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)	Sex Differences in Congenital Heart Disease in Down Syndrome: Study Data from Medical Records and Questionnaires in a Region of Japan
AUTHORS	Takano, Takako; Akagi, Michio; Takaki, Haruyoshi; Inuzuka, Ryo; Nogimori, Yoshitsugu; Ono, Hiroshi; Kaneko, Masahide; Hagiwara, Norifumi

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Joan Morris Institution and Country: St George's, University of London Competing interests: None
REVIEW RETURNED	18-Jan-2019

GENERAL COMMENTS	This is an interesting paper. However, I think that the authors need to expand it slightly by referring to existing literature more 1. It would be nice to have baseline characteristics of the sample in particular how old they are. 2. There are several studies showing that prevalence of congenital cardiac anomalies is greater in females than males –these references should be looked at and referenced. In fact the authors include reference 5 (Morris et al) yet do not comment on the table that shows the gender differences in the prevalence of cardiac anomalies. The data in this paper show a very similar pattern to that of Morris et al and of interest is that although VSD,ASD,AVSD and PDA are all more frequent in females TOF is more frequent in males in this and in the Morris study. It would be interesting if the authors could also just report “severe CHD” in addition to “All CHD”. Other references are : Kallen B, Mastroiacovo P, Robert E. 1996. Major congenital malformations in Down syndrome. Am J Med Genet 65:160–166. Freeman SB, Bean LH, Allen EG, Tinker SW, Locke AE, Druschel C, Hobbs CA, Romitti PA, Royle MH, Torfs CP, Dooley KJ, Sherman SL. 2008. Ethnicity, sex, and the incidence of congenital heart defects: A report from the National Down Syndrome Project. Genet in Med 10:r173– r180. 3. Also of interest is that the Morris study was births in 2000-2010 - indicating that the change over time observed in this study is as the authors suggest more a reporting bias. The change over time is commented on, but no figures are given – is the change statistically significant ? It would be good to know how many are in each age group. 3. I suggest that in the “what is already known” is a mention that prevalence of congenital cardiac anomalies is higher in females with Down Syndrome than males with Down Syndrome

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REVIEWER	Reviewer name: Jeremy Miles Institution and Country: Google, Inc, USA Competing interests:
REVIEW RETURNED	No competing interests

GENERAL COMMENTS	I know very little about CHD. Are the conditions mentioned in the methods all possible examples of CHD, or a selection? It is hard for a reader to understand the paper if they do not understand CHD. I don't understand the method section. This might be a language issue. E.g. "The questionnaires mailed to patients' parents were sent back if parents agreed with the content." Who sent them back? What happens if the parents did not agree? Confidence intervals in the results section would add useful information. Did the authors consider looking at differences in mortality? CHD itself seems to be an intermediate outcome, when the outcome that is discussed is mortality. Why does the introduction talk about Australia when the data are collected in Japan? Language needs tidying, possibly by a native speaker? (E.g. first sentence of the introduction is pretty clunky)

REVIEWER	Reviewer name: Dr Antony Hermuzi Institution and Country: Paediatric and Adult Congenital Cardiac Services. Freeman Hospital. The Newcastle upon Tyne Hospital NHS Foundation Trust. Newcastle upon Tyne. UK Competing interests: None
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	I thank the authors for submitting this study for review. A number of questions arise when reading and interpreting several aspects. I am pleased to see the authors contributing to the literature on patients with Trisomy 21 and the preponderance of congenital heart disease in the Japanese population. My concerns as regards publication are as follows: 1. I note the questionnaire is dated 2003 and I am not clear from the methodology to which era this data exactly applies. This is of significant relevance in the field of CHD treatment which continues to evolve at great pace 2. It is unfortunate as acknowledged by the authors that the questionnaire was not designed with the involvement of patients, families or interest groups associated with Trisomy 21 patients. This might have perhaps informed what families perceive as a "complication" of treatment 3. Complication of treatment is not defined in the manuscript. It would appear from the supplemental questionnaire that this is self reported by families. It is unclear, as families were not involved in the design of the questionnaire what they may perceive as important "complications".

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	4. Complications from congenital heart disease treatment are a very important entity to define and there are several recent publications considering this issue. It could be suggested that the complexity of surgery and demographic factors may significantly influence the rate of complication for a particular patient undergoing a specific procedure. The authors do not address this issue at any level. 5. The authors suggest the greater severity of CHD in females with DS may account for the higher rate of complications. It is unclear to me how this conclusion has been reached, if this refers to surgical CHD complications or complications associated with DS as both are addressed in the questionnaire. In essence, I unfortunately cannot suggest that this manuscript is accepted for publication.

VERSION 1 – AUTHOR RESPONSE

To Reviewer 1:

Thank you for your well-considered comments. We are very happy with your evaluation that this is an interesting article. We have revised the article according to your suggestions and those of the other reviewers.

1. Because this study is about congenital heart disease, we think that the patient's birth year is more important than age at investigation. In the "Results" and "Discussion" sections, we now mention that the data were divided into four birth year-cohort decades.

2. We have added a reference to Freeman et al. (2008) to the reference list because we had space to include an additional reference.

3. Our chosen article type (Original Research Letter) allows a maximum of two tables and/or figures. Thus, we added the number of patients in each age group in the text of the "Results" section. Unfortunately, the change over time was not statistically significant, probably because the sample size was not large enough.

4. We have added the following sentence in the "What is already known" section:

"Prevalence of congenital heart disease is higher in female patients with Down syndrome than in their male counterparts in the United States and Europe."

We hope that our revised manuscript will be accepted for publication as an Original Research Letter in BMJ Paediatrics Open.

Thank you again for your time and effort in refereeing our article.

To Reviewer 2:

Thank you very much for your comments. We have revised our manuscript according to your suggestions and those of the other reviewers.

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1. Most of the readers of BMJ Paediatrics Open are health care professionals working in the area of pediatrics. Therefore, we expect that the readers of our article will understand our research intent—to examine sex differences in congenital heart disease among patients with Down syndrome.

2. We sent the questionnaires to patients' parents by mail. Those parents who completed and returned the questionnaire were considered to have provided consent to participate, and only these respondents were included in the study. Those parents who did not consent to participate did not return the questionnaire. We have revised the sentence you mentioned in the article as follows:

"Questionnaires were mailed to patients' parents; completing and returning the questionnaire was considered to indicate consent to participate."

3. We have added confidence intervals in Table 1.

4. Unfortunately, there are no census data on Down syndrome in Japan. We were unable to investigate the mortality of patients with Down syndrome.

In the decision letter, Prof. Imti Choonara, Editor-in-Chief of BMJ Paediatrics Open, advised us as follows:

"Be more accurate with your conclusions and discussion - you have no data about life expectancy so cannot comment on this."

According to his advice, we have deleted the comment on life expectancy from the "Discussion" section of the article, and we have changed the beginning of the "Introduction" section to clarify the research objective.

5. The previous report from Australia that male patients with Down syndrome had significantly longer life expectancies, compared with their female counterparts, motivated us to examine sex differences in the prevalence and severity of congenital heart disease among patients with Down syndrome in Japan.

6. The revised manuscript was checked by a native English speaker.

We hope that our revised manuscript will be accepted for publication as an Original Research Letter in BMJ Paediatrics Open.

To Reviewer 3:

Thank you very much for your comments. We have revised our manuscript according to your suggestions and those of the other reviewers.

1. We apologize for this oversight; the questionnaire was administered in 2013, not 2003.

2–5. In this article, we focused on sex differences in the prevalence and severity of congenital heart disease in patients with Down syndrome in Japan, as a possible factor in the sex difference in life expectancy in this group—not on the outcomes of congenital heart disease. Unfortunately, we were unable to obtain accurate data on the treatment and complications of congenital heart disease. Therefore, we discussed only the prevalence and severity of congenital heart disease. In this article, "severity" means whether congenital heart disease had a surgical (including catheter intervention) indication, irrespective of the outcome of that surgery.

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We hope that you are satisfied with our reply to your comments regarding the complications of treatment, and we thank you in advance for your work in reviewing this revised version of our manuscript.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Joan Morris Institution and Country: St George's, University of London, UK Competing interests: None
REVIEW RETURNED	17-Mar-2019

GENERAL COMMENTS	The authors have adressed my earlier concerns. I think this is a nice informative letter that correctly acknowledges that the finding that females with Down syndrome have more congenital heart defects than males with Down syndrome. I am slightly concerned about over-interpretting the data from 2000; that males have similar levels of congenital heart defects to females - it is more likely that the females still have more severe CHD. There is clearly a great increase in diagnosis of less severe CHD in both genders.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1:

Thank you for your comments on our revised manuscript. We are encouraged by your comment that this is a nice and informative letter. We have revised the article according to your suggestions.

We have changed the last two sentences in the "Discussion" section as follows:

"Many factors seem to have contributed to this change, including the improvement of diagnostic techniques such as echocardiographic examination and improvements in heart surgery. This shift may be attributed to a great increase in the diagnosis of less severe CHD for both sexes."

We hope that our revised manuscript will be accepted for publication as an Original Research Letter in BMJ Paediatrics Open.

Thank you very much.

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