PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Lung function: Population epidemiology and concordance in 11-12 year old Australians and their parents
AUTHORS	Welsh, Liam; Kathriachchige, Gayan; Raheem, Tahmeed; Grobler, Anneke; Wake, Melissa; Ranganathan, Sarath

VERSION 1 - REVIEW

REVIEWER	Giovanni Viegi CNR Institute of Biomedicine and Molecular Immunology (IBIM), Palermo (Italy)
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	General comments This is an important epidemiological study, but it suffers of limitations which should be dealt with by the Authors. In view of the current recent literature about the applicability of GLI to individual populations (see Fasola et al. (2017). Global lung function initiative 2012 reference values for spirometry in south Italian children. Respiratory Medicine, Vol. 131, p. 11-17), prior to make any inference, the authors should check such applicability in their population normals. The discussion shall be thereafter changed. Major points - In the Introduction, the Authors refer to spirometry as “a clinical tool that can identify individuals with abnormal lung function and compare individuals and populations to international reference values”. If the aim was to compare the Australian population to “international norms”, the Authors should have included only healthy children (possibly of all ages) in their assessments. Indeed, the GLI 2012 equations were derived on healthy children; note also that the previous study the Authors refer to (Hall et al, 2012) was carried out in healthy children. Conversely, the Authors included diseased individuals like asthmatics. - The role of genetic factors has been widely investigated in previous studies. A PUBMED search “lung function AND heritability” yields 100 references. Indeed, the Authors should refine their search at page 16. Moreover, if the Authors aimed to provide tools for “better identification of at risk patients” (page 17, line 23) to “prevent the onset or limit the progression of lung disease” (page 17, line 33), the selected study population and methods might not be adequate.

	The Authors should provide more details about the prediction model (equations, estimated parameters and so on). In addition, the Authors should explain the reasons why they have limited their investigation to children of age 11-12 and whether their findings might be back-extrapolated to younger children. - Page 9, line 11: this huge gender unbalance of parents may constitute an important selection bias. Thus, the manuscript should be re-arranged and the Authors should analyse only children-mother relationships. The title should accordingly change. All the representativeness checks between the nested and the general sample should be restricted to children-mothers pairs. Minor points - Title and remainder of the text: it would be better to say "correlation" rather than "concordance", due to the continuous nature of the spirometry indices. - Abstract, line 11: you need to introduce the abbreviation (LSAC) here, since it is used at line 27. - Abstract, line 33: replace "Comparable values" with "Mean (SD)". - Abstract, line 35: replace "was" with "were". - Abstract, line 42 and remainder of the text: replace "norms" with "standards". - Abstract, line 42: "generally healthy population sample" is unclear. - Article summary, second bullet: please specify in which context "this is the largest cross-sectional study". - Page 4, line 7: replace "overall global" with "global". - Page 4, line 22: replace "which can identify" with "which allows to". - Page 4, line 28: replace "z-scores when compared" with "reflecting substantial agreement". - Page 4, line 37: "Tai et al. (2015)": herein it is missing the quotation of the pivotal study by Lange et al (NEJM, 2015). - Page 4, line 42: replace "as adults" with "later in life". - Page 4, line 45: replace "accounted for" with "explained". - Page 5, line 18: it is helpful for the reader to quote herein the sampling method and give some information on the representativeness. - Page 5, line 35: why was only one parent invited? How was gender taken into account? - Page 6, lines 10 and 11: "They consented to…or their child": unclear.

	- Page 6, line 33: replace “(GLI) equations” with “(GLI 2012) reference equations”. - Page 7, line 44: replace “are” with “were”. - Page 7, line 50: replace “position” with “status”. - Page 7, line 54: replace “conditions” with “status”. - Page 8, line 21: why did the Authors not use Australian charts? Aren’t population compositions different between US and Australia? - Page 8, line 41: reference 26 is difficult to find. Thus, some details on the calculation of the survey weights should be provided herein. - Table 1 does not report the percentages of males and females; the ranges in the reported “n” numbers per each category are unclear. - Figures 2 and 3: these figures are not fully described in the Results; moreover, the normality assessment was not mentioned in the Methods. - Page 11, line 4: the Authors included also FEV1/FVC in their analyses, so they should refer to it when introducing Table 2. - Page 11, line 15: replace “approximately 0.8 above the mean for the international reference populations, but FEV1/FVC and MEF approximately 0.8 and 0.5 below the reference means respectively” with “approximately 0.8, reflecting higher values than the international reference populations. Conversely, FEV1/FVC and MEF z-scores, approximately -0.8 and -0.5, indicated lower values than the international reference populations”. - Table 3: as expected, the estimate variability in the very small father-child sub-sample is much larger than for the mother-child subsample. This is a confirmation of the previous comment (Page 9, line 11). - Table 3, description at bottom: replace “correlation coefficients for Pearson” with “Pearson’s correlation coefficients”. - Discussion: in general, the Authors should take into account the general comments and the major points. - Page 16, lines 23 to 25: unclear. - Page 16, lines 35 to 43: this is an important issue to be discussed in more detail by quoting the relevant literature. - Page 16, lines 45 to 47: there is recent literature on intergenerational findings in the ECRHS. - Page 16, lines 46 to 52: in the abstract of “Lebowitz et al. 1984”, reported on PUBMED, it is written: “Initial regression analysis showed significant correlations of the pulmonary function variables after controlling for age and sex. Body habitus, as measured by the Ponderal Index, was highly aggregated as well. Pulmonary

	function measurements were aggregated in families independent of family size, reported diagnosed AOD, and children's smoking, even though both asthma and smoking showed significant familial aggregation. After controlling for the familial aggregation of body habitus, a major determinant of pulmonary function, there was no remaining independent aggregation of pulmonary function measurements.". Further, in the text at page 9 it is written "Thus, the relation between children's lung function and parents' lung function is likely to be related to their similar body habitus." Therefore, the summary of such an article reported by the Authors may be misleading.

REVIEWER	angela simpson University of Manchester
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	Lung function: Population epidemiology and concordance in 11-12 year old Australians and their parents This study used the Child Health CheckPoint as part of the Longitudinal Study of Australian Children to describe lung function in 11 year old children, and investigate concordance of measures with their parents Specific comments "The ability to identify those at highest risk of non-communicable respiratory disease could inform health policy that prevents the onset or limit the progression of lung disease." Is parental lung function likely to be more or less informative of long term respiratory health than measuring lung function in the child at age 11 years? Methods This is a very lengthy description of standard techniques (lung function and height and weight) that could be cross references or out in an OLS. This would greatly shorten the paper Results The correlation coefficient between child and parental lung function are ~ 0.2 which is comparatively low Why has no account been taken of cigarette smoking? In almost 20% of cases there is no concordance between abnormality in lung function; in only 3% of case is this concordant when outside the normal range. Discussion Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life from Dharmage's group has just published a larger collection of lung function in lancet respiratory medicine (although in younger children) It is not clear to me why the results were not adjusted for maternal cigarette smoking. 'Our findings indicate the need to explore factors relating to intergenerational concordance in lung function further …' I don't really understand this comment. The analysis needs to be adjusted cigarette smoking, pubertal stage and body fat (rather than BMI)

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

This is an important epidemiological study, but it suffers of limitations which should be dealt with by the Authors. In view of the current recent literature about the applicability of GLI to individual populations (see Fasola et al. (2017). Global lung function initiative 2012 reference values for spirometry in south Italian children. Respiratory Medicine, Vol. 131, p. 11-17), prior to make any inference, the authors should check such applicability in their population normals. The discussion shall be thereafter changed.

We acknowledge the findings of Fasola et al (2017) and recognise that the GLI reference equations are not without limitation. However, the GLI equations are the largest and most comprehensive dataset currently available and have previously been shown to be applicable in Australian children (Hall, 2012).

Major points

- In the Introduction, the Authors refer to spirometry as “a clinical tool that can identify individuals with abnormal lung function and compare individuals and populations to international reference values”. If the aim was to compare the Australian population to “international norms”, the Authors should have included only healthy children (possibly of all ages) in their assessments. Indeed, the GLI 2012 equations were derived on healthy children; note also that the previous study the Authors refer to (Hall et al, 2012) was carried out in healthy children. Conversely, the Authors included diseased individuals like asthmatics.

We acknowledge that the GLI equations were derived from healthy children. However, our primary aim was to describe the epidemiology of lung function in a population representative sample of Australian children aged 11-12 and their parents. While we considered our results in light of international standards, we made no statistical comparisons with the standards nor did we attempt to create such standards. Children and parents attending the CheckPoint assessment centre were well at the time they attended. If we exclude all children and adults who have or who ever have experienced asthma, then a large portion of the population is excluded which renders meaningless in terms of meeting its aims.

- The role of genetic factors has been widely investigated in previous studies. A PUBMED search “lung function AND heritability” yields 100 references. Indeed, the Authors should refine their search at page 16.

A PUBMED search that also includes the term “children” yields less than 30 references and many of those are focused on children with cystic fibrosis. We maintain that very few published studies have examined the intergenerational correlation of lung function and that are representative of a large population – the specific literature gap that we address.

Moreover, if the Authors aimed to provide tools for “better identification of at risk patients” (page 17, line 23) to “prevent the onset or limit the progression of lung disease” (page 17, line 33), the selected study population and methods might not be adequate. The Authors should provide more details about the prediction model (equations, estimated parameters and so on).

We are a little confused – this study did not aim to develop prediction models, but to study parent child concordance. However, we believe our statement provides an underlying logic– eg, if we do demonstrate that there is concordance, then if future parents manifest low lung function it is possible that targeting their offspring for screening and potential intervention might serve to prevent low lung function or lung function decline in the child. (See this same response below to a slightly different comment.)

In addition, the Authors should explain the reasons why they have limited their investigation to children of age 11-12 and whether their findings might be back-extrapolated to younger children.

LSAC is Australia's only nationally-representative longitudinal children's study and thus provides unique and valuable information regarding the state of Australian children's health. It began in 2004. In 2014 at Wave 6, families were notified about the upcoming Child Health CheckPoint data collection in 2015. The children participating in the study were aged 11-12 at that time, hence our age window. We have been careful not to generalise our results to children of other ages, and believe it is useful to publish this previously-unavailable information for a 2-year age band.

- Page 9, line 11: this huge gender unbalance of parents may constitute an important selection bias. Thus, the manuscript should be re-arranged and the Authors should analyse only children-mother relationships. The title should accordingly change. All the representativeness checks between the nested and the general sample should be restricted to children-mothers pairs.

We acknowledge that there is a low proportion of fathers in our study. However, our aim was to present results for a large sample of parent-child dyads. It would be artificial to exclude fathers, particularly as – though far less numerous than mothers – over 100 fathers took part, and this is one of very few studies to present data for both father-child and mother-child concordance in a community setting. This is just one paper in a Special Issue of 15 papers examining similar questions for a wide range of health domains, all of which present the data for both mothers and fathers. However, given this imbalance, we have purposely presented the data separately for mothers and fathers, so that readers can make their own judgements as to which values (combined or separate) they wish to focus on.

We have strengthened in the Limitations section the potential bias that could be introduced from such small numbers.

Minor points

- Title and remainder of the text: it would be better to say "correlation" rather than "concordance", due to the continuous nature of the spirometry indices.

Changing this term would make this paper differ from all other papers in this Special Issue, for which this term has not been challenged. We therefore prefer to remain with the term 'concordance'. However, we are happy to modify for this paper at the Editor's recommendation'.

- Abstract, line 11: you need to introduce the abbreviation (LSAC) here, since it is used at line 27.

Thank you, amended as suggested

- Abstract, line 33: replace "Comparable values" with "Mean (SD)".

Thank you, amended as suggested

- Abstract, line 35: replace "was" with "were".

Thank you, amended as suggested

- Abstract, line 42 and remainder of the text: replace "norms" with "standards".

Thank you, amended as suggested

- Abstract, line 42: "generally healthy population sample" is unclear.

The text has been modified as follows:

Mean lung volumes were larger but with smaller airway size than international standards both for parents and children in this population sample.

- Article summary, second bullet: please specify in which context “this is the largest cross-sectional study”.

The text has been modified as follows:

This is the largest cross-sectional study to investigate lung function correlation in Australian parent-child dyads, thereby providing new insight into cross-generational patterns.

- Page 4, line 7: replace “overall global” with “global”.

Amended as suggested

- Page 4, line 22: replace “which can identify” with “which allows to”.

Amended as suggested

- Page 4, line 28: replace “z-scores when compared” with “reflecting substantial agreement”.

Amended as suggested

- Page 4, line 37: “Tai et al. (2015)”: herein it is missing the quotation of the pivotal study by Lange et al (NEJM, 2015).

Thank you, the Lange reference has been added to the manuscript and the text has been modified as follows:

“In addition, low FEV1 in early adulthood contributes significantly to the genesis of COPD in later years.”

- Page 4, line 42: replace “as adults” with “later in life”.

Amended as suggested

- Page 4, line 45: replace “accounted for” with “explained”.

Amended as suggested

- Page 5, line 18: it is helpful for the reader to quote herein the sampling method and give some information on the representativeness.

The methodology description provided on page 5 describes the sampling method and recruitment. Importantly, this paper forms part of a larger series that includes a detailed methodology cohort profile paper which covers these topics and is referenced in this paper. We are happy to expand here too, but feel this would be unnecessary repetition - please advise if you wish us to do so.

- Page 5, line 35: why was only one parent invited? How was gender taken into account?

The study was designed to assess dyads comprising the child and one parent. This reflects the design of the underlying LSAC study, in which biennial interviews are conducted with the child and one parent, choice of whom is at the discretion of the family. (Data are collected from the second parent, but only in the form of a leave-behind survey questionnaire.) Further, studies that have attempted to have both parents attend have had very low uptake rates, which would be a more critical weakness.

- Page 6, lines 10 and 11: “They consented to…or their child”: unclear.

The text has been modified as follows:

Parents consented to take part knowing that they would not otherwise receive individual results about themselves or their child.

- Page 6, line 33: replace “(GLI) equations” with “(GLI 2012) reference equations”.

Amended as suggested

- Page 7, line 44: replace “are” with “were”.

Amended as suggested

- Page 7, line 50: replace “position” with “status”.

Amended as suggested

- Page 7, line 54: replace “conditions” with “status”.

Amended as suggested

- Page 8, line 21: why did the Authors not use Australian charts? Aren’t population compositions different between US and Australia?

There are no Australian z-score reference values available. It is usual practice to use widely-agreed international references for comparability with other datasets around the world.

- Page 8, line 41: reference 26 is difficult to find. Thus, some details on the calculation of the survey weights should be provided herein.

We have described survey weighting in detail in the overarching cohort profile/ methodology paper for this Special Issue, and we believe it is preferable not to repeat the same information across the multiple papers. Nonetheless, we are happy to add this additional information to this paper if further requested.

For your information, the text in the cohort profile and methodology paper reads as follows:

“Survey weights: CheckPoint survey weights were created using similar methods to those used for previous waves of LSAC, and are provided in the CheckPoint dataset. These methods account for the selection probability of each child to establish the target design sample, initial non-response to the baseline survey and subsequent loss to follow-up. LSAC and CheckPoint survey weights have been estimated to reflect the likelihood of participation from wave to wave within the limits of the information available from study measures.

“Applying LSAC survey weights produces analyses that will be as representative as possible for all Australian children born in 2004 and their parents. CheckPoint differs in that, for the majority of measures, only the attending parent (usually the mother) was assessed, and thus weighted analyses of the parent data are more difficult to interpret because the weighting does not estimate a representative sample of all parents.”

- Table 1 does not report the percentages of males and females; the ranges in the reported “n” numbers per each category are unclear.

Table 1 shows the range of n’s available for the various measures for children and parents, for the total samples and for males and females separately; in our view, adding the exact n’s will add 3 full additional columns of data to the table for very little extra meaning (if anything we think it will reduce meaning through increasing the ‘noise’ of the table). As noted in the Results text (page 9, immediately

prior to Table 1) the percentage of boys was 51.2 (ie 48.8% girls) and the percentage of mothers was 87.5 (ie fathers 12.5%).

- Figures 2 and 3: these figures are not fully described in the Results; moreover, the normality assessment was not mentioned in the Methods.

The contents of Figures 2 & 3 are described on page 11:

“plots of distribution and density for FEV1, FVC, FEV1/FVC and MEF z-scores are shown in Figures 2 & 3 for parents and children, respectively.”

Under statistical analyses the following text has been added: “The approximate normality or otherwise of the data’s distributions were assessed through visual inspection.”

- Page 11, line 4: the Authors included also FEV1/FVC in their analyses, so they should refer to it when introducing Table 2.

The text has been modified as follows:

The mean, standard deviations and z-scores for FEV1, FVC, FEV1/FVC and MEF are shown in Table 2.

- Page 11, line 15: replace “approximately 0.8 above the mean for the international reference populations, but FEV1/FVC and MEF approximately 0.8 and 0.5 below the reference means respectively” with “approximately 0.8, reflecting higher values than the international reference populations. Conversely, FEV1/FVC and MEF z-scores, approximately -0.8 and -0.5, indicated lower values than the international reference populations”.

Amended as suggested.

- Table 3: as expected, the estimate variability in the very small father-child sub-sample is much larger than for the mother-child subsample. This is a confirmation of the previous comment (Page 9, line 11).

As described above, we acknowledge that we have a low proportion of fathers in our study. As a result, we presented the data for mothers and fathers both separately and combined. The Limitations section of the Discussion explicitly acknowledges this in the sentence, “Nonetheless, the 221 fathers showed very similar patterns in the four parameters and their z-scores to mothers and to the children, although with some loss of precision in their estimates.”

- Table 3, description at bottom: replace “correlation coefficients for Pearson” with “Pearson’s correlation coefficients”.

Amended as suggested

- Discussion: in general, the Authors should take into account the general comments and the major points.

Every effort has been made to implement the suggestions made by reviewers to improve the discussion section of the manuscript.

- Page 16, lines 23 to 25: unclear.

The text has been modified as follows:

Even though all flow-volume loops were inspected it is possible that subtle sub-optimal efforts could have gone undetected, thereby underestimating FEV1. However, the similarities with the findings of those reported by Hall et al. suggest that our findings are replicable.

- Page 16, lines 35 to 43: this is an important issue to be discussed in more detail by quoting the relevant literature.

In those assessed we identified evidence of reversible airways obstruction in 30% of children with low lung function. We have amended the paragraph to clarify that this is considered a feature of asthma in children. The text has been modified as follows:

“All measurements were reported from pre-bronchodilator flow-volume loops as was reported in the lung function reference populations. We successfully measured response to bronchodilator (following 400 mcg Salbutamol) in 179 children with FEV1/FVC ratio less than -2 z-scores (data not shown). 53 (30%) had evidence of a significant response to bronchodilator (defined as ≥ 12% and ≥ 200 mL improvement in absolute FEV1), suggesting that many children with this ratio below the normal range have reversible airways obstruction. This is usually considered a characteristic feature of asthma.”

- Page 16, lines 45 to 47: there is recent literature on intergenerational findings in the ECRHS.

We believe we have included the appropriate and up-to-date references. We weren’t able to find a particular paper that relates directly to this manuscript from the ECRHS study, and wonder if the reviewer could be more specific? We are very willing to consider citing this or any other references deemed by the reviewer to be appropriate assuming they are relevant to this manuscript.

- Page 16, lines 46 to 52: in the abstract of “Lebowitz et al. 1984”, reported on PUBMED, it is written: “Initial regression analysis showed significant correlations of the pulmonary function variables after controlling for age and sex. Body habitus, as measured by the Ponderal Index, was highly aggregated as well. Pulmonary function measurements were aggregated in families independent of family size, reported diagnosed AOD, and children's smoking, even though both asthma and smoking showed significant familial aggregation. After controlling for the familial aggregation of body habitus, a major determinant of pulmonary function, there was no remaining independent aggregation of pulmonary function measurements.”. Further, in the text at page 9 it is written “Thus, the relation between children's lung function and parents' lung function is likely to be related to their similar body habitus.”

Therefore, the summary of such an article reported by the Authors may be misleading.

We believe we are reflecting the same points as alluded to here. We have amended our statement to make this clearer, as follows:

Our intergenerational correlation findings for lung function extend the small published literature on the heritability and familial aggregation of lung function.14 34 35 In the oldest published study dating back to 1984, Lebowitz et al. did not find any relationship between parents’ and children’s lung function after accounting for body habitus.14

Reviewer: 2

Please leave your comments for the authors below Lung function: Population epidemiology and concordance in 11-12 year old Australians and their parents This study used the Child Health CheckPoint as part of the Longitudinal Study of Australian Children to describe lung function in 11 year old children, and investigate concordance of measures with their parents

Specific comments

“The ability to identify those at highest risk of non-communicable respiratory disease could inform health policy that prevents the onset or limit the progression of lung disease.”

Is parental lung function likely to be more or less informative of long term respiratory health than measuring lung function in the child at age 11 years?

Measures at both time points are important, but the ability to identify early lung disease provides an opportunity to intervene sooner. If parents manifest low lung function, then it is possible that targeting their offspring for screening and potential intervention might serve to prevent low lung function or lung function decline in the child.

Methods

This is a very lengthy description of standard techniques (lung function and height and weight) that could be cross references or out in an OLS. This would greatly shorten the paper.

We agree, but this paper forms part of a series that also serves to document the Child Health CheckPoint study methods in sufficient detail for future users of this public-access database to refer to confidently.

The correlation coefficient between child and parental lung function are ~ 0.2 which is comparatively low Why has no account been taken of cigarette smoking?

Adjustments have now been made for cigarette smoke exposure in adjusted analyses.

In almost 20% of cases there is no concordance between abnormality in lung function; in only 3% of case is this concordant when outside the normal range.

We acknowledge again that there are only modest associations with regard to parent and child lung function but maintain that, if targeted correctly, there is potential to better identify ‘at risk’ populations.

Discussion

Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life from Dharmage’s group has just published a larger collection of lung function in lancet respiratory medicine (although in younger children) It is not clear to me why the results were not adjusted for maternal cigarette smoking. ‘Our findings indicate the need to explore factors relating to intergenerational concordance in lung function further …’ I don’t really understand this comment. The analysis needs to be adjusted cigarette smoking, pubertal stage and body fat (rather than BMI).

Adjustments have now been made for cigarette smoke exposure. Puberty and body fat have a significant number of missing values and were therefore not adjusted for in our analyses.

The text has been modified under the ‘Parent-child correlation section under Results:

The linear regression model also showed similar relationships between child and parent lung function indices, when adjusted for covariates (child and parental age, sex, BMI and parental smoking at Wave 6 in the preceding year), irrespective of the parent being a mother or a father.

VERSION 2 – REVIEW

REVIEWER	Giovanni Viegi CNR Institute of Biomedicine and molecular Immunology "A. Monroy", Palermo (Italy)
REVIEW RETURNED	08-Aug-2018

GENERAL COMMENTS	COMMENTS BY THE REVIEWER 1 (CR1) ON THE REPLIES OF THE AUTHORS New general comment of R1 The Author often did not answer satisfactorily the reviewer's comments. The aim of the paper by Hall et al was to assess applicability of GLI 2012 equations in a population of Australasian NORMALS. In that context, it made sense to report z-score means and to assess z-score normality, while it does not seem appropriate in the current study: e.g. referring to the "minimum physiologically relevant difference" of 0.5 z-scores. The Authors could have focused on reporting prevalence rates of lung function below the normal range, comparing them with other countries, in order to accomplish a study of "population epidemiology of lung function". Therefore, many sentences in the manuscript still remain not agreable or unclear. Moreover, it is still unclear how the present study should serve to "better identification of at risk patients" and "prevent the onset or limit the progression of lung disease". In fact, the very limited age range seriously jeopardize the generalizability of the results. Reviewer 1 This is an important epidemiological study, but it suffers of limitations which should be dealt with by the Authors. In view of the current recent literature about the applicability of GLI to individual populations (see Fasola et al. (2017). Global lung function initiative 2012 reference values for spirometry in south Italian children. Respiratory Medicine, Vol. 131, p. 11-17), prior to make any inference, the authors should check such applicability in their population normals. The discussion shall be thereafter changed. We acknowledge the findings of Fasola et al (2017) and recognise that the GLI reference equations are not without limitation. However, the GLI equations are the largest and most comprehensive dataset currently available and have previously been shown to be applicable in Australian children (Hall, 2012). CR1: Unsatisfactory reply. Major points - In the Introduction, the Authors refer to spirometry as “a clinical tool that can identify individuals with abnormal lung function and compare individuals and populations to international reference values”. If the aim was to compare the Australian population to “international norms”, the Authors should have included only healthy children (possibly of all ages) in their assessments. Indeed, the GLI 2012 equations were derived on healthy children; note also that the previous study the Authors refer to (Hall et al, 2012) was carried out in healthy children. Conversely, the Authors included diseased individuals like asthmatics. We acknowledge that the GLI equations were derived from healthy children. However, our primary aim was to describe the epidemiology of lung function in a population representative

	sample of Australian children aged 11-12 and their parents. While we considered our results in light of international standards, we made no statistical comparisons with the standards nor did we attempt to create such standards. Children and parents attending the CheckPoint assessment centre were well at the time they attended. If we exclude all children and adults who have or who ever have experienced asthma, then a large portion of the population is excluded which renders meaningless in terms of meeting its aims. CR1: Unsatisfactory reply. - The role of genetic factors has been widely investigated in previous studies. A PUBMED search “lung function AND heritability” yields 100 references. Indeed, the Authors should refine their search at page 16. A PUBMED search that also includes the term “children” yields less than 30 references and many of those are focused on children with cystic fibrosis. We maintain that very few published studies have examined the intergenerational correlation of lung function and that are representative of a large population – the specific literature gap that we address. CR1: Unsatisfactory reply. At least 11 references were not focused on children with cystic fibrosis. Moreover, if the Authors aimed to provide tools for “better identification of at risk patients” (page 17, line 23) to “prevent the onset or limit the progression of lung disease” (page 17, line 33), the selected study population and methods might not be adequate. The Authors should provide more details about the prediction model (equations, estimated parameters and so on). We are a little confused – this study did not aim to develop prediction models, but to study parent child concordance. However, we believe our statement provides an underlying logic– eg, if we do demonstrate that there is concordance, then if future parents manifest low lung function it is possible that targeting their offspring for screening and potential intervention might serve to prevent low lung function or lung function decline in the child. (See this same response below to a slightly different comment.) CR1: Unsatisfactory reply. In addition, the Authors should explain the reasons why they have limited their investigation to children of age 11-12 and whether their findings might be back-extrapolated to younger children. LSAC is Australia’s only nationally-representative longitudinal children’s study and thus provides unique and valuable information regarding the state of Australian children’s health. It began in 2004. In 2014 at Wave 6, families were notified about the upcoming Child Health CheckPoint data collection in 2015. The children participating in the study were aged 11-12 at that time, hence our age window. We have been careful not to generalise our results to children of other ages, and believe it is useful to publish this previously-unavailable information for a 2-year age band. - Page 9, line 11: this huge gender unbalance of parents may constitute an important selection bias. Thus, the manuscript should be re-arranged and the Authors should analyse only children-mother relationships. The title should accordingly change. All the representativeness checks between the nested and the general sample should be restricted to children-mothers pairs. We acknowledge that there is a low proportion of fathers in our study. However, our aim was to present results for a large sample

	of parent-child dyads. It would be artificial to exclude fathers, particularly as – though far less numerous than mothers – over 100 fathers took part, and this is one of very few studies to present data for both father-child and mother-child concordance in a community setting. This is just one paper in a Special Issue of 15 papers examining similar questions for a wide range of health domains, all of which present the data for both mothers and fathers. However, given this imbalance, we have purposely presented the data separately for mothers and fathers, so that readers can make their own judgements as to which values (combined or separate) they wish to focus on. We have strengthened in the Limitations section the potential bias that could be introduced from such small numbers. CR1: Unsatisfactory reply. Minor points - Title and remainder of the text: it would be better to say "correlation" rather than "concordance", due to the continuous nature of the spirometry indices. Changing this term would make this paper differ from all other papers in this Special Issue, for which this term has not been challenged. We therefore prefer to remain with the term 'concordance'. However, we are happy to modify for this paper at the Editor's recommendation'. CR1: Unsatisfactory reply. - Abstract, line 11: you need to introduce the abbreviation (LSAC) here, since it is used at line 27. Thank you, amended as suggested - Abstract, line 33: replace "Comparable values" with "Mean (SD)". Thank you, amended as suggested - Abstract, line 35: replace "was" with "were". Thank you, amended as suggested - Abstract, line 42 and remainder of the text: replace "norms" with "standards". Thank you, amended as suggested - Abstract, line 42: "generally healthy population sample" is unclear. The text has been modified as follows: Mean lung volumes were larger but with smaller airway size than international standards both for parents and children in this population sample. - Article summary, second bullet: please specify in which context "this is the largest cross-sectional study". The text has been modified as follows: This is the largest cross-sectional study to investigate lung function correlation in Australian parent-child dyads, thereby providing new insight into cross-generational patterns. - Page 4, line 7: replace "overall global" with "global". Amended as suggested - Page 4, line 22: replace "which can identify" with "which allows to". Amended as suggested - Page 4, line 28: replace "z-scores when compared" with "reflecting substantial agreement". Amended as suggested - Page 4, line 37: "Tai et al. (2015)": herein it is missing the quotation of the pivotal study by Lange et al (NEJM, 2015). Thank you, the Lange reference has been added to the manuscript and the text has been modified as follows:

	"In addition, low FEV1 in early adulthood contributes significantly to the genesis of COPD in later years." - Page 4, line 42: replace "as adults" with "later in life". Amended as suggested - Page 4, line 45: replace "accounted for" with "explained". Amended as suggested - Page 5, line 18: it is helpful for the reader to quote herein the sampling method and give some information on the representativeness. The methodology description provided on page 5 describes the sampling method and recruitment. Importantly, this paper forms part of a larger series that includes a detailed methodology cohort profile paper which covers these topics and is referenced in this paper. We are happy to expand here too, but feel this would be unnecessary repetition - please advise if you wish us to do so. - Page 5, line 35: why was only one parent invited? How was gender taken into account? The study was designed to assess dyads comprising the child and one parent. This reflects the design of the underlying LSAC study, in which biennial interviews are conducted with the child and one parent, choice of whom is at the discretion of the family. (Data are collected from the second parent, but only in the form of a leave-behind survey questionnaire.) Further, studies that have attempted to have both parents attend have had very low uptake rates, which would be a more critical weakness. - Page 6, lines 10 and 11: "They consented to…or their child": unclear. The text has been modified as follows: Parents consented to take part knowing that they would not otherwise receive individual results about themselves or their child. - Page 6, line 33: replace "(GLI) equations" with "(GLI 2012) reference equations". Amended as suggested - Page 7, line 44: replace "are" with "were". Amended as suggested - Page 7, line 50: replace "position" with "status". Amended as suggested - Page 7, line 54: replace "conditions" with "status". Amended as suggested - Page 8, line 21: why did the Authors not use Australian charts? Aren't population compositions different between US and Australia? There are no Australian z-score reference values available. It is usual practice to use widely-agreed international references for comparability with other datasets around the world. - Page 8, line 41: reference 26 is difficult to find. Thus, some details on the calculation of the survey weights should be provided herein. We have described survey weighting in detail in the overarching cohort profile/methodology paper for this Special Issue, and we believe it is preferable not to repeat the same information across the multiple papers. Nonetheless, we are happy to add this additional information to this paper if further requested. For your information, the text in the cohort profile and methodology paper reads as follows: "Survey weights: CheckPoint survey weights were created using similar methods to those used for previous waves of LSAC, and are provided in the CheckPoint dataset. These methods account for the selection probability of each child to establish the target design sample, initial non-response to the baseline survey and

	subsequent loss to follow-up. LSAC and CheckPoint survey weights have been estimated to reflect the likelihood of participation from wave to wave within the limits of the information available from study measures. "Applying LSAC survey weights produces analyses that will be as representative as possible for all Australian children born in 2004 and their parents. CheckPoint differs in that, for the majority of measures, only the attending parent (usually the mother) was assessed, and thus weighted analyses of the parent data are more difficult to interpret because the weighting does not estimate a representative sample of all parents." - Table 1 does not report the percentages of males and females; the ranges in the reported "n" numbers per each category are unclear. Table 1 shows the range of n's available for the various measures for children and parents, for the total samples and for males and females separately; in our view, adding the exact n's will add 3 full additional columns of data to the table for very little extra meaning (if anything we think it will reduce meaning through increasing the 'noise' of the table). As noted in the Results text (page 9, immediately prior to Table 1) the percentage of boys was 51.2 (ie 48.8% girls) and the percentage of mothers was 87.5 (ie fathers 12.5%). - Figures 2 and 3: these figures are not fully described in the Results; moreover, the normality assessment was not mentioned in the Methods. The contents of Figures 2 & 3 are described on page 11: "plots of distribution and density for FEV1, FVC, FEV1/FVC and MEF z-scores are shown in Figures 2 & 3 for parents and children, respectively." Under statistical analyses the following text has been added:"The approximate normality or otherwise of the data's distributions were assessed through visual inspection." CR1: Unsatisfactory reply. - Page 11, line 4: the Authors included also FEV1/FVC in their analyses, so they should refer to it when introducing Table 2. The text has been modified as follows: The mean, standard deviations and z-scores for FEV1, FVC, FEV1/FVC and MEF are shown in Table 2. - Page 11, line 15: replace "approximately 0.8 above the mean for the international reference populations, but FEV1/FVC and MEF approximately 0.8 and 0.5 below the reference means respectively" with "approximately 0.8, reflecting higher values than the international reference populations. Conversely, FEV1/FVC and MEF z-scores, approximately -0.8 and -0.5, indicated lower values than the international reference populations". Amended as suggested. - Table 3: as expected, the estimate variability in the very small father-child sub-sample is much larger than for the mother-child subsample. This is a confirmation of the previous comment (Page 9, line 11). As described above, we acknowledge that we have a low proportion of fathers in our study. As a result, we presented the data for mothers and fathers both separately and combined. The Limitations section of the Discussion explicitly acknowledges this in the sentence, "Nonetheless, the 221 fathers showed very similar patterns in the four parameters and their z-scores to mothers and

	to the children, although with some loss of precision in their estimates." CR1: Unsatisfactory reply. - Table 3, description at bottom: replace "correlation coefficients for Pearson" with "Pearson's correlation coefficients". Amended as suggested - Discussion: in general, the Authors should take into account the general comments and the major points. Every effort has been made to implement the suggestions made by reviewers to improve the discussion section of the manuscript. - Page 16, lines 23 to 25: unclear. The text has been modified as follows: Even though all flow-volume loops were inspected it is possible that subtle sub-optimal efforts could have gone undetected, thereby underestimating FEV1. However, the similarities with the findings of those reported by Hall et al. suggest that our findings are replicable. - Page 16, lines 35 to 43: this is an important issue to be discussed in more detail by quoting the relevant literature. In those assessedwe identified evidence of reversible airways obstruction in 30% of children with low lung function. We have amended the paragraph to clarify that this is considered a feature of asthma in children. The text has been modified as follows: "All measurements were reported from pre-bronchodilator flow-volume loops as was reported in the lung function reference populations. We successfully measured response to bronchodilator (following 400 mcg Salbutamol) in 179 children with FEV1/FVC ratio less than -2 z-scores (data not shown). 53 (30%) had evidence of a significant response to bronchodilator (defined as ≥ 12% and ≥ 200 mL improvement in absolute FEV1), suggesting that many children with this ratio below the normal range have reversible airways obstruction. This is usually considered a characteristic feature of asthma." - Page 16, lines 45 to 47: there is recent literature on intergenerational findings in the ECRHS. We believe we have included the appropriate and up-to-date references. We weren't able to find a particular paper that relates directly to this manuscript from the ECRHS study, and wonder if the reviewer could be more specific? We are very willing to consider citing this or any other references deemed by the reviewer to be appropriate assuming they are relevant to this manuscript. Possible choices: 1. BMC Pulm Med. 2018 Jul 27;18(1):122. doi: 10.1186/s12890-018-0687-4. Agreement in reporting of asthma by parents or offspring - the RHINESSA generation study. Kuiper IN(1), Svanes C(2)(3), Benediktsdottir B(4), Bertelsen RJ(2)(5), Bråbäck L(6), Dharmage SC(7), Holm M(8), Janson C(9), Jögi R(10), Malinovschi A(11), Matheson M(7), Moratalla JM(12), Real FG(5)(13), Sánchez-Ramos JL(14), Schlünssen V(15)(16), Timm S(15), Johannessen A(2)(3). 2. J Allergy ClinImmunol. 2018 Jul 21. pii: S0091-6749(18)31058-3. doi:

	10.1016/j.jaci.2018.07.007. [Epub ahead of print] Trans- and inter-generational epigenetic inheritance in allergic diseases. Mørkve Knudsen T(1), Rezwan FI(2), Jiang Y(3), Karmaus W(3), Svanes C(4), Holloway JW(5). 3. Ann Am Thorac Soc. 2018 Jun 12. doi: 10.1513/AnnalsATS.201806-374OC. [Epub ahead of print] Childhood Respiratory Risk Factor Profiles, Their Interactions and Mediators, and Middle-age Lung Function: A Prospective Cohort Study from the 1st to 6th Decade. Bui DS(1), Walters HE(2), Burgess JA(3), Perret JL(4), Bui MQ(5), Bowatte G(6), Lowe AJ(7), Russell MA(8), Thompson BR(9), Hamilton GS(10)(11), James AL(12)(13), Giles GG(14), Thomas PS(15), Jarvis D(16), Svanes C(17), Garcia-Aymerich J(18), ErbasB(19), Frith PA(20)(21), Allen KJ(22), Abramson MJ(23), Lodge CJ(24), DharmageSC(25). 4. EurRespir J. 2018 Jun 7;51(6). pii: 1601611. doi: 10.1183/13993003.01611-2016. Print 2018 Jun. Maternal age at delivery, lung function and asthma in offspring: a population-based survey. Gómez Real F(1)(2), Burgess JA(3), Villani S(4), Dratva J(5), Heinrich J(6), Janson C(7), Jarvis D(8), Koplin J(3), Leynaert B(9)(10), Lodge C(3), Lærum BN(1), Matheson MC(3), Norbäck D(7), Omenaas ER(1)(11), Skulstad SM(1)(12), SunyerJ(13), Dharmage SC(3)(14), Svanes C(12)(15)(14). 5. Lancet Respir Med. 2018 Jul;6(7):535-544. doi: 10.1016/S2213-2600(18)30100-0. Epub 2018 Apr 5. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. Bui DS(1), Lodge CJ(2), Burgess JA(2), Lowe AJ(2), Perret J(3), Bui MQ(2), BowatteG(4), Gurrin L(2), Johns DP(5), Thompson BR(6), Hamilton GS(7), Frith PA(8), James AL(9), Thomas PS(10), Jarvis D(11), Svanes C(12), Russell M(2), Morrison SC(13), Feather I(14), Allen KJ(15), Wood-Baker R(5), Hopper J(2), Giles GG(16), Abramson MJ(17), Walters EH(18), Matheson MC(2), Dharmage SC(19). 6. Int J Epidemiol. 2018 Mar 9. doi: 10.1093/ije/dyy031. [Epub ahead of print] A three-generation study on the association of tobacco smoking with asthma. Accordini S(1), Calciano L(1), Johannessen A(2), Portas L(1), Benediktsdóttir B(3), Bertelsen RJ(4)(5), Bråbäck L(6), Carsin AE(7)(8)(9), Dharmage SC(10), DratvaJ(11)(12), Forsberg B(6), Gomez Real F(4), Heinrich J(13), Holloway

	JW(14), Holm M(15), Janson C(16), Jögi R(17), Leynaert B(18), Malinovschi A(19), MarconA(1), Martínez-MoratallaRovira J(20)(21), Raherison C(22), Sánchez-Ramos JL(23), Schlünssen V(24)(25), Bono R(26), Corsico AG(27), Demoly P(28)(29), Dorado Arenas S(30), Nowak D(13)(31), Pin I(32)(33)(34), Weyler J(35), Jarvis D(36)(37), Svanes C(2)(5); Ageing Lungs in European Cohorts (ALEC) Study. 7. ClinExp Allergy. 2017 May;47(5):627-638. doi: 10.1111/cea.12906. Epub 2017 Mar 28. Clinical markers of asthma and IgE assessed in parents before conception predict asthma and hayfever in the offspring. BertelsenRJ(1)(2), Rava M(3)(4)(5), Carsin AE(6)(7)(8), Accordini S(9), BenediktsdóttirB(10), Dratva J(11), Franklin KA(12), Heinrich J(13)(14), Holm M(15), Janson C(16), Johannessen A(17)(18), Jarvis DL(19), Jogi R(20), Leynaert B(21)(22), Norback D(16), Omenaas ER(1)(18), Raherison C(23), Sánchez-Ramos JL(24), Schlünssen V(25)(26), Sigsgaard T(25), Dharmage SC(27), Svanes C(2)(17). 8. Int J Epidemiol. 2017 Feb 1;46(1):235-245. doi: 10.1093/ije/dyw151. Father's environment before conception and asthma risk in his children: a multi-generation analysis of the Respiratory Health In Northern Europe study. Svanes C(1)(2)(3), Koplin J(1)(4)(5), Skulstad SM(3)(6), Johannessen A(3)(7), BertelsenRJ(2)(3), Benediktsdottir B(8)(9), Bråbäck L(10), ElieCarsin A(11), DharmageS(3)(4), Dratva J(1)(12), Forsberg B(10), Gislason T(8)(9), Heinrich J(13), Holm M(14), Janson C(15), Jarvis D(16), Jögi R(17)(18), Krauss-Etschmann S(19), Lindberg E(15), Macsali F(20), Malinovschi A(15), Modig L(1)(10), Norbäck D(15), Omenaas E(3)(7), Waatevik Saure E(3), Sigsgaard T(21), Skorge TD(2), SvanesØ(2)(3), Torén K(14), Torres C(3), Schlünssen V(21), Gomez Real F(3)(20). - Page 16, lines 46 to 52: in the abstract of “Lebowitz et al. 1984”, reported on PUBMED, it is written: “Initial regression analysis showed significant correlations of the pulmonary function variables after controlling for age and sex. Body habitus, as measured by the Ponderal Index, was highly aggregated as well. Pulmonary function measurements were aggregated in families independent of family size, reported diagnosed AOD, and children's smoking, even though both asthma and smoking showed significant familial aggregation. After controlling for the familial aggregation of body habitus, a major determinant of pulmonary function, there was no remaining independent aggregation of pulmonary function measurements.”. Further, in the text at page 9 it is written “Thus, the relation between children's lung function and parents' lung function is likely to be related to their similar body habitus.”

	Therefore, the summary of such an article reported by the Authors may be misleading. We believe we are reflecting the same points as alluded to here. We have amended our statement to make this clearer, as follows: Our intergenerational correlation findings for lung function extend the small published literature on the heritability and familial aggregation of lung function.143435 In the oldest published study dating back to 1984, Lebowitz et al. did not find any relationship between parents' and children's lung function after accounting for body habitus.14