BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023486
Article Type:	Research
Date Submitted by the Author:	09-Apr-2018
Complete List of Authors:	Welsh, Liam; Murdoch Childrens Research Institute; The Royal Children's Hospital, Respiratory Medicine Kathriachchige, Gayan; The University of Melbourne, Department of Paediatrics Raheem, Tahmeed; The University of Melbourne, Department of Paediatrics Grobler, Anneke; Murdoch Children's Research Institute Wake, Melissa; Murdoch Childrens Research Institute; The University of Melbourne, Department of Paediatrics Ranganathan, Sarath ; Murdoch Children's Research Institute; The Royal Children's Hospital, Respiratory Medicine
Keywords:	Lung function, Spirometry, Reference values, Children, Inheritance patterns, Epidemiologic studies

Lung function: Population epidemiology and concordance in 11-12 year old Australians and their parents

Authors: Liam Welsh[1,2], Gayan Kathriachchige[3], Tahmeed Raheem[3], Anneke Grobler[1], Melissa Wake[1,3,4], Sarath Ranganathan[1,2,3]

Affiliations: [1]Murdoch Children's Research Institute, Parkville, VIC, Australia; [2]Respiratory Medicine, The Royal Children's Hospital, Parkville, VIC, Australia;[3]Department of Paediatrics, The University of Melbourne, Parkville, VIC, Australia; [4]Department of Paediatrics & The Liggins Institute, The University of Auckland, Grafton, Auckland, New Zealand

Correspondence to: Professor Melissa Wake
Murdoch Children's Research Institute
The Royal Children's Hospital
Flemington Road, Parkville VIC 3052, AUSTRALIA
T: +61 3 9345 5937 E: melissa.wake@mcri.edu.au

Keywords: Lung function, spirometry, reference values, parents, children, inheritance patterns, correlation studies, epidemiologic studies, cross-sectional studies

Abbreviations : ATS: American Thoracic Society; BMI: body mass index; CC: correlation coefficient; CI: confidence interval; Disadvantage Index: Socio-Economic Index for Areas Index of Relative Socioeconomic Disadvantage; ERS: European Respiratory Society; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; GLI: Global Lung Initiative; LSAC: Longitudinal Study of Australian Children; MEF: Mid Expiratory Flow; n: number of participants in cohort with measure; N: number of biological child-parent pairs with measure; RC: estimated regression coefficient; SD: standard deviation.

Word count: 3446

ABSTRACT

Objectives: To describe the epidemiology of lung function in Australian children aged 11-12 and their parents, and explore the degree of intergenerational concordance.

Design: Cross-sectional study (the Child Health CheckPoint) nested in the Longitudinal Study of Australian Children.

Setting: Assessment centres in seven Australian cities and eight regional towns, Feb 2016 – Mar 2016. Families unable to attend a clinic appointment were offered a home visit during the same period.

Participants: 1874 families (53% of all eligible) participated in the study. Lung function data were available for 1759 children aged 11-12 and 1774 parents (1668 biological pairs).

Outcome measures: Participants completed spirometry with measures, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mid expiratory flow (MEF), converted to z-scores using Global Lung Initiative equations. Parent-child concordance was assessed using Pearson's correlation coefficients and multivariable linear regression models. Survey weights and methods accounted for LSAC's complex sampling, stratification and clustering within postcodes.

Results: All lung function measures followed approximately normal distributions. Mean (SD) for FEV_1, FVC and MEF z-scores in children were 0.33 (1.07), 0.83 (1.14) and -0.48 (1.09), respectively. Comparable values in parents were 0.28 (1.10), 0.85 (1.15) and -0.45 (1.10), respectively. Parent FEV_1, FVC and MEF was associated with child lung function with significant positive correlation coefficients (0.22, 95% CI 0.17 to 0.26; 0.24, 95% CI 0.20 to 0.29; and 0.24, 95% CI 0.20 to 0.29, respectively).

Conclusions: Mean lung volumes were larger but with smaller airway size than international norms for both parents and children in this generally healthy population sample. Modest associations between parent and child lung function highlight the potential for better identification of 'at risk' populations. Therefore, these findings may aid the development of health policy that aims to prevent the onset or limit the progression of lung disease.

ARTICLE SUMMARY

Strengths and limitations of this study

- Population based sampling of Australian children provides a contemporary reference for future studies investigating lung function.
- This is the largest cross-sectional study to investigate lung function concordance in parent-child dyads, thereby providing new insight into cross-generational patterns.
- Results were not adjusted for exposure to maternal or postnatal smoking or for sitting height, which should be taken into consideration when interpreting the results.
- Most of the participating parents were mothers, resulting in less precise descriptive and concordance estimates for fathers.

INTRODUCTION

Non-communicable respiratory diseases such as chronic obstructive pulmonary disease, asthma, pulmonary fibrosis and lung cancer are the third leading cause of overall global mortality.[1 2] In Australia, mortality from chronic respiratory disease is currently 25.6 deaths per 100,000 males and 15.5 deaths per 100,000 females aged <70 years.[3] In addition, these diseases can have extra-pulmonary manifestations and therefore worsen the burden placed on healthcare resources.[3] Without well-informed policy there is likely to be further demand on healthcare expenditure.[4] 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.

Spirometry is a well-established clinical tool for assessing, diagnosing and monitoring respiratory disease in children and adults. It is a non-invasive method which can identify individuals with low or abnormal lung function, and compare both individuals and populations to international reference values.[5] For example, a recent population study of spirometry data from 2066 Australian subjects aged 4-80 years reported a mean difference of <0.25 for FEV_1 and FVC z-scores when compared with international norms.[6] The current literature also demonstrates clear modifiable, environmental risk factors for chronic respiratory disease, such as smoking and occupational exposures.[7]

In childhood, genetic factors and developmental influences also appear to be relevant. Early life evidence suggests that the complex causal pathways to several non-communicable diseases occur in childhood through a variety of bio-psycho-social factors.[8] For example, Tai et al. (2015) found that lung function in adult life is mainly determined in childhood, and that those with lower lung function in childhood were more likely to have asthma and chronic obstructive pulmonary disease as adults.[9] Published studies provide consistent evidence for familial aggregation of spirometric indices, suggesting that around 20–60% of total phenotypic variance may be accounted for by familial factors,[10-15] but few studies have quantified inter-generational concordance at the population level. This could lead to new ways of predicting the population risk of non-communicable respiratory disease or even the possibility of targeted screening to individuals when a relative is identified with a heritable condition.[16]

The Child Health CheckPoint, nested within the Longitudinal Study of Australian Children (LSAC), offered a comprehensive health assessment to participants. This included lung

function testing of children aged 11-12 years and one of their parents using reliable, valid epidemiologic measures, specifically FEV_1, FVC, and MEF, on the same day and using the same equipment and protocols. Drawing on this population-based sample, the aims of this study were to (1) describe the epidemiology of lung function in Australian children aged 11-12 and their parents, and (2) investigate parent-child concordance in these same measures.

METHODS

Study Design and Participants: Growing Up in Australia: The Longitudinal Study of Australian Children (LSAC) is Australia's only national longitudinal child study. Details of the LSAC study design and recruitment are provided elsewhere.[17 18 19] Briefly, commenced in 2004 as the B and K cohorts, data collection has taken place every two years. This included home-visits and mailed questionnaires. The LSAC B cohort (reported in this paper) included 5107 families in the first wave, a 57.2% uptake of the 8921 families contacted. After 10 years of the study, 4484 of these families participated in Wave 6 (2014). During this Wave 6 home visit, B cohort families were introduced to the upcoming Child Health CheckPoint and asked to consent to their contact details being shared with the CheckPoint team. Those that consented (3513 families, 78% of Wave 6 cohort and 69% of original cohort) received an information pack via mail, and an information and recruitment phone call during 2015.

Child Health CheckPoint data collection spanned February 2015 to March 2016, and 1874 families participated (Figure 1). In seven major Australian cities, the study child and one of their parents were invited to participate in a 3.5 hour clinic assessment which included 17 different assessment stations. In eight regional towns there were 2¾-hour mini assessment centres, which included the same assessments as those made in major cities except for those requiring large equipment that could not be checked in as personal luggage on commercial flights. Families unable to attend a clinic appointment were offered a 1.5 hour home visit with a subset of measures that could be conducted in the home by a researcher using portable equipment. A more detailed description of the CheckPoint study design is provided elsewhere.[20 21]

Ethics and Consent: The study protocol was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (33225D) and Australian Institute of Family Studies Ethics Committee (14-26). The attending parent provided written informed consent for themselves and their child to participate in the study.

Patient and Public Involvement: Because LSAC is a population-based longitudinal study, no patient groups were involved in its design or conduct. To our knowledge, the public was not involved in the study design, recruitment or conduct of LSAC study or its CheckPoint module. Parents received a summary health report for their child and themselves at or soon after the assessment visit. They consented to take part knowing that they would not otherwise receive individual results about themselves or their child.

Procedures: Spirometry, height and weight were measured at an assessment centre or at a home visit. Participants were included in these analyses if they met American Thoracic Society (ATS) / European Respiratory Society (ERS) criteria for spirometry (see below). Reasons for a lack of useable data included equipment failure, poor quality data or time constraints. Data from 20 non-biological child-parent pairs were excluded from concordance analyses.

Lung function measures: Participants completed spirometry testing with measures including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mid expiratory flow (MEF). Prior to testing, spirometers were calibrated using a 3-litre syringe with adjustments made for current ambient conditions. Spirometry was performed using a Vyntus Pneumo spirometer running SentrySuite software (Care Fusion, Germany) with a bacterial filter and nose clip in place. These data were converted to z-scores using the Global Lung Initiative (GLI) equations.[22] Children also undertook post-bronchodilator spirometry, which is not reported here.

Spirometry was performed in accordance with ATS/ERS guidelines.[5] Firstly, the researcher explained and demonstrated the correct performance of spirometry to study participants. This included an emphasis on correct posture with the head slightly elevated, a tight seal around the mouthpiece with no leak, a rapid and complete inhalation to total lung capacity, followed by a rapid maximal exhalation until residual volume was reached while maintaining an upright posture. Adhering to these instructions, participants then performed a minimum of three and a maximum of eight spirometry trials. Via its DataCube function, data were exported from the SentrySuite platform into a Microsoft Excel spreadsheet. The quality of all flow-volumes loops were assessed by LW and SR. Data were assessed to determine if the loops met ATS/ERS criteria (see acceptability criteria below), if two acceptable manoeuvres were obtained, each participant's best loop was identified. FEV_1, FVC and MEF scores were derived from the best loop.

ATS/ERS Acceptability Criteria

A. Start of test

Assessed by visual inspection of the flow-volume trace.

A rapid rise to and clearly defined peak expiratory flow.

B. Within manoeuvre

Assessed by visual inspection of the flow-volume trace.

Manoeuvre was free from artefact, cough within the first second, glottic closure, or obvious leak.

C. End of test

Assessed by visual inspection of the volume-time trace.

Clear end-expiratory plateau on volume–time trace with no sharp drop or cessation of flow. There was no specification for a minimal forced expiratory time.

D. **Repeatability**

Two largest FEV_1 and FVC values were within 150 ml.

A quality score between 1 and 5 was assigned to each loop:

1. Meets all of the ATS/ERS criteria (Met acceptability criteria for A, B, C and D)
2. Meets all ATS/ERS criteria except for repeatability. Two largest FVC values had a difference of >150 mls
3. Meets all ATS/ERS criteria except for repeatability. Two largest FEV_1 values had a difference >150 mls
4. Does not meet ATS/ERS guidelines; data excluded from dataset
5. Meets all ATS/ERS criteria except for repeatability. Two largest FVC and FEV_1 values had a difference >150 mls

Loops that were assigned a quality control score of 1, 2, 3 or 5 are included in the dataset.

Other sample characteristics: Age and gender were obtained via the Medicare Australia database for children and were self-reported by parents. In Australia, Socio-Economic Indexes for Areas provide standardised scores for socioeconomic position by geographic area (postcode of family domicile) compiled from 2011 Australian Census data. We used the Index of Relative Socioeconomic Disadvantage (disadvantage index) which numerically summarises the social and economic conditions of Australian neighbourhoods (national mean

of 1000 and a standard deviation (SD) of 100, with a higher score indicating less disadvantage and a lower score indicating more disadvantage).[23]

Height and weight were recorded prior to spirometry measurement. Standing height was measured to the nearest 0.1 cm without shoes and socks, in duplicate, using a portable rigid stadiometer (Invicta IP0955, Leicester, UK). A third measurement was taken if the difference of the first two measurements exceeded 0.5 cm; final height was the mean of all measurements made. Weight to the nearest 0.1 kg was measured wearing light clothing without shoes or socks using an InBody230 bio-electrical impedance analysis scale (Biospace Co. Ltd. Seoul, South Korea) at assessment centres or with a 2-limb body composition scale (Tanita BC-351, USA) at home visits. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. For children, an age- and sex-adjusted BMI z-score was calculated using the US Centers for Disease Control growth reference charts.[24]

A pre-clinic checklist including questions about a diagnosis of asthma and shortness of breath causing restriction was completed by parents and brought to the assessment**.**

Statistical Analysis: Statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, TX). Continuous descriptive variables were summarised using weighted means and standard deviations (SD); categorical variables were summarised by number and weighted percentage for children and adults separately, by sex and overall.

Population summary statistics and proportions were estimated by applying survey weights and survey procedures that corrected for the sampling frame, participation and non-response, and took into account clustering in the sampling frame. Standard errors were calculated taking into account the complex design and weights.[25] More detail on the calculation of the survey weights is provided elsewhere. [26]

Parent-child concordance was assessed by 1) Pearson's correlation coefficients with 95% confidence intervals and 2) linear regression with the child variable as the dependent variable and the parent variable as the independent variable adjusted for the potential confounders. The Pearson's correlation and linear regression analyses were repeated using weighted multi-level survey analyses; as these yielded similar results, unweighted results are presented.

An abnormal FEV_1/FVC z-score was defined as any result less than -2.0. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools.[27]

RESULTS

Sample characteristics: Figure 1 depicts participation in the Child Health CheckPoint study. 1759 children and 1774 parents successfully completed spirometry testing in line with ATS/ERS criteria,[5] including 1668 biological parent-child dyads.

Sample characteristics are presented in Table 1. Among the child cohort, boys and girls were roughly equally represented (51.2% boys), but most (87.5%) parents were mothers. For children, the sample population had a somewhat higher mean BMI than the historical reference population, in keeping with the known current epidemiology of BMI for Australian children. For parents, mean BMI fell within the 'overweight' category according to the US Centres for Disease Control and Prevention.[24] The mean disadvantage index was 1009 (62) which is marginally above the Australian national mean of 1000, but with a lower spread (SD 62 vs 100 nationally) such that very disadvantaged families were under-represented.[28]

241 children (13.7%) and 179 parents (10%) reported a diagnosis of asthma. Only 11 children and 24 parents reported shortness of breath causing restriction.

Table 1. Sample characteristics; values are weighted mean (standard deviation), except where specified as (%)

Characteristic	All	Male	Female
Child			
n	1627-1759	848-902	741-857
Age, years	12.0 (0.4)	12.0 (0.4)	12.0 (0.4)
Height, cm	153.8 (8.0)	153.4 (8.3)	154.3 (7.7)
Weight, kg	46.6 (11.4)	45.8 (11.4)	47.3 (11.3)
BMI, kg/m^2	19.5 (3.7)	19.3 (3.6)	19.7 (3.7)
BMI z-score	0.37 (1.03)	0.36 (1.07)	0.39 (1.00)
Waist circumference, cm	66.9 (9.0)	67.5 (9.0)	66.1 (8.9)
Disadvantage Index	1009 (62)	1009 (62)	1010 (62)
Started puberty (%)	91.8	88.5	95.5
Asthma reported (%)	14.0	15.5	12.3
Shortness of breath causing restriction (%)	0.5	0.3	0.7
Parent			
n	1756-1774	218-221	1536-1553
Age, years	43.7 (5.6)	46.2 (7.0)	43.4 (5.3)
Height, cm	165.9 (7.8)	177.7 (7.4)	164.2 (6.3)
Weight, kg	78.2 (19.1)	91.4 (17.4)	76.4 (18.6)
BMI, kg/m^2	28.4 (6.4)	28.9 (4.9)	28.3 (6.6)
Waist circumference, cm	87.9 (15.1)	98.1 (13.4)	86.4 (14.8)
Asthma reported (%)	9.9	3.6	10.8
Shortness of breath causing restriction (%)	1.8	2.2	1.8

BMI, body mass index; Disadvantage Index: Index of Relative Socioeconomic Disadvantage; n: number of participants in cohort with this measure.

Population epidemiology of lung function: The mean, standard deviations and z-scores for FEV_1, FVC and MEF are shown in Table 2. All measures of lung function in children and adults followed approximately normal distributions; plots of distribution and density for FEV_1, FVC, FEV_1/FVC and MEF z-scores are shown in Figures 2 & 3 for parents and children, respectively.

On average, boys and girls had FEV_1, FVC and MEF z-scores that were within normal limits, as did parents. Lung function followed similar distributions in children and parents, with mean FEV_1 z-scores approximately 0.3 and FVC z-scores approximately 0.8 above the mean for the international reference populations, but FEV_1/FVC and MEF approximately 0.8 and 0.5 below the reference means respectively (see table 2). The proportion of children with lung function z-score below the normal range (<-2 z-score) was 1.7% for FEV_1; 0.6% for FVC; 12.9% for FEV_1/FVC and 8.1% for MEF respectively. This was similar in parents, where the proportion of lung function below the lower limit of normal was 2.7% for FEV_1; 1.3% for FVC; 13.7% for FEV_1/FVC ratio and 7.9% for MEF respectively.

Table 2. Distribution of lung function markers in Australian children and parents

Lung function measure	All				Males				Females			
	n	Mean	SD	95% CI	n	Mean	SD	95% CI	n	Mean	SD	95% CI
Children												
Raw												
FEV1 (litres)	1759	2.47	0.43	2.45 to 2.50	902	2.47	0.44	2.43 to 2.50	857	2.48	0.41	2.45 to 2.51
FVC (litres)	1759	2.99	0.53	2.96 to 3.02	902	3.04	0.55	3.00 to 3.09	857	2.93	0.49	2.89 to 2.97
FEV1/FVC ratio	1759	83.1	7.29	82.7 to 83.5	902	81.40	7.00	80.9 to 81.9	857	85.01	7.13	84.4 to 85.6
MEF (FEF25-75%) (l/s)	1759	2.6	0.73	2.56 to 2.64	902	2.47	0.69	2.42 to 2.52	857	2.74	0.75	2.68 to 2.80
z-scores												
FEV1	1754	0.33	1.07	0.27 to 0.39	900	0.26	1.07	0.17 to 0.35	854	0.41	1.06	0.32 to 0.49
FVC	1754	0.83	1.14	0.76 to 0.90	900	0.8	1.14	0.71 to 0.90	854	0.85	1.14	0.76 to 0.95
FEV1/FVC ratio	1754	-0.72	1.16	-0.79 to -0.66	900	-0.78	1.14	-0.87 to -0.69	854	-0.67	1.18	-0.76 to -0.57
MEF (FEF25-75%)	1754	-0.48	1.09	-0.54 to -0.42	900	-0.54	1.08	-0.62 to -0.45	854	-0.42	1.11	-0.51 to -0.33
Parents												
Raw												
FEV1 (litres)	1774	3.03	0.59	2.99 to 3.06	221	3.85	0.62	3.76 to 3.94	1553	2.91	0.49	2.88 to 2.94
FVC (litres)	1774	3.95	0.77	3.90 to 3.99	221	5.08	0.81	4.95 to 5.20	1553	3.79	0.62	3.75 to 3.83
FEV1/FVC ratio	1774	77.0	7.04	76.6 to 77.4	221	76.1	6.75	75.1 to 77.0	1553	77.1	7.07	76.7 to 77.6
MEF (FEF25-75%) (l/s)	1774	2.72	0.93	2.67 to 2.78	221	3.34	1.06	3.17 to 3.50	1553	2.64	0.88	2.58 to 2.70
z-scores												
FEV1	1760	0.28	1.10	0.22 to 0.35	221	0.15	0.93	0.03 to 0.28	1539	0.3	1.12	0.23 to 0.37
FVC	1760	0.85	1.15	0.79 to 0.92	221	0.65	0.97	0.51 to 0.78	1539	0.88	1.17	0.81 to 0.95
FEV1/FVC ratio	1760	-0.85	1.07	-0.92 to -0.79	221	-0.74	1.04	-0.89 to -0.60	1539	-0.87	1.07	-0.94 to -0.80
MEF (FEF25-75%)	1760	-0.45	1.10	-0.52 to -0.39	221	-0.31	0.98	-0.46 to -0.17	1539	-0.47	1.11	-0.55 to -0.40

Sample weights applied to data. CI: confidence intervals; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; MEF: Mid Expiratory Flow; FEF: Forced Expiratory Flow; l/s: litres per second; n: number of participants in cohort with this measure (denominator); SD: standard deviation.

Parent-child concordance: Two models of child-parent concordance are displayed in Table 3. Pearson's correlations between children and parents for FEV_1, FVC and MEF z-score all showed modest significant positive correlations. The strongest association was seen in FEV_1/FVC z-score (correlation coefficient 0.25, 95% CI 0.20 to 0.29). Associations strengthened marginally on conversion to z-scores and thereby adjusting for age, sex, and height. The linear regression model also showed similar relationships between child and parent lung function indices, when adjusted for covariates, irrespective of the parent being a mother or a father.

When using a FEV_1/FVC ratio z-score of < -2.0 to define abnormality we found the following: parent and child both normal, 1282 (77.6%); parent abnormal but child normal, 163 (9.9%); parent normal but child abnormal, 159 (9.6%); both abnormal 49 (3.0%).

Table 3. Parent-child concordance

	Parent-child			Mother-child			Father-child		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Raw									
FEV_1	1668	0.19	0.15 to 0.24	1454	0.20	0.15 to 0.25	214	0.21	0.07 to 0.33
FVC	1668	0.21	0.17 to 0.26	1454	0.24	0.19 to 0.29	214	0.20	0.07 to 0.33
FEV_1/FVC ratio	1668	0.23	0.18 to 0.27	1454	0.24	0.19 to 0.29	214	0.17	0.04 to 0.30
MMEF (FEF25-75%)	1668	0.20	0.15 to 0.24	1454	0.21	0.16 to 0.26	214	0.15	0.02 to 0.28
z-score									
FEV_1	1653	0.22	0.17 to 0.26	1439	0.22	0.17 to 0.27	214	0.25	0.12 to 0.38
FVC	1653	0.24	0.20 to 0.29	1439	0.25	0.20 to 0.29	214	0.22	0.09 to 0.35
FEV_1/FVC ratio	1653	0.25	0.20 to 0.29	1439	0.26	0.21 to 0.30	214	0.21	0.08 to 0.34
MMEF	1653	0.24	0.20 to 0.29	1439	0.24	0.19 to 0.29	214	0.26	0.13 to 0.38
Adjusted Linear Regression	**N**	**RC**	**P value**	**N**	**RC**	**P value**	**N**	**RC**	**P value**
Raw									
FEV_1	1660	0.17	<0.001	1449	0.16	<0.001	211	0.20	<0.001
FVC	1660	0.17	<0.001	1449	0.17	<0.001	211	0.15	0.001
FEV_1/FVC ratio	1660	0.26	<0.001	1449	0.27	<0.001	211	0.19	0.004
MEF (FEF25-75%)	1660	0.19	<0.001	1449	0.20	<0.001	211	0.16	<0.001
z-score									
FEV_1	1648	0.21	<0.001	1437	0.21	<0.001	211	0.32	<0.001
FVC	1648	0.25	<0.001	1437	0.25	<0.001	211	0.28	0.001
FEV_1/FVC ratio	1648	0.28	<0.001	1437	0.29	<0.001	211	0.22	0.002
MEF	1648	0.25	<0.001	1437	0.25	<0.001	211	0.30	<0.001

Covariates models include child and parental age, sex and BMI. CC: correlation coefficients for Pearson; CI: confidence interval; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; MEF: Mid Expiratory Flow; FEF: Forced Expiratory Flow; N: number of biological child-parent pairs with this measure; RC: estimated regression coefficient.

DISCUSSION

Principal findings: This study represents the largest report of spirometry in children aged 11-12 years across Australia. Lung function parameters were on average within normal limits for parents and children, with mean above the international predicted mean for FEV_1 and FVC while being below the predicted mean for FEV_1/FVC. With regard to concordance, there were modest positive correlations between child and parent lung function indices of around 0.20-0.25 including FEV_1, FVC and MEF. Importantly, the strongest concordance between children and parents was for the FEV_1/FVC z-score, which represents the relationship between airway size and lung volume and is the most sensitive spirometric index for detecting airway obstruction.

Strengths and limitations: Within this large child cohort there was equal representation from boys (51.2%) and girls, but mothers were over-represented (87.5%). 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. This could also be viewed as a strength of our study given the influence of maternal factors and *in utero* environment on the future development of non-communicable disease.[29] We acknowledge that this was a cross-sectional study and that these results have not been adjusted for exposure to maternal or postnatal smoking. Although smoking rates during pregnancy in Australia have declined significantly and are currently at their lowest levels in history,[29] it is well established that exposure to maternal smoking can have a life-long impact on peak lung function.[30]

Interpretation in light of current literature: Compared with previous population studies of lung function, we showed somewhat larger mean absolute volume for FEV_1 and FVC in children and adults of similar age and height.[31] Hall et al. defined the minimum physiologically relevant difference to be 0.5 z-scores, equating to a difference of ~6% predicted in their study of contemporary Australasian individuals. Mean (SD) z-scores for their data were 0.23 (1.00) for FEV_1, 0.23 (1.00) for FVC, −0.03 (0.87) for FEV_1/FVC and 0.07 (0.95) for FEF_{25-75}, all of which were considered well within the range considered to be physiologically irrelevant.[6] When adjusted for age, sex and height using the GLI prediction models, [22] mean FEV_1, FVC and MEF z-scores were all within normal limits for children and their parents but above the GLI predicted mean, with patterns similar to but more marked than identified by Hall et al. This suggests that on average children, and their parents, in Australia have better lung volumes than the GLI reference population. This could be

associated with the lower prevalence of smoking in Australia or that those with significant disadvantage, who might have lower lung function, were relatively under-represented in this study.

The FEV_1/FVC ratio was below normal in approximately 13% of either children or their parents. This ratio reflects airway size relative to lung volume and might be explained by the concept of dysanaptic growth where the airways and lung parenchyma grow disproportionately. This is thought to be influenced by gender-specific pubertal status. A low ratio can indicate airway obstruction. Differences in technique and equipment may also have contributed. For example, sub-optimal effort during the initial part of a forced expiratory manoeuvre, where flows remain partly effort-dependent, could underestimate FEV_1 but FVC would be preserved if the expiration proceeded to residual volume (akin to a slow vital capacity manoeuvre). Even though all flow-volume loops were inspected it is possible subtle sub-optimal effort could have gone undetected. However, the similarities with the findings of those reported by Hall et al. suggest that these findings are replicable. Additionally, FVC increases with sitting height, and a lower FEV_1/FVC ratio might occur if our population was of greater sitting height than the reference population but we were not able to adjust for this as sitting height was not measured.[32] Matched FEV_1/FVC ratio below the normal range occurred in only 3% of child-parent dyads.

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 FEV_1/FVC ratio less than -2 z-scores (data not shown). 53 (30%) had evidence of a significant response to bronchodilator (defined as $\geq$ 12% and $\geq$ 200 mL improvement in absolute FEV_1), suggesting that many children with this ratio below the normal range have reversible airways obstruction.

Our intergenerational concordance findings for lung function extend the small published literature on the heritability and familial aggregation of lung function.[13 33 34] 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, even after controlling for age and sex.[13] However, our child-one parent dyadic concordance values of around 0.20 to 0.25 are very consistent with the Busselton Health Study in Western Australia,[33] whose narrow-sense heritability (which takes into account contributions from both parents) for FEV_1 and FVC were 38.9% and 40.6%. In contrast to the Busselton study where assessments were

made at an offspring age of 45 years, we identified this concordance when children were between 11 and 12 years of age, prior to the likely influence of cigarette smoking and genetic susceptibility to lung injury on heritability. Xu *et al*. identified significant correlations in parent child lung function in both families of children with asthma and healthy, non-asthmatic children. In healthy children this correlation was similar for maternal (0.22) and paternal 1st child (0.24) $FEV_{1,}$ both again being remarkably similar to those identified in the current study. These data indicate that heritability of lung function requires further exploration when considering long-term outcomes of early lung function.[34]

Meaning and interpretation for clinicians and policy makers: Taken together, these results show lung volumes above predicted population means for Australian children aged 11-12 years and positive intergenerational concordance between their lung function and those of their parents. Though modest, the associations highlight the potential for better identification of 'at risk' patients while also indicating that there are likely to be many other factors at play.

Conclusions and future directions: Lung function indicating lower airway size relative to lung volume in this population may be due to multiple factors but warrants further assessment over time for evidence of airway obstruction. Our findings indicate the need to explore factors relating to intergenerational concordance in lung function further in order to develop health policy that aims to prevent the onset or limit the progression of lung disease.

ACKNOWLEDGEMENTS: The MCRI administered the research grant for the study and provided infrastructural support to its staff but played no role in the conduct or analysis of the trial. Research at the MCRI is supported by the Victorian Government's Operational Infrastructure Support Program.

The funding bodies had no role in relation to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

This paper uses unit record data from Growing Up in Australia, the Longitudinal Study of Australian Children. The study is conducted in partnership between the Department of Social Services (DSS), the Australian Institute of Family Studies (AIFS) and the Australian Bureau of Statistics (ABS). The findings and views reported in this paper are those of the author and should not be attributed to DSS, AIFS or the ABS.

Some study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools. REDCap is a secure, web-based application designed to support data capture for research studies. More information about this software can be found at: www.project-redcap.org. We thank the LSAC and CheckPoint study participants, staff and students for their contributions.

COMPETING INTERESTS: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare financial support as described in the funding section. MW received support from Sandoz to present at a symposium outside the submitted work.

FUNDING: This work was supported by the National Health and Medical Research Council (NHMRC) of Australia (Project Grants 1041352, 1109355), The Royal Children's Hospital Foundation (2014-241), the Murdoch Children's Research Institute (MCRI), The University of Melbourne, the Financial Markets Foundation for Children (2014-055, 2016-310) and the National Centre for Longitudinal Data (NCLD). MW was supported by a NHMRC Senior Research Fellowship (1046518).

The MCRI administered the research grants for the study and provided infrastructural support (IT and biospecimen management) to its staff and the study, but played no role in the conduct or analysis of the trial. DSS played a role in study design; however, no other funding bodies had a role in the study design and conduct; data collection, management, analysis, and interpretation; preparation, review, or approval of the manuscript; and decision to submit the

manuscript for publication. Research at the MCRI is supported by the Victorian Government's Operational Infrastructure Support Program.

CONTRIBUTIONS:

LW, GK and TR contributed to the interpretation of results, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

AG performed the statistical analyses, contributed interpretation of results and critical review of the manuscript.

SR contributed to the interpretation of results and provided critical review of the manuscript.

MW is the Principal Investigator of the Child Health CheckPoint, planned the analyses and provided critical review of the manuscript.

DATA SHARING STATEMENT: Dataset and technical documents available from Growing Up in Australia: The Longitudinal Study of Australian Children via low-cost license for bone fide researchers. More information is available at www.growingupinaustralia.gov.au

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1. Participant diagram

Figure 2. Lung function distribution & density plots for parents
FEV_1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV_1/FVC ratio, MEF: Mid Expiratory Flow

Figure 3. Lung function distribution & density plots for children
FEV_1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV_1/FVC ratio, MEF: Mid Expiratory Flow

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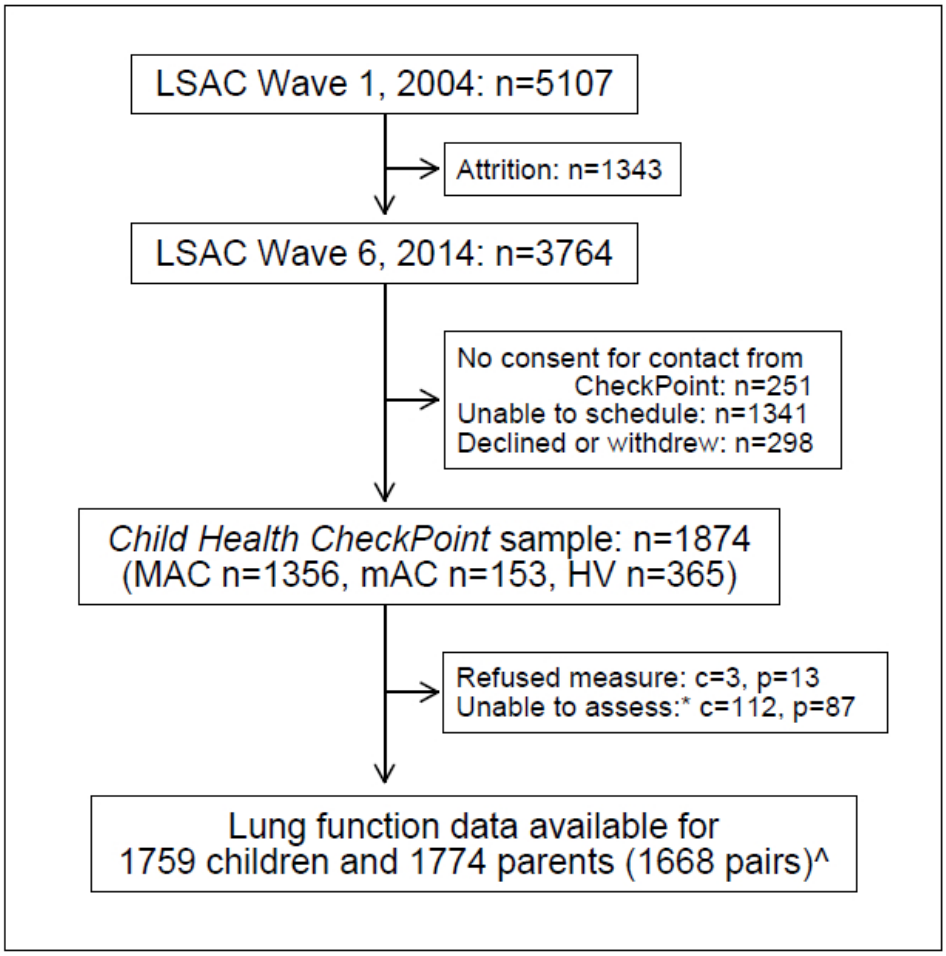
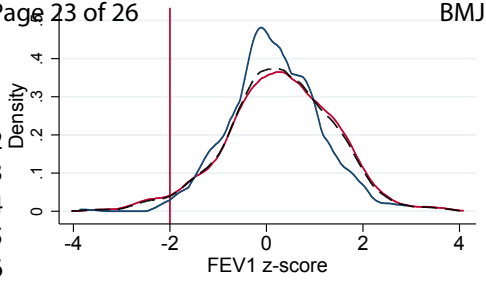
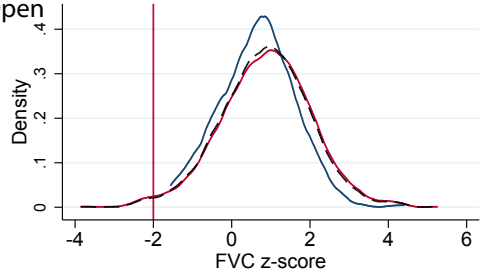


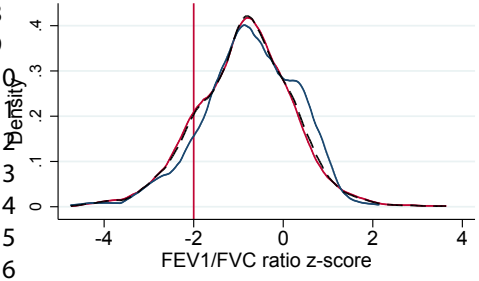
n=number of families, c=number of children, p=number of attending adults,
MAC=Main assessment centre, mAC=Mini assessment centre, HV=Home visit assessment,
LSAC=Longitudinal Study of Australian Children
*Unable to assess due to equipment failure, poor quality data or time contraints
^Data from 20 non-biological child-parent pairs excluded from concordance analyses

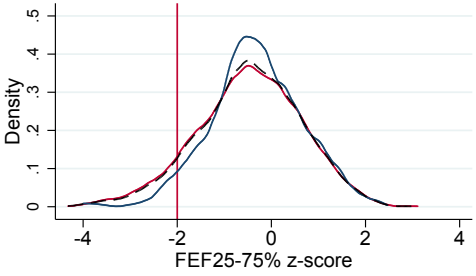
Figure 1. Participant diagram

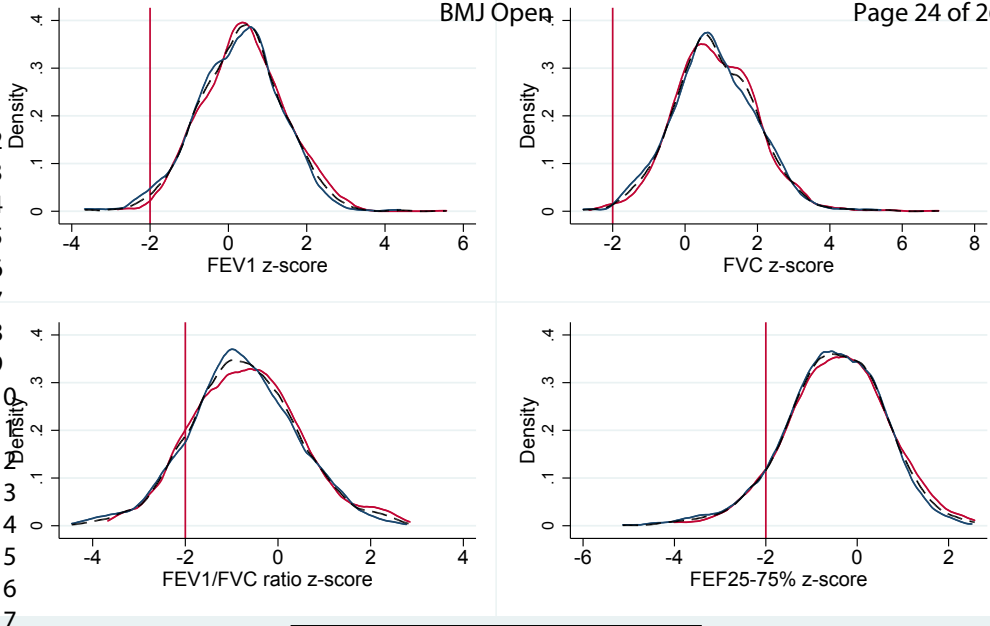
171x193mm (96 x 96 DPI)











STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale~~ for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	NA 5-6
		~~(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed~~ ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	7-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-12
		(*b*) Report category boundaries when continuous variables were categorized	7-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Lung function: Population epidemiology and concordance in 11-12 year old Australians and their parents

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023486.R1
Article Type:	Research
Date Submitted by the Author:	07-Jun-2018
Complete List of Authors:	Welsh, Liam; Murdoch Childrens Research Institute; The Royal Children's Hospital, Respiratory Medicine Kathriachchige, Gayan; The University of Melbourne, Department of Paediatrics Raheem, Tahmeed; The University of Melbourne, Department of Paediatrics Grobler, Anneke; Murdoch Children's Research Institute Wake, Melissa; Murdoch Childrens Research Institute; The University of Melbourne, Department of Paediatrics Ranganathan, Sarath ; Murdoch Children's Research Institute; The Royal Children's Hospital, Respiratory Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Paediatrics, Public health, Respiratory medicine
Keywords:	Lung function, Spirometry, Reference values, Children, Inheritance patterns, Epidemiologic studies

Lung function: Population epidemiology and concordance in 11-12 year old Australians and their parents

Authors: Liam Welsh[1,2], Gayan Kathriachchige[3], Tahmeed Raheem[3], Anneke Grobler[1], Melissa Wake[1,3,4], Sarath Ranganathan[1,2,3]

Affiliations: [1]Murdoch Children's Research Institute, Parkville, VIC, Australia; [2]Respiratory Medicine, The Royal Children's Hospital, Parkville, VIC, Australia;[3]Department of Paediatrics, The University of Melbourne, Parkville, VIC, Australia; [4]Department of Paediatrics & The Liggins Institute, The University of Auckland, Grafton, Auckland, New Zealand

Correspondence to: Professor Melissa Wake
Murdoch Children's Research Institute
The Royal Children's Hospital
Flemington Road, Parkville VIC 3052, AUSTRALIA
T: +61 3 9345 5937 E: melissa.wake@mcri.edu.au

Keywords: Lung function, spirometry, reference values, parents, children, inheritance patterns, correlation studies, epidemiologic studies, cross-sectional studies

Abbreviations : ATS: American Thoracic Society; BMI: body mass index; CC: correlation coefficient; CI: confidence interval; Disadvantage Index: Socio-Economic Index for Areas Index of Relative Socioeconomic Disadvantage; ERS: European Respiratory Society; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; GLI: Global Lung Initiative; LSAC: Longitudinal Study of Australian Children; MEF: Mid Expiratory Flow; n: number of participants in cohort with measure; N: number of biological child-parent pairs with measure; RC: estimated regression coefficient; SD: standard deviation.

Word count: 3485

ABSTRACT

Objectives: To describe the epidemiology of lung function in Australian children aged 11-12 and their parents, and explore the degree of intergenerational concordance.

Design: Cross-sectional study (the Child Health CheckPoint) nested in the Longitudinal Study of Australian Children (LSAC).

Setting: Assessment centres in seven Australian cities and eight regional towns, Feb 2016 – Mar 2016. Families unable to attend a clinic appointment were offered a home visit during the same period.

Participants: 1874 families (53% of all eligible) participated in the study. Lung function data were available for 1759 children aged 11-12 and 1774 parents (1668 biological pairs).

Outcome measures: Participants completed spirometry with measures, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mid expiratory flow (MEF), converted to z-scores using Global Lung Initiative (GLI) equations. Parent-child concordance was assessed using Pearson's correlation coefficients and multivariable linear regression models. Survey weights and methods accounted for LSAC's complex sampling, stratification and clustering within postcodes.

Results: All lung function measures followed approximately normal distributions. Mean (SD) for FEV_1, FVC and MEF z-scores in children were 0.33 (1.07), 0.83 (1.14) and -0.48 (1.09), respectively. Mean (SD) in parents were 0.28 (1.10), 0.85 (1.15) and -0.45 (1.10), respectively. Parent FEV_1, FVC and MEF were associated with child lung function with significant positive correlation coefficients (0.22, 95% CI 0.17 to 0.26; 0.24, 95% CI 0.20 to 0.29; and 0.24, 95% CI 0.20 to 0.29, respectively).

Conclusions: Mean lung volumes were larger but with smaller airway size than international standards for both parents and children in this population sample. Modest associations between parent and child lung function highlight the potential for better identification of 'at risk' populations. Therefore, these findings may aid the development of health policy that aims to prevent the onset or limit the progression of lung disease.

ARTICLE SUMMARY

Strengths and limitations of this study

- Population based sampling of Australian children provides a contemporary reference for future studies investigating lung function.
- This is the largest cross-sectional study to investigate lung function concordance in Australian parent-child dyads, thereby providing new insight into cross-generational patterns.
- Results were not adjusted for sitting height, which should be taken into consideration when interpreting the results.
- Most of the participating parents were mothers, resulting in less precise descriptive and concordance estimates for fathers.

INTRODUCTION

Non-communicable respiratory diseases such as chronic obstructive pulmonary disease, asthma, pulmonary fibrosis and lung cancer are the third leading cause of global mortality.[1 2] In Australia, mortality from chronic respiratory disease is currently 25.6 deaths per 100,000 males and 15.5 deaths per 100,000 females aged <70 years.[3] In addition, these diseases can have extra-pulmonary manifestations and therefore worsen the burden placed on healthcare resources.[3] Without well-informed policy there is likely to be further demand on healthcare expenditure.[4] 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.

Spirometry is a well-established clinical tool for assessing, diagnosing and monitoring respiratory disease in children and adults. It is a non-invasive method which allows to identify individuals with low or abnormal lung function, and compare both individuals and populations to international reference values.[5] For example, a recent population study of spirometry data from 2066 Australian subjects aged 4-80 years reported a mean difference of <0.25 for FEV_1 and FVC reflecting substantial agreement with international standards.[6] The current literature also demonstrates clear modifiable, environmental risk factors for chronic respiratory disease, such as smoking and occupational exposures.[7]

In childhood, genetic factors and developmental influences also appear to be relevant. Early life evidence suggests that the complex causal pathways to several non-communicable diseases occur in childhood through a variety of bio-psycho-social factors.[8] For example, Tai et al. (2015) found that lung function in adult life is mainly determined in childhood, and that those with lower lung function in childhood were more likely to have asthma and chronic obstructive pulmonary disease later in life.[9] In addition, low FEV_1 in early adulthood contributes significantly to the genesis of COPD in later years.[10] Published studies provide consistent evidence for familial aggregation of spirometric indices, suggesting that around 20–60% of total phenotypic variance may be explained by familial factors,[11-16] but few studies have quantified inter-generational concordance at the population level. This could lead to new ways of predicting the population risk of non-communicable respiratory disease or even the possibility of targeted screening to individuals when a relative is identified with a heritable condition.[17]

The Child Health CheckPoint, nested within the Longitudinal Study of Australian Children (LSAC), offered a comprehensive health assessment to participants. This included lung function testing of children aged 11-12 years and one of their parents using reliable, valid epidemiologic measures, specifically FEV_1, FVC, and MEF, on the same day and using the same equipment and protocols. Drawing on this population-based sample, the aims of this study were to (1) describe the epidemiology of lung function in Australian children aged 11-12 and their parents, and (2) investigate parent-child concordance in these same measures.

METHODS

Study Design and Participants: Growing Up in Australia: The Longitudinal Study of Australian Children (LSAC) is Australia's only national longitudinal child study. Details of the LSAC study design and recruitment are provided elsewhere.[18 19 20] Briefly, commenced in 2004 as the B and K cohorts, data collection has taken place every two years. This included home-visits and mailed questionnaires. The LSAC B cohort (reported in this paper) included 5107 families in the first wave, a 57.2% uptake of the 8921 families contacted. After 10 years of the study, 4484 of these families participated in Wave 6 (2014). During this Wave 6 home visit, B cohort families were introduced to the upcoming Child Health CheckPoint and asked to consent to their contact details being shared with the CheckPoint team. Those that consented (3513 families, 78% of Wave 6 cohort and 69% of original cohort) received an information pack via mail, and an information and recruitment phone call during 2015.

Child Health CheckPoint data collection spanned February 2015 to March 2016, and 1874 families participated (Figure 1). In seven major Australian cities, the study child and one of their parents were invited to participate in a 3.5 hour clinic assessment which included 17 different assessment stations. In eight regional towns there were 2¾-hour mini assessment centres, which included the same assessments as those made in major cities except for those requiring large equipment that could not be checked in as personal luggage on commercial flights. Families unable to attend a clinic appointment were offered a 1.5 hour home visit with a subset of measures that could be conducted in the home by a researcher using portable equipment. A more detailed description of the CheckPoint study design is provided elsewhere.[21 22]

Ethics and Consent: The study protocol was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (33225D) and Australian Institute of Family

Studies Ethics Committee (14-26). The attending parent provided written informed consent for themselves and their child to participate in the study.

Patient and Public Involvement: Because LSAC is a population-based longitudinal study, no patient groups were involved in its design or conduct. To our knowledge, the public was not involved in the study design, recruitment or conduct of LSAC study or its CheckPoint module. Parents received a summary health report for their child and themselves at or soon after the assessment visit. Parents consented to take part knowing that they would not otherwise receive individual results about themselves or their child.

Procedures: Spirometry, height and weight were measured at an assessment centre or at a home visit. Participants were included in these analyses if they met American Thoracic Society (ATS) / European Respiratory Society (ERS) criteria for spirometry (see below). Reasons for a lack of useable data included equipment failure, poor quality data or time constraints. Data from 20 non-biological child-parent pairs were excluded from concordance analyses.

Lung function measures: Participants completed spirometry testing with measures including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mid expiratory flow (MEF). Prior to testing, spirometers were calibrated using a 3-litre syringe with adjustments made for current ambient conditions. Spirometry was performed using a Vyntus Pneumo spirometer running SentrySuite software (Care Fusion, Germany) with a bacterial filter and nose clip in place. These data were converted to z-scores using the GLI 2012 reference equations.[23] Children also undertook post-bronchodilator spirometry, which is not reported here.

Spirometry was performed in accordance with ATS/ERS guidelines.[5] Firstly, the researcher explained and demonstrated the correct performance of spirometry to study participants. This included an emphasis on correct posture with the head slightly elevated, a tight seal around the mouthpiece with no leak, a rapid and complete inhalation to total lung capacity, followed by a rapid maximal exhalation until residual volume was reached while maintaining an upright posture. Adhering to these instructions, participants then performed a minimum of three and a maximum of eight spirometry trials. Via its DataCube function, data were exported from the SentrySuite platform into a Microsoft Excel spreadsheet. The quality of all flow-volumes loops were assessed by LW and SR. Data were assessed to determine if the loops met ATS/ERS criteria (see acceptability criteria below), if two acceptable manoeuvres

were obtained, each participant's best loop was identified. FEV_1, FVC and MEF scores were derived from the best loop.

ATS/ERS Acceptability Criteria

A. Start of test

Assessed by visual inspection of the flow-volume trace.

A rapid rise to and clearly defined peak expiratory flow.

B. Within manoeuvre

Assessed by visual inspection of the flow-volume trace.

Manoeuvre was free from artefact, cough within the first second, glottic closure, or obvious leak.

C. End of test

Assessed by visual inspection of the volume-time trace.

Clear end-expiratory plateau on volume–time trace with no sharp drop or cessation of flow. There was no specification for a minimal forced expiratory time.

D. **Repeatability**

Two largest FEV_1 and FVC values were within 150 ml.

A quality score between 1 and 5 was assigned to each loop:

1. Meets all of the ATS/ERS criteria (Met acceptability criteria for A, B, C and D)
2. Meets all ATS/ERS criteria except for repeatability. Two largest FVC values had a difference of >150 mls
3. Meets all ATS/ERS criteria except for repeatability. Two largest FEV_1 values had a difference >150 mls
4. Does not meet ATS/ERS guidelines; data excluded from dataset
5. Meets all ATS/ERS criteria except for repeatability. Two largest FVC and FEV_1 values had a difference >150 mls

Loops that were assigned a quality control score of 1, 2, 3 or 5 were included in the dataset.

Other sample characteristics: Age and gender were obtained via the Medicare Australia database for children and were self-reported by parents. In Australia, Socio-Economic Indexes for Areas provide standardised scores for socioeconomic status by geographic area (postcode of family domicile) compiled from 2011 Australian Census data. We used the Index of Relative Socioeconomic Disadvantage (disadvantage index) which numerically

summarises the social and economic status of Australian neighbourhoods (national mean of 1000 and a standard deviation (SD) of 100, with a higher score indicating less disadvantage and a lower score indicating more disadvantage).[24]

Height and weight were recorded prior to spirometry measurement. Standing height was measured to the nearest 0.1 cm without shoes and socks, in duplicate, using a portable rigid stadiometer (Invicta IP0955, Leicester, UK). A third measurement was taken if the difference of the first two measurements exceeded 0.5 cm; final height was the mean of all measurements made. Weight to the nearest 0.1 kg was measured wearing light clothing without shoes or socks using an InBody230 bio-electrical impedance analysis scale (Biospace Co. Ltd. Seoul, South Korea) at assessment centres or with a 2-limb body composition scale (Tanita BC-351, USA) at home visits. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. For children, an age- and sex-adjusted BMI z-score was calculated using the US Centers for Disease Control growth reference charts.[25]

A pre-clinic checklist including questions about a diagnosis of asthma and shortness of breath causing restriction was completed by parents and brought to the assessment**.**

Statistical Analysis: Statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, TX). Continuous descriptive variables were summarised using weighted means and standard deviations (SD); categorical variables were summarised by number and weighted percentage for children and adults separately, by sex and overall. The approximate normality or otherwise of the data's distributions were assessed through visual inspection.

Population summary statistics and proportions were estimated by applying survey weights and survey procedures that corrected for the sampling frame, participation and non-response, and took into account clustering in the sampling frame. Standard errors were calculated taking into account the complex design and weights.[26] More detail on the calculation of the survey weights is provided elsewhere. [27]

Parent-child concordance was assessed by 1) Pearson's correlation coefficients with 95% confidence intervals and 2) linear regression with the child variable as the dependent variable and the parent variable as the independent variable adjusted for the potential confounders. The Pearson's correlation and linear regression analyses were repeated using weighted multi-level survey analyses; as these yielded similar results, unweighted results are presented.

An abnormal FEV_1/FVC z-score was defined as any result less than -2.0. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools.[28]

RESULTS

Sample characteristics: Figure 1 depicts participation in the Child Health CheckPoint study. 1759 children and 1774 parents successfully completed spirometry testing in line with ATS/ERS criteria,[5] including 1668 biological parent-child dyads.

Sample characteristics are presented in Table 1. Among the child cohort, boys and girls were roughly equally represented (51.2% boys), but most (87.5%) parents were mothers. For children, the sample population had a somewhat higher mean BMI than the historical reference population, in keeping with the known current epidemiology of BMI for Australian children. For parents, mean BMI fell within the 'overweight' category according to the US Centres for Disease Control and Prevention.[25] The mean disadvantage index was 1009 (62) which is marginally above the Australian national mean of 1000, but with a lower spread (SD 62 vs 100 nationally) such that very disadvantaged families were under-represented.[29]

241 children (13.7%) and 179 parents (10%) reported a diagnosis of asthma. Only 11 children and 24 parents reported shortness of breath causing restriction.

Table 1. Sample characteristics; values are weighted mean (standard deviation), except where specified as (%)

Characteristic	All	Male	Female
Child			
n	1627-1759	848-902	741-857
Age, years	12.0 (0.4)	12.0 (0.4)	12.0 (0.4)
Height, cm	153.8 (8.0)	153.4 (8.3)	154.3 (7.7)
Weight, kg	46.6 (11.4)	45.8 (11.4)	47.3 (11.3)
BMI, kg/m^2	19.5 (3.7)	19.3 (3.6)	19.7 (3.7)
BMI z-score	0.37 (1.03)	0.36 (1.07)	0.39 (1.00)
Waist circumference, cm	66.9 (9.0)	67.5 (9.0)	66.1 (8.9)
Disadvantage Index	1009 (62)	1009 (62)	1010 (62)
Started puberty (%)	91.8	88.5	95.5
Asthma reported (%)	14.0	15.5	12.3
Shortness of breath causing restriction (%)	0.5	0.3	0.7
Parent			
n	1756-1774	218-221	1536-1553
Age, years	43.7 (5.6)	46.2 (7.0)	43.4 (5.3)
Height, cm	165.9 (7.8)	177.7 (7.4)	164.2 (6.3)
Weight, kg	78.2 (19.1)	91.4 (17.4)	76.4 (18.6)
BMI, kg/m^2	28.4 (6.4)	28.9 (4.9)	28.3 (6.6)
Waist circumference, cm	87.9 (15.1)	98.1 (13.4)	86.4 (14.8)
Asthma reported (%)	9.9	3.6	10.8
Shortness of breath causing restriction (%)	1.8	2.2	1.8

BMI, body mass index; Disadvantage Index: Index of Relative Socioeconomic Disadvantage; n: number of participants in cohort with this measure.

Population epidemiology of lung function: The mean, standard deviations and z-scores for FEV_1, FVC, FEV1/FVC and MEF are shown in Table 2. All measures of lung function in children and adults followed approximately normal distributions; plots of distribution and density for FEV_1, FVC, FEV_1/FVC and MEF z-scores are shown in Figures 2 & 3 for parents and children, respectively.

On average, boys and girls had FEV_1, FVC and MEF z-scores that were within normal limits, as did parents. Lung function followed similar distributions in children and parents, with mean FEV_1 z-scores approximately of 0.3 and FVC z-scores of approximately 0.8, reflecting higher values than the international reference populations. Conversely, FEV1/FVC and MEF z-scores, of approximately -0.8 and -0.5, indicated lower values than the international reference populations(see table 2). The proportion of children with lung function z-score below the normal range (<-2 z-score) was 1.7% for FEV_1; 0.6% for FVC; 12.9% for FEV_1/FVC and 8.1% for MEF respectively. This was similar in parents, where the proportion of lung function below the lower limit of normal was 2.7% for FEV_1; 1.3% for FVC; 13.7% for FEV_1/FVC ratio and 7.9% for MEF respectively.

Table 2. Distribution of lung function markers in Australian children and parents

Lung function measure	All				Males				Females			
	n	Mean	SD	95% CI	n	Mean	SD	95% CI	n	Mean	SD	95% CI
Children												
Raw												
FEV1 (litres)	1759	2.47	0.43	2.45 to 2.50	902	2.47	0.44	2.43 to 2.50	857	2.48	0.41	2.45 to 2.51
FVC (litres)	1759	2.99	0.53	2.96 to 3.02	902	3.04	0.55	3.00 to 3.09	857	2.93	0.49	2.89 to 2.97
FEV1/FVC ratio	1759	83.1	7.29	82.7 to 83.5	902	81.40	7.00	80.9 to 81.9	857	85.01	7.13	84.4 to 85.6
MEF (FEF25-75%) (l/s)	1759	2.6	0.73	2.56 to 2.64	902	2.47	0.69	2.42 to 2.52	857	2.74	0.75	2.68 to 2.80
z-scores												
FEV1	1754	0.33	1.07	0.27 to 0.39	900	0.26	1.07	0.17 to 0.35	854	0.41	1.06	0.32 to 0.49
FVC	1754	0.83	1.14	0.76 to 0.90	900	0.8	1.14	0.71 to 0.90	854	0.85	1.14	0.76 to 0.95
FEV1/FVC ratio	1754	-0.72	1.16	-0.79 to -0.66	900	-0.78	1.14	-0.87 to -0.69	854	-0.67	1.18	-0.76 to -0.57
MEF (FEF25-75%)	1754	-0.48	1.09	-0.54 to -0.42	900	-0.54	1.08	-0.62 to -0.45	854	-0.42	1.11	-0.51 to -0.33
Parents												
Raw												
FEV1 (litres)	1774	3.03	0.59	2.99 to 3.06	221	3.85	0.62	3.76 to 3.94	1553	2.91	0.49	2.88 to 2.94
FVC (litres)	1774	3.95	0.77	3.90 to 3.99	221	5.08	0.81	4.95 to 5.20	1553	3.79	0.62	3.75 to 3.83
FEV1/FVC ratio	1774	77.0	7.04	76.6 to 77.4	221	76.1	6.75	75.1 to 77.0	1553	77.1	7.07	76.7 to 77.6
MEF (FEF25-75%) (l/s)	1774	2.72	0.93	2.67 to 2.78	221	3.34	1.06	3.17 to 3.50	1553	2.64	0.88	2.58 to 2.70
z-scores												
FEV1	1760	0.28	1.10	0.22 to 0.35	221	0.15	0.93	0.03 to 0.28	1539	0.3	1.12	0.23 to 0.37
FVC	1760	0.85	1.15	0.79 to 0.92	221	0.65	0.97	0.51 to 0.78	1539	0.88	1.17	0.81 to 0.95
FEV1/FVC ratio	1760	-0.85	1.07	-0.92 to -0.79	221	-0.74	1.04	-0.89 to -0.60	1539	-0.87	1.07	-0.94 to -0.80
MEF (FEF25-75%)	1760	-0.45	1.10	-0.52 to -0.39	221	-0.31	0.98	-0.46 to -0.17	1539	-0.47	1.11	-0.55 to -0.40

Sample weights applied to data. CI: confidence intervals; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; MEF: Mid Expiratory Flow; FEF: Forced Expiratory Flow; l/s: litres per second; n: number of participants in cohort with this measure (denominator); SD: standard deviation.

Parent-child concordance : Two models of child-parent concordance are displayed in Table 3. Pearson's correlations between children and parents for FEV_1, FVC and MEF z-score all showed modest significant positive correlations. The strongest association was seen in FEV_1/FVC z-score (correlation coefficient 0.25, 95% CI 0.20 to 0.29). Associations strengthened marginally on conversion to z-scores and thereby adjusting for age, sex, and height. 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), irrespective of the parent being a mother or a father.

When using a FEV_1/FVC ratio z-score of < -2.0 to define abnormality we found the following: parent and child both normal, 1282 (77.6%); parent abnormal but child normal, 163 (9.9%); parent normal but child abnormal, 159 (9.6%); both abnormal 49 (3.0%).

Table 3. Parent-child concordance

	Parent-child			Mother-child			Father-child		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Raw									
FEV_1	1668	0.19	0.15 to 0.24	1454	0.20	0.15 to 0.25	214	0.21	0.07 to 0.33
FVC	1668	0.21	0.17 to 0.26	1454	0.24	0.19 to 0.29	214	0.20	0.07 to 0.33
FEV_1/FVC ratio	1668	0.23	0.18 to 0.27	1454	0.24	0.19 to 0.29	214	0.17	0.04 to 0.30
MMEF (FEF25-75%)	1668	0.20	0.15 to 0.24	1454	0.21	0.16 to 0.26	214	0.15	0.02 to 0.28
z-score									
FEV_1	1653	0.22	0.17 to 0.26	1439	0.22	0.17 to 0.27	214	0.25	0.12 to 0.38
FVC	1653	0.24	0.20 to 0.29	1439	0.25	0.20 to 0.29	214	0.22	0.09 to 0.35
FEV_1/FVC ratio	1653	0.25	0.20 to 0.29	1439	0.26	0.21 to 0.30	214	0.21	0.08 to 0.34
MMEF	1653	0.24	0.20 to 0.29	1439	0.24	0.19 to 0.29	214	0.26	0.13 to 0.38
Adjusted Linear Regression	**N**	**RC**	**P value**	**N**	**RC**	**P value**	**N**	**RC**	**P value**
Raw									
FEV_1	1610	0.16	<0.001	1435	0.16	<0.001	175	0.19	<0.001
FVC	1610	0.17	<0.001	1435	0.17	<0.001	175	0.15	0.001
FEV_1/FVC ratio	1610	0.26	<0.001	1435	0.26	<0.001	175	0.21	0.004
MEF (FEF25-75%)	1610	0.19	<0.001	1435	0.20	<0.001	175	0.17	<0.001
z-score									
FEV_1	1598	0.21	<0.001	1423	0.21	<0.001	175	0.29	<0.001
FVC	1598	0.24	<0.001	1423	0.25	<0.001	175	0.30	0.001
FEV_1/FVC ratio	1598	0.28	<0.001	1423	0.29	<0.001	175	0.24	0.002
MEF	1598	0.25	<0.001	1423	0.25	<0.001	175	0.30	<0.001

Covariates models include child and parental age, sex BMI and current parental smoking. CC: Pearson's correlation coefficients; CI: confidence interval; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; MEF: Mid Expiratory Flow; FEF: Forced Expiratory Flow; N: number of biological child-parent pairs with this measure; RC: estimated regression coefficient.

DISCUSSION

Principal findings: This study represents the largest report of spirometry in children aged 11-12 years across Australia. Lung function parameters were on average within normal limits for parents and children, with mean above the international predicted mean for FEV_1 and FVC while being below the predicted mean for FEV_1/FVC. With regard to concordance , there were modest positive correlations between child and parent lung function indices of around 0.20-0.25 including FEV_1, FVC and MEF. Importantly, the strongest concordance between children and parents was for the FEV_1/FVC z-score, which represents the relationship between airway size and lung volume and is the most sensitive spirometric index for detecting airway obstruction.

Strengths and limitations: Within this large child cohort there was equal representation from boys (51.2%) and girls, but mothers were over-represented (87.5%). 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. Despite this, we recognise that we probably do not have a random selection of mothers and fathers, and suggest that our results should therefore be interpreted with the acknowledgement that the father sample could be biased. Importantly, aa large proportion of mothers could also be viewed as a strength of our study given the influence of maternal factors and *in utero* environment on the future development of non-communicable disease.[30] We acknowledge that this was a cross-sectional study but highlight that our analyses have been adjusted for current parental smoking. . Although smoking rates in Australia have declined significantly and are currently at their lowest levels in history,[30] it is well established that exposure to smoking can have a life-long impact on peak lung function.[31]

Interpretation in light of current literature: Compared with previous population studies of lung function, we showed somewhat larger mean absolute volume for FEV_1 and FVC in children and adults of similar age and height.[32] Hall et al. defined the minimum physiologically relevant difference to be 0.5 z-scores, equating to a difference of ~6% predicted in their study of contemporary Australasian individuals. Mean (SD) z-scores for their data were 0.23 (1.00) for FEV_1, 0.23 (1.00) for FVC, −0.03 (0.87) for FEV_1/FVC and 0.07 (0.95) for FEF_{25-75}, all of which were considered well within the range considered to be physiologically irrelevant.[6] When adjusted for age, sex and height using the GLI prediction models, [23] mean FEV_1, FVC and MEF z-scores were all within normal limits for children and their parents but above the GLI predicted mean, with patterns similar to but more marked

than identified by Hall et al. This suggests that on average children, and their parents, in Australia have better lung volumes than the GLI reference population. This could be associated with the lower prevalence of smoking in Australia or that those with significant disadvantage, who might have lower lung function, were relatively under-represented in this study.

The FEV_1/FVC ratio was below normal in approximately 13% of either children or their parents. This ratio reflects airway size relative to lung volume and might be explained by the concept of dysanaptic growth where the airways and lung parenchyma grow disproportionately. This is thought to be influenced by gender-specific pubertal status. A low ratio can indicate airway obstruction. Differences in technique and equipment may also have contributed. For example, sub-optimal effort during the initial part of a forced expiratory manoeuvre, where flows remain partly effort-dependent, could underestimate FEV_1 but FVC would be preserved if the expiration proceeded to residual volume (akin to a slow vital capacity manoeuvre). Even though all flow-volume loops were inspected it is possible that subtle sub-optimal efforts could have gone undetected, thereby underestimating FEV_1. However, the similarities with the findings of those reported by Hall et al. suggest that our findings are replicable. Additionally, FVC increases with sitting height, and a lower FEV_1/FVC ratio might occur if our population was of greater sitting height than the reference population but we were not able to adjust for this as sitting height was not measured.[33] Matched FEV_1/FVC ratio below the normal range occurred in only 3% of child-parent dyads.

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 FEV_1/FVC ratio less than -2 z-scores (data not shown). 53 (30%) had evidence of a significant response to bronchodilator (defined as $\geq$ 12% and $\geq$ 200 mL improvement in absolute FEV_1), suggesting that many children with this ratio below the normal range have reversible airways obstruction. This is usually considered a characteristic feature of asthma.

Our intergenerational concordance 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] However, our child-one parent dyadic concordance values of around 0.20 to 0.25 are very consistent with the Busselton Health Study in Western Australia,[34] whose narrow-sense heritability (which

takes into account contributions from both parents) for FEV_1 and FVC were 38.9% and 40.6%. In contrast to the Busselton study where assessments were made at an offspring age of 45 years, we identified this concordance when children were between 11 and 12 years of age, prior to the likely influence of cigarette smoking and genetic susceptibility to lung injury on heritability. Xu *et al*. identified significant correlations in parent child lung function in both families of children with asthma and healthy, non-asthmatic children. In healthy children this correlation was similar for maternal (0.22) and paternal 1st child (0.24) $FEV_{1,}$ both again being remarkably similar to those identified in the current study. These data indicate that heritability of lung function requires further exploration when considering long-term outcomes of early lung function.[35]

Meaning and interpretation for clinicians and policy makers: Taken together, these results show lung volumes above predicted population means for Australian children aged 11-12 years and positive intergenerational concordance between their lung function and those of their parents. Though modest, the associations highlight the potential for better identification of 'at risk' patients while also indicating that there are likely to be many other factors at play. 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.

Conclusions and future directions: Lung function indicating lower airway size relative to lung volume in this population may be due to multiple factors but warrants further assessment over time for evidence of airway obstruction. Our findings indicate the need to explore factors relating to intergenerational concordance in lung function further in order to develop health policy that aims to prevent the onset or limit the progression of lung disease.

ACKNOWLEDGEMENTS: The MCRI administered the research grant for the study and provided infrastructural support to its staff but played no role in the conduct or analysis of the trial. Research at the MCRI is supported by the Victorian Government's Operational Infrastructure Support Program.

The funding bodies had no role in relation to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

This paper uses unit record data from Growing Up in Australia, the Longitudinal Study of Australian Children. The study is conducted in partnership between the Department of Social Services (DSS), the Australian Institute of Family Studies (AIFS) and the Australian Bureau of Statistics (ABS). The findings and views reported in this paper are those of the author and should not be attributed to DSS, AIFS or the ABS.

Some study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools. REDCap is a secure, web-based application designed to support data capture for research studies. More information about this software can be found at: www.project-redcap.org. We thank the LSAC and CheckPoint study participants, staff and students for their contributions.

COMPETING INTERESTS: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare financial support as described in the funding section. MW received support from Sandoz to present at a symposium outside the submitted work.

FUNDING: This work was supported by the National Health and Medical Research Council (NHMRC) of Australia (Project Grants 1041352, 1109355), The Royal Children's Hospital Foundation (2014-241), the Murdoch Children's Research Institute (MCRI), The University of Melbourne, the Financial Markets Foundation for Children (2014-055, 2016-310) and the National Centre for Longitudinal Data (NCLD). MW was supported by a NHMRC Senior Research Fellowship (1046518).

The MCRI administered the research grants for the study and provided infrastructural support (IT and biospecimen management) to its staff and the study, but played no role in the conduct or analysis of the trial. DSS played a role in study design; however, no other funding bodies had a role in the study design and conduct; data collection, management, analysis, and interpretation; preparation, review, or approval of the manuscript; and decision to submit the

manuscript for publication. Research at the MCRI is supported by the Victorian Government's Operational Infrastructure Support Program.

CONTRIBUTIONS:

LW, GK and TR contributed to the interpretation of results, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

AG performed the statistical analyses, contributed interpretation of results and critical review of the manuscript.

SR contributed to the interpretation of results and provided critical review of the manuscript.

MW is the Principal Investigator of the Child Health CheckPoint, planned the analyses and provided critical review of the manuscript.

DATA SHARING STATEMENT: Dataset and technical documents available from Growing Up in Australia: The Longitudinal Study of Australian Children via low-cost license for bone fide researchers. More information is available at www.growingupinaustralia.gov.au

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1. Participant diagram

Figure 2. Lung function distribution & density plots for parents
FEV_1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV_1/FVC ratio, MEF: Mid Expiratory Flow

Figure 3. Lung function distribution & density plots for children
FEV_1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV_1/FVC ratio, MEF: Mid Expiratory Flow

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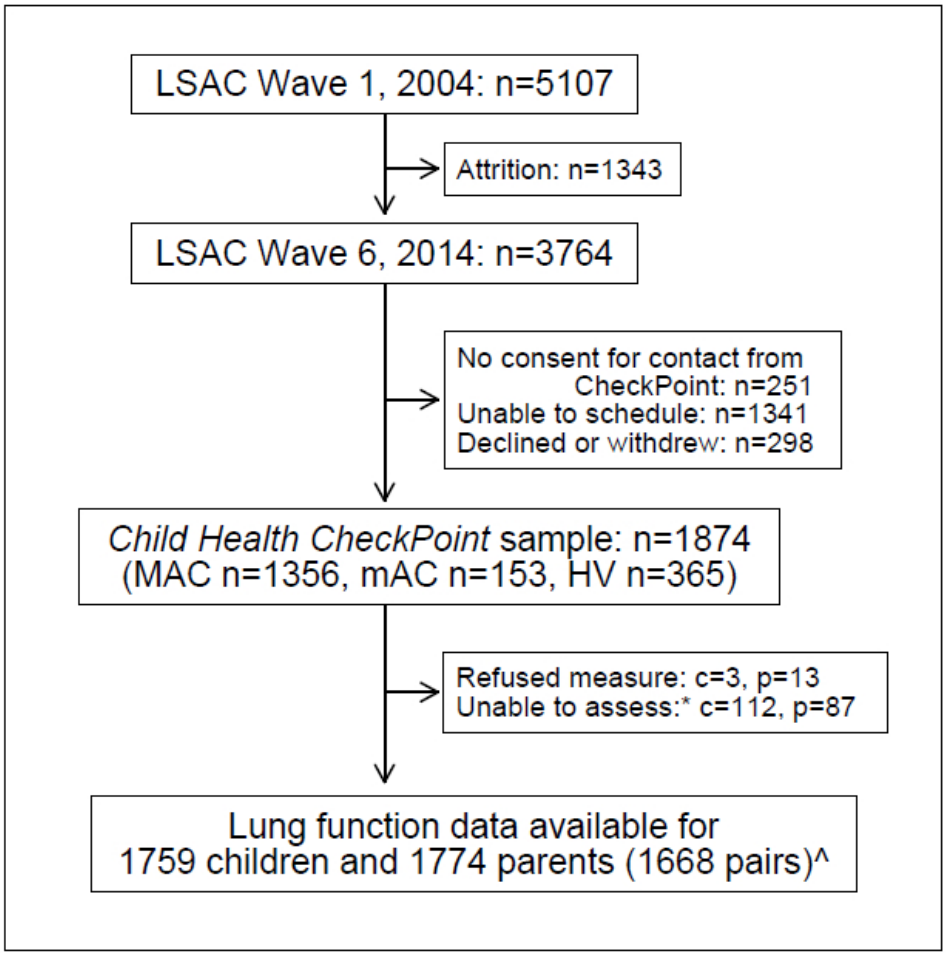

n=number of families, c=number of children, p=number of attending adults,
MAC=Main assessment centre, mAC=Mini assessment centre, HV=Home visit assessment,
LSAC=Longitudinal Study of Australian Children
*Unable to assess due to equipment failure, poor quality data or time contraints
^Data from 20 non-biological child-parent pairs excluded from concordance analyses

Figure 1. Participant diagram

171x193mm (96 x 96 DPI)

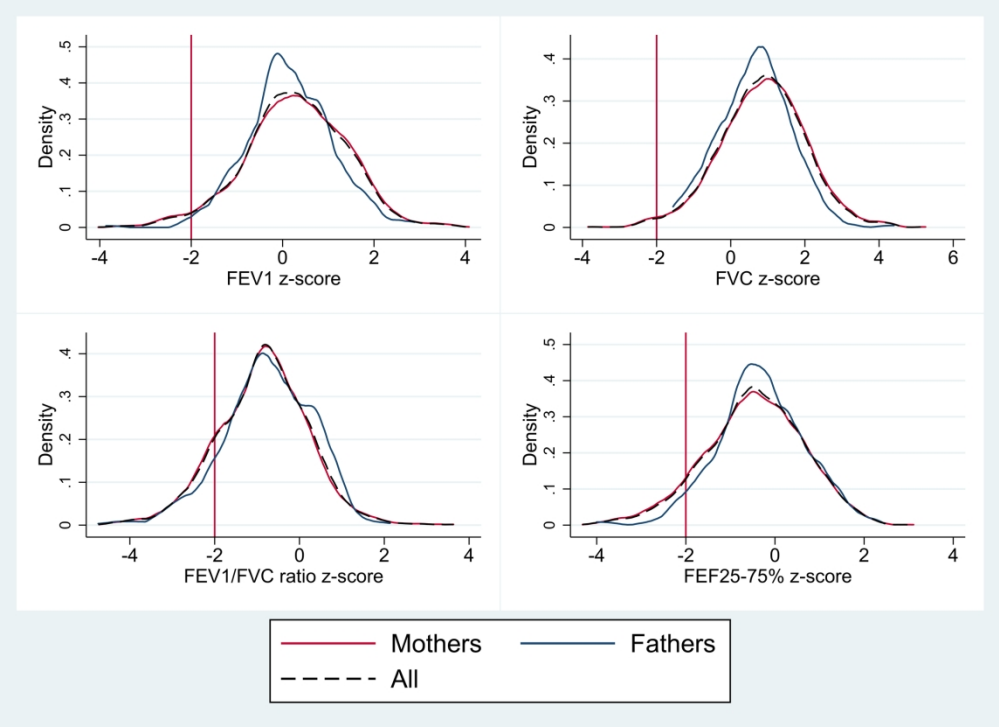

Figure 2. Lung function distribution & density plots for parents
FEV1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV1/FVC ratio, MEF: Mid Expiratory Flow

101x73mm (600 x 600 DPI)

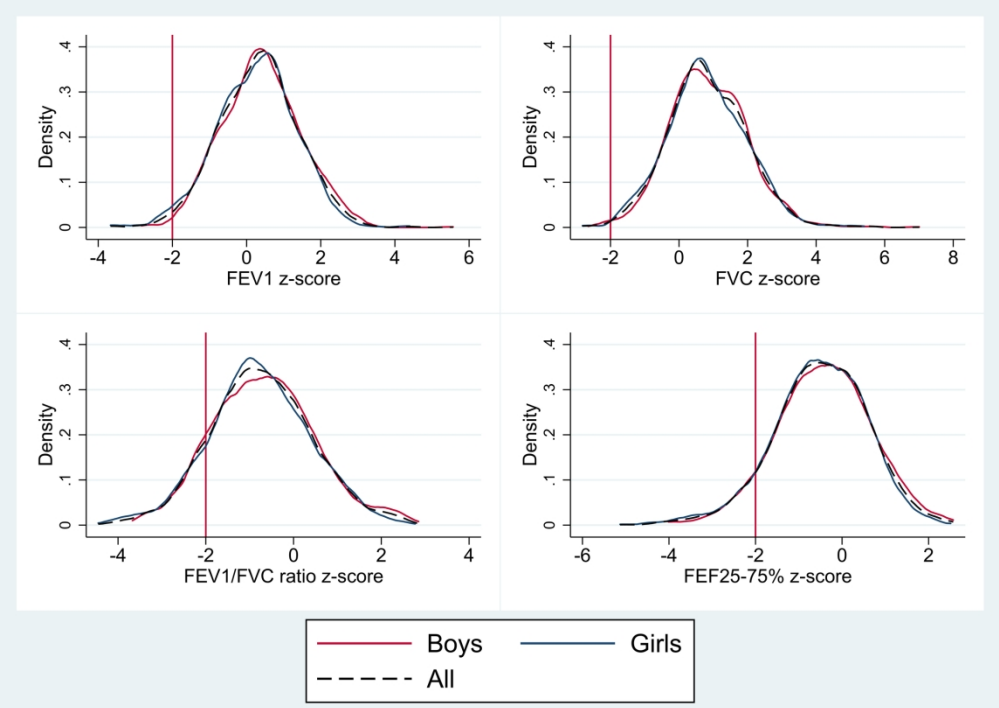

Figure 3. Lung function distribution & density plots for children
FEV1: Forced Expiratory Volume in 1 Second, FVC: Forced Vital Capacity, FEV1/FVC ratio, MEF: Mid Expiratory Flow

101x73mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale~~ for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	NA 5-6
		~~(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed~~ ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	7-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-12
		(*b*) Report category boundaries when continuous variables were categorized	7-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.