS can breastfeed exclusively for six months as per WHO guidelines. Our study shows that almost two-thirds of babies with DS were being breast fed at 6 months. This may require significant perseverance from the mother and supportive….. page 19 lines 384 - 388