Lung function and cognitive ability in children: a UK birth cohort study

Jack Grenville,¹ Raquel Granell,² James Dodd³,⁴

ABSTRACT

Background Decreased adult lung function is associated with subsequent impairment in cognition. A similar relationship in early life could be of great policy importance, since childhood cognitive ability determines key adult outcomes, including socioeconomic status and mortality. We aimed to expand the very limited data available on this relationship in children, and hypothesised that reduced lung function would be longitudinally associated with decreased cognitive ability.

Methods Lung function was measured at age 8 (forced expiratory volume in one second (FEV₁), forced vital capacity (FVC); % predicted), and cognitive ability was measured at ages 8 (Wechsler Intelligence Scale for Children, third edition) and 15 (Wechsler Abbreviated Scale of Intelligence), in the Avon Longitudinal Study of Parents and Children. Potential confounders were identified as preterm birth, birth weight, breastfeeding duration, prenatal maternal smoking, childhood environmental tobacco smoke exposure, socioeconomic status and prenatal/childhood air pollution exposure. Univariable and multivariable linear models (n range=2332–6672) were fitted to assess the cross-sectional and longitudinal associations of lung function with cognitive ability, and change in cognitive ability between ages 8 and 15.

Results In univariate analyses, both FEV₁ and FVC at age 8 were associated with cognitive ability at both ages, but after adjustment, only FVC was associated with full-scale IQ (FSIQ) at ages 8 (β=0.09 (95% CI 0.05 to 0.12; p<0.001)) and 15 (β=0.06 (0.03 to 0.10; p=0.001)). We did not find evidence of an association between either lung function parameter and interval change in standardised FSIQ.

Discussion Reduced FVC, but not FEV₁, is independently associated with decreased cognitive ability in children. This low-magnitude association attenuates between ages 8 and 15, while no association is evident with longitudinal change in cognitive ability. Our results support a link between FVC and cognition across the life course, possibly due to shared genetic or environmental risk, rather than causation.

INTRODUCTION

Decreased lung function is associated with a range of adverse multisystem health outcomes, including impaired cognition.¹ ² The recurrent observation of an independent, and temporally sequential, association between reduced lung function and cognition has led some to hypothesise that it might be causal.³ ⁴

Due to the importance of childhood measurements of cognition in predicting adult socioeconomic and health outcomes,⁵ ⁶ if they were shown to be causally affected by reduced childhood lung function, there would be profound implications for policy to protect children’s lung health. However, at present, only very limited research exists in this age group.⁷ Our study aims to investigate, using data from a large UK birth cohort, whether decreased lung function is longitudinally associated with lower cognitive ability in children.

Multiple studies, including a meta-analysis of 8 cohorts comprising 20586 participants in Europe and North America,² ⁸ ⁹ US-based cohort studies of 14184 participants⁸ and 1377 participants,⁹ and a Swedish-based twin study (n=832),³ have demonstrated an independent, longitudinal association between reduced lung function and subsequent impairment of cognition in older adults.

Studies in adults tend to measure cognition using clinical records of the development of pathological cognitive impairment or dementia, or cognitive testing to detect milder impairments. In children, it is typical to assess...
cognitive ability (also known as general intelligence or g), through tests of intelligence quotient (IQ). While IQ is not free from controversy as a measure of cognitive ability,10 childhood IQ scores are independently predictive of key adult life outcomes, including adult socioeconomic status (SES)5 and mid-to-late life mortality.6 The importance of investigating possible determinants of such a major contributor to children’s life chances should not be in doubt.

Only one study has specifically sought to investigate the relationship between lung function and cognitive ability in children.7 165 children in Boston, USA, had lung function measured at age 6, and cognition measured at age 9, using the Kaufman Brief Intelligence Test (K-BIT) and the Wide Range Assessment of Memory and Learning (WRAML). Increases in forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) (% predicted values for age, height, sex and ethnicity), were associated with higher composite scores on the K-BIT (β=0.23 (95% CI 0.07 to 0.39) and 0.18 (95% CI 0.03 to 0.33), respectively) and verbal, visual and learning subscales of the WRAML. Our study aims to expand the data addressing this research question with a larger sample from a UK birth cohort, and we hypothesise that a similar independent longitudinal association between lung function and cognitive ability will be observed.

METHODS

Study participants
The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective cross-generational cohort study based in Bristol, UK. A total of 14541 pregnant women living in the former administrative county of Avon were recruited between 1 April 1991 and 31 December 1992. From those pregnancies initially recruited, 13988 children were alive at 1 year, with a further 913 children born during the recruitment period later enrolled.11 12 Data on potential exposures and outcomes was collected through multiple questionnaires and clinic visits during pregnancy and childhood. Triples and quadruplets were not included in our sample, and to reduce data clustering, twins were removed at random in relation to their birth order. A total of 14684 children were therefore eligible for this study, with 6644 having lung function and cognitive ability data at age 8 and 4234 having exposure data at age 8 and outcome data at age 15 (figure 1). A full description of the study data, along with a searchable data dictionary and variable catalogue, is available on the study website.13

Exposure
Lung function was measured using a hand-held spirometer (Vitalograph 2120; Vitalograph, UK), to American Thoracic Society standards, at age 8 (median 8.6 years; range 7.5–10.7), producing prebronchodilation measurements of FEV1, and FVC, in millilitres. Our exposure variables, expressed as percentages of values predicted for age, height, sex and ethnicity, were derived from equations from the Global Lung Function Initiative (GLI).14

Outcome
Cognitive ability was measured using the Wechsler Intelligence Scale for Children—third Edition (WISC-III)15 at age 8, and the Wechsler Abbreviated Scale of Intelligence (WASI)16 at age 15 (median 15.4 years; range 14.3–17.7). The Wechsler scales have a long history, strong theoretical underpinnings, wide acceptance, and good external validation as tools for measuring cognitive ability in children.10 The WISC-III produces scores for full-scale IQ (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ). VIQ relates
to ‘crystallised intelligence’, which is context specific and
dependent on prior education, while PIQ attempts to
measure ‘fluid intelligence’, which involves visuospatial
problem-solving, and is therefore less influenced by these
factors.17 VIQ can be further subdivided into the Verbal
Comprehension (VC) and Freedom From Distractibility
(FD) Indices, which are derived from information, similar-
ities, vocabulary, comprehension, digit span, and arith-
cmetic tasks.17 PIQ can be subdivided into the Perceptual
Organisation (PO) and Processing Speed (PS) Indices,
which are compiled from picture completion and arrange-
ment, block design, object assembly, coding, and symbol search tasks.17 PS is not recorded in the ALSPAC
dataset, but VIQ, PIQ, VC, FD, and PO at age 8 were all
included as outcomes in regression models, in an attempt
to discern if lung function parameters share distinctive
associations with specific facets of children’s cognition.

The WASI is an abbreviated version of the Wechsler
Adult Intelligence Scale, and normally produces scores
for FSIQ. VIQ derived from vocabulary and similarities
subtests, and PIQ derived from matrix reasoning and
block design subtests.18 However, for logistical reasons,
and using a method validated by the test authors, ALSPAC
participants completed only the vocabulary and matrix
reasoning subtests at age 15. This produced FSIQ, but not
VIQ or PIQ scores. This variation in methodology means
that the FSIQ scores at ages 8 and 15 are not directly
comparable. Therefore, we standardised these variables
(γ-mean/SD), before calculating interval change in SD
from the mean FSIQ between ages 8 and 15.

**Covariates**

Potential confounders were identified through a combi-
nation of the authors’ prior subject knowledge, a system-
atic literature search for evidence on risk factors for
exposure and outcome, and construction of a directed
acyclic graph (DAG) (figure 2).19 We found evidence
for a common effect on lung function and cognitive
ability in childhood from parental SES,20 21 prenatal

![Figure 2 Directed acyclic graph codifying assumptions about relationships between exposure, outcome, and related variables. Diagram constructed using DAGitty - http://www.daggity.net.19](https://www.daggity.net)
maternal smoking and air pollution exposure, preterm birth, birth weight, duration of breast feeding, childhood environmental tobacco smoke and air pollution exposure. The relationships identified by the DAG determined what would be adjusted for in our multivariable analysis. Age, height, sex and ethnicity were not included in our models due to the use of GLI % predicted values for lung function, which are preadjusted for these. Following suggestions from a reviewer, we conducted a sensitivity analysis to ensure that these variables had been adequately controlled for, by including them in the multivariable models estimating the effect of FEV₁ and FVC at age 8 on FSIQ at ages 8 and 15, and on interval change in standardised FSIQ. We then included sex as an interaction term in these models, to investigate whether the effect of lung function parameters on FSIQ might differ between males and females. Those models that provided evidence of effect modification by sex were refitted separately for males and females.

Obstetric records provided data on birth weight (categorised into quintiles) and preterm birth (gestational age 37 weeks). Prenatal maternal smoking (yes/no) was measured by a maternal questionnaire for the first and second trimesters at 18 weeks’ gestation, and for the third trimester at 8 weeks postnatal. The duration of breast feeding (never/6 months) was measured by questionnaire at 15 months of age. The child’s reported daily exposure to environmental tobacco smoke in hours was measured by a maternal questionnaire at 6, 15, 24, 38, 54, 65, 77 and 104 months of age. The mean reported value (disregarding missing values) was then categorised as ‘never’, less than, or greater than 1-hour mean reported daily exposure. Parental SES was measured by a maternal questionnaire using the proxy variables of maternal education (32 weeks’ gestation; ‘low’ if ‘O’ level or below), and housing tenure (6 weeks’ gestation; owner occupied or rented). Prenatal and childhood air pollution exposure were measured using data for exposure to particulate matter less than 10 μm in diameter (PM₁₀; mean daily maternal exposure during pregnancy and cumulative childhood exposure to age 7) produced by Gulliver et al. Asthma diagnosis and childhood wheezing phenotype, which our DAG identified as potentially being on the causal pathway between exposure and outcome, were included in a separate multivariable model, in order to assess their contribution to any observed association (see online supplemental file 1).

Statistical analysis
Cognitive test scores (FSIQ at ages 8 and 15, subscale scores at 8), FEV₁ and FVC were treated as continuous variables and used to fit univariable and multivariable linear regression models. Linear regression assumptions were examined for these variables by visual inspection of scatter plots, histograms and Q–Q plots of model residuals, and by assessing if inclusion of polynomial terms improved model fit.

Continuous covariates (birth weight, PM₁₀ exposure data) were categorised into quintiles because of failure to satisfy linearity assumptions. All hypothesised confounders were included a priori in the multivariable models. Univariable and multivariable linear models were fitted for participants with complete data for all covariates. The final sample in these models, depending on the precise combination of outcome and exposure, was between 3501 and 4362 for cognitive ability outcomes at age 8, and between 2782 and 2861 for the outcomes requiring FSIQ at age 15 (see Table 1). For comparison, we also fitted univariable models for all participants with exposure and outcome, but not necessarily covariate data, at each age (see online supplemental file 1).

Statistical models were fitted using Stata V.15.0 (StataCorp, Texas, USA).

RESULTS
Table 2 provides sociodemographic information on participants in the whole sample, and in the subsamples with FVC measured at age 8, cognitive ability at ages 8 and 15, and for those with complete covariate data. Those who attended clinic at ages 8 and 15 were increasingly female, white, living in owner-occupied accommodation, and had mothers who were educated to a higher level, compared with the original sample. The complete cases in our study had a still higher proportion of owner occupiers (88.9% vs 85.8% with only exposure at age 8 and outcome at age 15).

Results of crude and adjusted linear regression models are shown in Table 1. In the unadjusted analysis, we found that FSIQ at age 8 increased by a mean of 0.11 points (0.07–0.15; p<0.001), and FSIQ at age 15 by a mean of 0.09 (0.05, 0.12; p<0.001) points (Figure 3), per percentage point increase in FVC at age 8. Beta coefficients for the association between FEV₁ and FSIQ were 0.07 (0.03–0.11; p=0.001) at age 8, and 0.04 (0.001–0.08; p=0.05) at age 15. There was little evidence of heterogeneity of association of FEV₁ or FVC with different subscale scores at age 8, with similar point estimates, and overlapping CIs, for VIQ and PIQ, as well as for the lower-order subscales of VC, PO and FD. We did not find evidence to suggest that differences in FEV₁ or FVC were associated with change in standardised FSIQ between ages 8 and 15.

Participant and public involvement
Through the ALSPAC ethics and law committee, participants are involved in the ethical oversight of the study, and through the original cohort advisory panel, they regularly advise on appropriate and relevant use of the study data, as well as study design and methods. The ALSPAC executive provided approval for this study, but neither participants nor members of the public were involved in its conception or design. The manuscript will be available to participants and the public via an open-access online journal article.
15, with $\beta=-0.0004 \text{ (} -0.003 \text{ to } 0.002; \ p=0.76\text{), and } 0.0001 \text{ (} -0.003 \text{ to } 0.003; \ p=0.99\text{), respectively.}

In the multivariable analysis, FSIQ at age 8 increased by a mean of 0.08 (0.05–0.12; $p<0.001$) points, and FSIQ at 15 by a mean of 0.06 (0.03–0.10; $p=0.001$) points (figure 3), for each 1% increase in FVC at age 8. However, little to no evidence remained of a cross-sectional or longitudinal association between FEV$_1$ and FSIQ; $\beta$ at age 8 was reduced to 0.03 (–0.01 to 0.07; $p=0.10$), and at 15 to 0.014 (–0.02 to 0.05; $p=0.47$). We again did not find evidence for a heterogenous association of FVC with subscale scores at age 8, or for an association of either lung function parameter with interval change in standardised FSIQ. Inclusion of sex, age and height at age 8 in our models yielded virtually identical results (see online supplemental file 1).
term in multivariable models, we found that sex, after also adjusting for age and height, did modify the effect of FEV1 on FSIQ at age 8 (p value for interaction=0.032), but not of FEV1 on FSIQ at age 15, nor of FVC on FSIQ at either age 8 or 15 (see online supplemental file 1). Separate multivariable analyses of the cross-sectional association between FEV1 and FSIQ at age 8 revealed β=0.07 (0.02–0.13; p=0.005) in girls, and β=−0.01 (−0.07 to 0.04; p=0.63) in boys (see online supplemental file 1). In our models including asthma and childhood wheezing as covariates, there was no attenuation of the association of FVC with cognitive ability (eg, for FSIQ at 15, β=0.06 (0.02–0.10); see online supplemental file 1).

**DISCUSSION**

**Summary of main findings**

Our results reproduce the previously noted association between reduced FVC and lower cognitive ability in childhood. This was evident in the cross-sectional analysis at age 8, with an attenuated association persisting at age 15. Adjustment for hypothesised confounders resulted in a reduction of the estimated magnitude of the association of FVC with FSIQ at both 8 and 15 years of age, but there remained strong evidence for an association at both ages. We did not find evidence to suggest wide variations in the cross-sectional associations of FVC with the different elements of cognitive ability, as represented by the WISC-III subscale scores. While there was little evidence for an independent cross-sectional or longitudinal association between FEV1 and cognitive ability in the sample overall, we did find a cross-sectional association between FEV1 and FSIQ at age 8 in girls only. We failed to find evidence for an association of either FEV1 or FVC with longitudinal change in cognitive ability between ages 8 and 15. Inclusion in our models of asthma diagnosis and childhood wheezing as covariates did not attenuate the effect of FVC on cognition (see online supplemental file 1), suggesting that these two disorders do not contribute greatly to the observed effect, as might be expected, given that the bronchoconstriction characterising these conditions principally impairs FEV1.

**Summary of previous evidence**

Our study replicates previous findings of an association between lung function and cognition, evidence for which has previously come mainly from middle-aged and older adults. One meta-analysis of 8 cohorts in the UK, Netherlands, Sweden and the USA, with a total of 20586 participants (mean study recruitment age 65.6–82.8 years), examined associations between baseline measurements and longitudinal change in FEV1 and peak expiratory flow rate (PEFR), and multiple measures of cognitive performance over time.2 The authors found low-magnitude, but robust, associations between lower baseline measurements of, and rates of decline in, lung function parameters and scores on tests of multiple cognitive domains including mental status, PS, attention and working memory, perceptual reasoning, learning and...
memory, and verbal abilities. A large US-based cohort, following 14184 participants (mean recruitment age 54.2 years) over 23 years, found increased odds of mild cognitive impairment or dementia with reduced baseline FEV₁ (OR 1.11 (1.04–1.20) per SD decrease), FVC (OR 1.12 (1.05–1.20) per SD decrease) and obstructive (OR 1.33 (1.07–1.64)) or restrictive (OR 1.58 (1.14–2.19)) patterns of spirometry. Results from another US-based cohort of 1377 participants (mean recruitment age 79.4 years, 76% women) found that baseline reductions in a composite measure of lung function, derived from the average z-score of FEV₁, FVC and PEFR, were longitudinally associated with more rapidly declining overall and domain-specific cognition. A study of 832 twins in Sweden (mean recruitment age 65.3 years), at 7 time points over 19 years, examined the question of directionality between lung function and cognition using dual change score models (DCSMS), and found evidence that declining FEV₁ led to subsequent decrements in performance on assessments of spatial performance and PS. Those authors subsequently applied bivariate DCSMs to the same twin data, concluding that genetic influences on pulmonary function were the principal determinants of cognitive decline, rather than the observed relationship being explained by genetic or environmental confounding, or reverse causality. While cohort studies producing evidence of a longitudinal association between lung function and cognition in older adults are numerous, a systematic review of the literature in 2020 called into question the methodological quality of this evidence base, finding few studies meeting the inclusion criteria of having measured both variables on multiple occasions.

Our study is only the second to find an association between lung function and cognition in children. The magnitude of our estimate of the association between FVC at age 8 and FSIQ at age 15 (0.06 (0.03–0.10)) is one-third that noted by Suglia et al between FVC at age 6 and IQ at age 9 (0.18 (0.05–0.33)), with a 20-point increase in FVC (% predicted) at age 8 in our cohort, conferring a 1.2-point difference in FSIQ at age 15. We did not replicate their finding of an independent effect of FEV₁ on FSIQ in the sample overall, although an independent cross-sectional association was evident for girls at age 8 (see online supplemental file 1).

Significance of main findings

Other authors have suggested the existence of a causal association between lung function and cognition across the life course, with possible mechanisms including intermittent cerebral hypoxia, nocturnal respiratory symptoms causing sleep disruption, or impairment of attention due to respiratory illness. More recently, the proposed causality of this association has been thrown into doubt by a Mendelian Randomisation analysis, which suggested that previously noted associations may be due to residual confounding. While our methods do not permit strong statements about causality, it is possible to make inferences by observing the reduction in magnitude of the observed association between FVC and FSIQ between ages 8 and 15, and the lack of an association between FVC and longitudinal change in FSIQ. If the observed association between lung function and cognitive ability was indeed causal, it might be reasonable to postulate that those with lower lung function at age 8 would, over time, develop worsening cognition relative to peers, and that the association between FVC and FSIQ would not weaken over time, notwithstanding the introduction of other environmental effects on cognitive ability, or the possibility of selection bias due to participant dropout. Therefore, our results do not appear to support a causal link between lung function and cognitive ability between 8 and 15 years of age. They do not provide evidence for or against such a causal link earlier in life. However, rather than being causatively associated, it is also possible, and indeed may be more likely, that our findings reflect a pre-existing association arising from common genetic, prenatal, or early-life vulnerabilities. The independent association with cognitive ability found for FVC, but not FEV₁, could be due to the fact that it is affected by a wider range of pathologies which might also impact childhood IQ, such as neurodevelopmental disorders and morbid obesity, or its greater heritability resulting in a higher proportion of genetic risk being shared with IQ (see online supplemental file 1 for further discussion).

Strengths and limitations

Our study has several strengths when compared with the solitary previous cohort study in children. The first of these is the much larger sample size permitted by the use of data from a pre-existing birth cohort, which likely resulted in the greater precision of our estimates. The second advantage of our study is that we selected covariates in a more systematic manner. The multivariable analysis in the aforementioned study adjusted for birth weight, gestational age, parental SES, prenatal maternal smoking, environmental tobacco smoke exposure, blood lead levels, childhood respiratory infection and asthma diagnosis. While the authors included a detailed rationale for the selection of each variable, we have conceptualised the relationships between our variables in a DAG, a more systematic approach that aims to avoid inappropriate inclusion of variables in the multivariable analysis, which may bias results. Indeed, in our DAG, we identified that childhood wheezing and asthma diagnosis might be on the causal pathway between exposure and outcome, meaning they were not adjusted for in the main analysis. A third advantage of our study, when compared with previous studies in both adults and children, is that cognitive ability was measured on more than one occasion, allowing for estimation of the association between lung function and
longitudinal change in cognitive ability, and therefore inferences regarding the likelihood of a causal relationship.

Our study has a number of limitations. It is an observational study, and therefore it is quite possible that the observed association reflects residual confounding, selection or information bias, or reverse causality. It is probable that the confounding variables we have adjusted for in our multivariable analysis are not exhaustive, nor will their measurement have been without error. Even if of small magnitude for each variable, unmeasured confounding from omission of, or error in measuring, relevant factors may be a source of bias or loss of precision.

Table 2 illustrates that the missingness in our dataset is socially patterned, with participants of lower SES more likely to be absent from our sample, or to have missing data. While we have included correlates of social class as covariates, if there is a relationship between our outcomes and missingness in the dataset which is not accounted for by adjustment for these variables (either due to measurement error or unmeasured variability), our effect estimates will be subject to selection bias (see online supplemental file 1 for further details). Additionally, the generalisability of our findings is limited by the fact that our subsample is less representative of the population of Avon and the UK than the original ALSPAC sample, which itself had lower rates of households with single parents, who rented, had no car access, inhabited multiple-occupancy rooms, or were non-white, than the county and country at large. The ethnic homogeneity of the sample (96.2% white), in particular, means that our results can be considered of greatest relevance to Western European Caucasian populations.

In addition to these potential sources of bias, a further possible explanation of the observed association between FVC and cognitive ability might be the volitional nature of the measurement of FVC, which, unlike FEV\textsubscript{1}, is effort dependent. It is possible that those children with lower IQ might have had more difficulty in understanding the instructions for how to perform the procedure. This would result in lower FVC measurements in those with lower IQ, or in other words, reverse causality between outcome and exposure. This could explain the signals in our data against a causal relationship in the other direction, and the observation of an association with cognitive ability for FVC, but not FEV\textsubscript{1}.

**Directions for future research**

Future research could interrogate the possibility of a causal effect of FVC on cognitive ability in children, by employing methods for causal inference such as Mendelian Randomisation, as was recently performed in adults. If no evidence for causality were forthcoming, examination of the genetic and epigenetic risk shared between lung function and cognition might help explain the association.

**CONCLUSION**

In summary, our results support an independent association between childhood FVC and cognitive ability, while refuting such a relationship for FEV\textsubscript{1}. Between ages 8 and 15, the association of FVC with cognitive ability attenuates, and FVC is not associated with longitudinal change in cognitive ability. These findings may imply a non-causal association, which could instead be due to shared genetic or environmental vulnerabilities.

**Acknowledgements**

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**Contributors**

JG formulated the study design, conducted a literature search, analysed the data and wrote the manuscript. RG provided advice on study design and conduct, assisted in compiling the dataset (including providing several variables), advised on statistical analysis, and reviewed the manuscript. JD conceived the study idea, provided advice on study design and conduct, and reviewed the manuscript. JD acts as guarantor for the study.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication**

Not applicable.

**Ethics approval**


**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data may be obtained from a third party and are not publicly available. The informed consent obtained from Avon Longitudinal Study of Parents and Children (ALSPAC) participants does not allow the data to be made freely available through any third party maintained public repository. However, data used for this submission can be made available on request to the ALSPAC Executive. The ALSPAC data management plan describes in detail the policy regarding data sharing, which is through a system of managed open access. Full instructions for applying for data access can be found here: [http://www.bristol.ac.uk/alspac/researchers/access/](http://www.bristol.ac.uk/alspac/researchers/access/). The ALSPAC study website contains details of all the data that are available ([http://www.bristol.ac.uk/alspac/researchers/our-data/](http://www.bristol.ac.uk/alspac/researchers/our-data/)).

**Supplemental material**

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ONLINE SUPPLEMENT

Supplementary methods

In order to ascertain whether or not GLI equations had adequately controlled for age, sex and height in our main multivariable models, we conducted a sensitivity analysis which adjusted for these variables, in addition to other hypothesised confounders, in those models estimating the association of FEV₁ and FVC at age 8 with FSIQ at ages 8 and 15, and with interval change in standardised FSIQ. In these models, we then included sex as an interaction term to assess for any modification of the association of lung function parameters with FSIQ, or change in FSIQ, by sex. For those models providing evidence of interaction, we conducted separate multivariable analyses for males and females.

To facilitate comparison of the crude effect estimate in the sample as a whole with those who had complete data, we fitted univariable linear models including all participants for the outcomes of FSIQ at 8 and 15, and change in standardised FSIQ between these ages. Sample size with this approach increased to between 6,548 and 6,672 for the outcome of FSIQ at age 8, and between 4,122 and 4,234 for outcomes requiring FSIQ at age 15.

We wished to attempt to estimate the contribution of asthma and childhood wheezing illness to any observed association of lung function with cognitive ability. We therefore fitted univariable models restricted to participants with data on asthma diagnosis and childhood wheezing phenotype in addition to other covariates, and added these variables to the multivariate models of the effect of lung function on FSIQ at ages 8 and 15, and change in standardised FSIQ. These models permitted sample sizes of 3,346 to 3,372 for the outcome of FSIQ at age 8, and 2,306 to 2,365 for outcomes requiring FSIQ at age 15.

Asthma diagnosis was measured using a combination of parental questionnaire at 91 months (which asked if the child had ever been diagnosed with asthma by a doctor), as well as symptoms of asthma and medication history in the clinic at 8 years of age. Childhood wheezing phenotypes have been described for the ALSPAC cohort, and describe the trajectory of a child’s wheezing in terms of onset and persistence. They can be characterised as transient early, prolonged early, intermediate onset, late onset, persistent, or never/infrequent. Different phenotypes have differing strengths of association with atopy, asthma diagnosis, and reduced lung function; persistent, intermediate and late onset wheezing confer a greater risk. The phenotypes used in our study were derived by Henderson et al. from maternal questionnaire data on wheezing symptoms collected at seven time points between 0 and 7 years of age, which was then used to categorise participants into one of the phenotype described above. Wheezing phenotype was included in multivariate analyses as an unordered categorical variable.
Lung function and cognitive ability in children: A UK birth cohort study

To facilitate estimation of the likelihood of our results being subject to selection bias due to missing data, following a method outlined by Cornish et al,\textsuperscript{2} we fitted logistic regression models with the outcome of being a complete case at age 8 and 15. These models included as covariates all variables in our main multivariable linear models.

Supplementary results

Supplementary table 1 shows the results of multivariable models including sex, age and height. Results changed very little with their addition, with identical point estimates for the effect of FEV\textsubscript{1} and FVC at age 8 on FSIQ at ages 8 and 15, with some minor changes to confidence intervals and p values. Point estimates for the effect of lung function parameters on interval change in standardised FSIQ differed slightly, but remained very close to zero, with very large p values.

Supplementary table 1. Results of multivariable linear regression models including sex, exact age and height at age 8

<table>
<thead>
<tr>
<th>Outcome ↓</th>
<th>Exposure →</th>
<th>FEV\textsubscript{1} % predicted at age 8</th>
<th>FVC % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ (WASI) at age 15</td>
<td>Number of participants</td>
<td>2,814</td>
<td>2,861</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference* (95% CI; p)</td>
<td>0.01 (-0.02, 0.05; p=0.45)</td>
<td>0.06 (0.03, 0.10; p=0.001)</td>
</tr>
<tr>
<td>Change in standardised FSIQ age 8 to 15</td>
<td>Number of participants</td>
<td>2,782</td>
<td>2,828</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference** (95% CI; p)</td>
<td>-0.0003 (-0.003, 0.002; p=0.86)</td>
<td>0.0001 (-0.003, 0.003; p=0.94)</td>
</tr>
<tr>
<td>FSIQ (WISC-III) at age 8</td>
<td>Number of participants</td>
<td>4,273</td>
<td>4,346</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean difference* (95% CI; p)</td>
<td>0.03 (-0.01, 0.07; p=0.16)</td>
<td>0.08 (0.04, 0.11; p&lt;0.001)</td>
</tr>
</tbody>
</table>

FEV\textsubscript{1} -- Forced Expiratory Volume in 1 second; FVC -- Forced Vital Capacity; FSIQ -- Full-scale Intelligence Quotient (IQ); WASI -- Wechsler Abbreviated Scale of Intelligence; WISC-III -- Wechsler Scale of Intelligence for Children 3rd Edition

*Mean difference in IQ points per point increase in GLI per cent predicted values of FEV\textsubscript{1} and FVC
**Mean difference in interval change in FSIQ (standard deviations), per point increase in GLI per cent predicted values of FEV\textsubscript{1} and FVC
\*Adjusted for sex, age, height, preterm birth, birth weight, breastfeeding duration, prenatal maternal smoking, childhood environmental tobacco smoke exposure, maternal education, housing tenure, prenatal and childhood PM10 air pollution exposure.

All values to 2 decimal places, unless <0.005, then to 1 significant figure.

Supplementary table 2 shows the p-values for interaction when sex was included as an interaction term to assess for any modification of the association between FEV\textsubscript{1} and FVC at age 8 and cognitive scores at ages 8 and 15, as well as interval change in standardised FSIQ. There was minimal evidence for any interaction, except in the association between FEV\textsubscript{1} at age 8 and FSIQ at age 8, where the p value for interaction was 0.03.
Lung function and cognitive ability in children: A UK birth cohort study

Supplementary table 2. P values for interaction of exposure-outcome association with sex

<table>
<thead>
<tr>
<th>Outcome ↓</th>
<th>Exposure →</th>
<th>FEV₁ % predicted at age 8</th>
<th>FVC % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ (WASI) at age 15</td>
<td></td>
<td>0.51</td>
<td>0.75</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in standardised FSIQ age 8 to 15</td>
<td></td>
<td>0.23</td>
<td>0.23</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ (WISC-III) at age 8</td>
<td></td>
<td>0.03</td>
<td>0.22</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIQ at age 8</td>
<td></td>
<td>0.10</td>
<td>0.35</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIQ at age 8</td>
<td></td>
<td>0.08</td>
<td>0.32</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC at age 8</td>
<td></td>
<td>0.11</td>
<td>0.48</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FD at age 8</td>
<td></td>
<td>0.55</td>
<td>0.33</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO at age 8</td>
<td></td>
<td>0.12</td>
<td>0.40</td>
</tr>
<tr>
<td>p value for interaction with sex</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ – Forced Expiratory Volume in 1 second; FSIQ – Full-scale Intelligence Quotient (IQ); WISC-III – Wechsler Scale of Intelligence for Children 3rd Edition

Supplementary table 3 shows the separate multivariable analyses we conducted to assess the cross-sectional association between FEV₁ and FSIQ at age 8 in males and in females. This shows that the data did demonstrate a cross-sectional association between FEV₁ and FSIQ at age 8 for females, with FSIQ increasing by 0.07 points (0.02, 0.13; p=0.005), for each one per cent increase in the GLI per cent predicted value of FEV₁. No such association was evident for males, with a point estimate close to zero, a confidence estimate crossing the null, and a large p value. Despite the interaction p values providing only weak evidence of interaction with the effect of FEV₁ on subscale scores at age 8, we also fitted separate models for males and females with these outcomes, in order to determine whether any particular facet of cognitive ability could explain this observation. For simplicity, we have not displayed these here, but the pattern was similar, with strong evidence for an association between FEV₁ at age 8 and all subscale scores in females, but not in males. No specific subscale score appeared to explain the association between FEV₁ and FSIQ in females at age 8 more than others. Given this isolated gender-specific cross-sectional association of FEV₁ with FSIQ, we ran models to include asthma diagnosis and childhood wheezing phenotype as covariates in females only, to see if these variables might explain it. Results changed very little, with β=0.09 (0.03, 0.16; p=0.006), indicating that these variables did not explain the association.
Lung function and cognitive ability in children: A UK birth cohort study

Supplementary table 3. Results of multivariable linear regression of FSIQ at age 8 with FEV$_1$ at age 8 in males and females

<table>
<thead>
<tr>
<th>Outcome (WSIC-III) at age 8 – males</th>
<th>Exposure: FEV$_1$ % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>2,166</td>
</tr>
<tr>
<td>Adjusted mean difference* ($\phi$, 95% CI; p)</td>
<td>-0.01 (-0.07, 0.04; p=0.63)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome (WSIC-III) at age 8 – females</th>
<th>Exposure: FEV$_1$ % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>2,107</td>
</tr>
<tr>
<td>Adjusted mean difference* ($\phi$, 95% CI; p)</td>
<td>0.07 (0.02, 0.13; p=0.005)</td>
</tr>
</tbody>
</table>

FEV$_1$ – Forced Expiratory Volume in 1 second; FSIQ – Full-scale Intelligence Quotient (IQ); WISC-III – Wechsler Scale of Intelligence for Children 3rd Edition
*Mean difference in IQ points per point increase in GLI per cent predicted values of FEV$_1$
†Adjusted for age, height, preterm birth, birth weight, breastfeeding duration, prenatal maternal smoking, childhood environmental tobacco smoke exposure, maternal education, housing tenure, prenatal and childhood PM10 air pollution exposure.
All values to 2 decimal places, unless <0.005, then to 1 significant figure.

Supplementary table 4 shows the results of the univariable linear regression models for all participants with data for exposures and FSIQ outcomes, but not necessarily covariates. In this model, estimates for the associations of FEV$_1$ and FVC with FSIQ at ages 8 and 15 were slightly higher than in the main univariate analysis, which was restricted to participants with complete data (e.g. for FVC and FSIQ at 8 years $\beta = 0.13 [0.10, 0.16; \ p<0.001]$, compared to 0.11 [0.07, 0.15; \ p<0.001] in the main analysis). As in the main analysis, there was little to no evidence of an association of either FEV$_1$ or FVC with change in standardised FSIQ between 8 and 15 years of age.

Supplementary table 4. Results of univariable (unadjusted) linear regression for the outcomes of full-scale intelligence quotient (FSIQ) and change in standardised FSIQ for all study participants

<table>
<thead>
<tr>
<th>Outcome (WASI) at age 15</th>
<th>Exposure: FEV$_1$ % predicted at age 8</th>
<th>FVC % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>4,179</td>
<td>4,234</td>
</tr>
<tr>
<td>Mean difference* (95% CI; p)</td>
<td>0.05 (0.02, 0.08 p=0.002)</td>
<td>0.09 (0.06, 0.12; p&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in standardised FSIQ age 8 to 15</th>
<th>Exposure: FEV$_1$ % predicted at age 8</th>
<th>FVC % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>4,122</td>
<td>4,175</td>
</tr>
<tr>
<td>Mean difference** (95% CI; p)</td>
<td>-0.001 (-0.003, 0.001; p=0.32)</td>
<td>-0.001 (-0.003,0.0009; p=0.27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FSIQ (WISC-III) at age 8</th>
<th>Exposure: FEV$_1$ % predicted at age 8</th>
<th>FVC % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>6,548</td>
<td>6,672</td>
</tr>
<tr>
<td>Mean difference* (95% CI; p)</td>
<td>0.09 (0.05, 0.12; p&lt;0.001)</td>
<td>0.13 (0.10, 0.16; p&lt;0.001)</td>
</tr>
</tbody>
</table>

FEV$_1$ – Forced Expiratory Volume in 1 second; FVC – Forced Vital Capacity; WASI – Wechsler Abbreviated Scale of Intelligence; WISC-III – Wechsler Scale of Intelligence for Children 3rd Edition
*Mean difference in IQ points per point increase in GLI per cent predicted values of FEV$_1$ and FVC
** Mean difference in interval change in standardised FSIQ, measured in standard deviations from the mean, per point increase in GLI per cent predicted values of FEV$_1$ and FVC
These models include all participants, regardless of whether complete covariate data were available.
All values to 2 decimal places, unless <0.005, then to 1 significant figure.
Lung function and cognitive ability in children: A UK birth cohort study

Supplementary table 5 shows the results of uni- and multivariable models fitted for participants with complete data for asthma diagnosis and childhood wheezing phenotype, in addition to all other covariates. In the unadjusted analysis, the magnitude of effect estimates for FEV₁ and FVC is only very marginally reduced compared to the main univariable analysis (e.g. for effect of FVC on FSIQ at 15 β = 0.08 [0.04, 0.12; p<0.001], compared to 0.09 [0.05, 0.12; p<0.001] in the main analysis). In this analysis, while there remains strong evidence for a cross-sectional association between FEV₁ and FSIQ at age 8, the estimate for the association of FEV₁ at age 8 with FSIQ at age 15 is reduced such that the 95% confidence intervals crosses the null, suggesting little evidence of a relationship between these two variables in the unadjusted analysis of this subsample. As in the main multivariable analysis, there is little to no evidence of an independent association between FEV₁ at age 8 and FSIQ at ages 8 or 15, or between FEV₁ or FVC at age 8 and interval change in standardised FSIQ. Point estimates for the association of FVC with FSIQ at ages 8 and 15 are unchanged, with a slight widening of confidence intervals (e.g. for FVC and FSIQ at 15 β = 0.06 [0.02, 0.10; p=0.004], compared to 0.06 [0.03, 0.10; p=0.001] in the main analysis).

Supplementary table 5. Results of univariable (unadjusted) and multivariable linear regression for the outcomes of FSIQ at ages 8 and 15, and change in standardised FSIQ, for participants with complete covariates, including asthma diagnosis and childhood wheezing phenotype

<table>
<thead>
<tr>
<th>Outcome ↓</th>
<th>Exposure →</th>
<th>FEV₁ % predicted at age 8</th>
<th>FVC % predicted at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ (WASI) at age 15</td>
<td>Number of participants</td>
<td>2,332</td>
<td>2,365</td>
</tr>
<tr>
<td></td>
<td>Mean difference* (95% CI; p)</td>
<td>0.04 (-0.002, 0.09; p=0.06)</td>
<td>0.08 (0.04, 0.12; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean differenceφ (95% CI; p)</td>
<td>0.02 (-0.02, 0.06; p=0.38)</td>
<td>0.06 (0.02, 0.10; p=0.004)</td>
</tr>
<tr>
<td>Change in standardised FSIQ age 8 to 15</td>
<td>Number of participants</td>
<td>2,306</td>
<td>2,342</td>
</tr>
<tr>
<td></td>
<td>Mean difference** (95% CI; p)</td>
<td>-0.001 (-0.004, 0.002; p=0.50)</td>
<td>-0.0002 (-0.003, 0.003; p=0.86)</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean differenceφ (95% CI; p)</td>
<td>-0.0007 (-0.004, 0.002; p=0.62)</td>
<td>-0.0003 (-0.003, 0.002; p=0.81)</td>
</tr>
<tr>
<td>FSIQ (WISC-III) at age 8</td>
<td>Number of participants</td>
<td>3,346</td>
<td>3,372</td>
</tr>
<tr>
<td></td>
<td>Mean difference* (95% CI; p)</td>
<td>0.08 (0.03, 0.12; p=0.001)</td>
<td>0.11 (0.06, 0.15; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Adjusted mean differenceφ (95% CI; p)</td>
<td>0.03 (-0.01, 0.07; p=0.16)</td>
<td>0.08 (0.04, 0.12; p&lt;0.001)</td>
</tr>
</tbody>
</table>

FEV₁ – Forced Expiratory Volume in 1 second; FVC – Forced Vital Capacity; WASI – Wechsler Abbreviated Scale of Intelligence; WISC-III – Wechsler Scale of Intelligence for Children 3rd Edition

*Mean difference in IQ points per point increase in GLI per cent predicted values of FEV₁ and FVC

**Mean difference in interval change in standardised FSIQ, measured in standard deviations from the mean, per point increase in GLI per cent predicted values of FEV₁ and FVC

φAfter adjustment for preterm birth, birth weight, breastfeeding duration, prenatal maternal smoking, childhood environmental tobacco smoke exposure, maternal education, housing tenure, prenatal maternal and childhood PM10 air pollution exposure, asthma diagnosis and childhood wheezing phenotype.

All values to 2 decimal places, unless <0.005, then to 1 significant figure.
Lung function and cognitive ability in children: A UK birth cohort study

Supplementary table 6 summarises the results of logistic regression models which were fitted to identify determinants of being a complete case, and therefore of selection, at ages 8 and 15. After adjustment for all other covariates included in our original linear models, the odds of selection were reduced by having a mother educated to the equivalent of ‘O’ level or below at both ages 8 (Odds ratio [OR] 0.76 [0.60, 0.97; p=0.03]) and 15 (OR 0.58 [0.47, 0.72; p<0.001]). Meanwhile, those with higher FSIQ scores were increasingly likely to be included at ages 8 (OR 1.01 [1.00, 1.02; p=0.003]) and 15 (OR 1.01 [1.01, 1.02; p<0.001]).

Supplementary table 6. Results of logistic regression to identify determinants of selection at ages 8 and 15

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio – complete case at 8y</th>
<th>Odds ratio – complete case at 15y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal education ≤‘O’ level</td>
<td>0.76 (0.60, 0.97; p=0.03)</td>
<td>0.58 (0.47, 0.72; p&lt;0.001)</td>
</tr>
<tr>
<td>FSIQ (WISC-III) at 8y</td>
<td>1.01 (1.00, 1.02; p=0.003)</td>
<td>1.02 (1.01, 1.02; p&lt;0.001)</td>
</tr>
<tr>
<td>FSIQ (WASI) at 15y</td>
<td>N/A</td>
<td>1.01 (1.01, 1.02; p=0.001)</td>
</tr>
</tbody>
</table>

Coefficients are shown only for variables which were identified as determinants of being a complete case, and therefore of selection, after adjustment for all covariates included in original linear models. Coefficients represent odds ratios for the likelihood of selection at ages 8 and 15. For FSIQ at ages 8 and 15, these are the odds ratios per point increase in FSIQ. All values to 2 decimal places, unless <0.005, then to 1 significant figure (95% CI; p value). N/A – not applicable.

Supplementary discussion

Inclusion of age, height and sex in our multivariable models resulted in near identical results for the estimates of the association of FEV₁ and FVC at age 8 with FSIQ at age 8 and 15, and very minimal change in the estimates of the association with interval change in standardised FSIQ. These results indicate that these variables had indeed been adequately controlled for in the original analysis.

When we investigated for interaction of the association between exposure and outcome with sex in the multivariable regression models, we found that while there was strong evidence of a cross-sectional association between FEV₁ and FSIQ at age 8 in females, in males there was none. This sex-specific association was not explained by asthma diagnosis or childhood wheezing phenotype. The association was not explained by any specific facet of cognitive ability, as measured by the WISC-III subscale scores. It is difficult to explain why decreased FEV₁ should be cross-sectionally associated with decreased FSIQ in girls, but not boys, at age 8. FEV₁ is an effort independent measurement, meaning it is very unlikely that this association can be explained by differences between males and females in the ability to perform the procedure correctly. The association was not explained by asthma diagnosis or wheezing phenotype, despite the fact that these were associated with reduced FSIQ in separate univariate modelling. Both asthma and pathological wheezing phenotypes were more prevalent in males than females (e.g. 17.6% of boys at age 8 had a diagnosis of asthma, versus 12.7% of girls), so if this were the explanation for the sex-specific association it would be expected...
Lung function and cognitive ability in children: A UK birth cohort study

that the association would be stronger in boys. The sex-specific association for FEV$_1$ with FSIQ did not remain evident at age 15. Overall, the significance of this finding is unclear.

Our univariable models including all participants with data for exposure and outcome, but not necessarily covariates, had slightly larger coefficients than the main univariable analysis, and narrower confidence intervals. Although a larger sample size confers greater precision, it is likely that these effect estimates are inflated by confounding, for which it is not possible to control in the additional individuals included, due to a lack of covariate data. On the other hand, the fact that the coefficients are larger in this more unselected group, than in the main univariable analysis, may also support the notion that any selection bias, from analysing an increasingly select and affluent subsample, is likely to be towards the null. This is discussed further below.

Estimated coefficients for the association of FVC with FSIQ were only very slightly attenuated by inclusion of asthma and wheezing phenotype as covariates. This indicates that these diagnoses do not account for much of the variance in IQ explained by FVC. The notion that asthma and wheezing are important in explaining the relationship between FVC and FSIQ is also contested by a loss of precision, as demonstrated by the widening of confidence intervals in the estimates from models including these variables (although this might also be due to a smaller sample size). Another explanation for the attenuation of the coefficients in these models might be the aforementioned effect of selection bias towards the null, due to a more select subsample. The evidence from our results against asthma and wheezing being important explanators of the relationship between FVC and FSIQ is unsurprising, because FEV$_1$ is a better measure of the airflow obstruction which characterises asthma and bronchospasm.

It is useful to highlight the clinical differences between FEV$_1$ and FVC to potentiate the formulation of hypotheses as to why we have detected an effect on childhood cognition from the latter but not the former. West conceptualises the lungs and thorax as an air pump, the function of which is dependent on stroke volume, resistance of the airways, and the force applied to the piston. The latter is unimportant in forced expiration, due to dynamic compression of the airways, which means that flow is independent of effort. FEV$_1$ is the metric of airways resistance, which is affected by pathological processes which cause their narrowing or premature collapse. The most common of these are asthma, which causes reversible bronchoconstriction due to hyperresponsiveness and inflammation of the airways, and chronic obstructive pulmonary disease (COPD), which causes airflow limitation due to chronically inflamed and narrowed airways (chronic bronchitis), and premature collapse due to the loss of radial traction caused by destruction of lung parenchyma distal to the terminal bronchiole (emphysema). FVC is a measure of the ‘stroke volume’
Lung function and cognitive ability in children: A UK birth cohort study

of the air pump, which is determined by the capacity for the thoracic cage, respiratory muscles, pleura and lung parenchyma to fill the lungs with air, and then expel it, through alterations in intrathoracic pressure. This can be negatively impacted by diseases of the thoracic cage, such as kyphoscoliosis, neuromuscular disorders such as muscular dystrophy, diseases of the lung parenchyma such as pulmonary and cystic fibrosis, and diseases of the pleura such as effusion or pneumothorax. A ratio of the FEV₁ to FVC is often used to distinguish ‘obstructive’ from ‘restrictive’ patterns of spirometry, with the former showing a ratio of less than 0.8 due to airflow limitation (FVC may be normal or reduced, while total lung capacity measured by helium dilution may be increased), and the latter showing a normal or increased ratio, but in the presence of reduced FVC and total lung capacity.

We have noted an effect on childhood cognition from FVC, but not FEV₁. However, as discussed elsewhere, our results do not appear to support causality. The most plausible explanation for the association may therefore be genetic and/or early developmental vulnerabilities shared between lung function and cognitive ability. Accordingly, it seems reasonable to suggest that the reason for FVC, but not FEV₁, being associated with cognitive ability is that it may be a better correlate of respiratory and overall health in early life. As discussed above, FVC measures respiratory ‘pump function’, and this is affected by a wider range of pathology than is FEV₁. Airflow limitation typically develops over a number of years in young asthmatic children and over decades in adults with COPD, whereas many of the disorders predominantly affecting FVC occur earlier in life. An example would be cerebral palsy, a developmental neurological disorder which can affect FVC and IQ. This and other early life neurodevelopmental disorders with a common effect on the two traits, which have not been controlled for in our analysis, could explain a proportion of the observed effect.

Another consideration is the increasing problem of childhood obesity, because morbid obesity can cause a restrictive lung function defect with reduced FVC. Elevated body mass index (BMI) has been associated with reduced IQ, although it is not clear if this is a causal relationship. BMI was not controlled for in the multivariable analysis, so it is possible that part of the observed association of FVC with FSIQ is explained by obesity. Estimates of the heritability of pulmonary function traits vary widely, but FVC has generally been assessed to be slightly more heritable than FEV₁ or FEV₁/FVC. Another explanation for the observed association, for FVC but not FEV₁, is that FVC might share more genetic architecture in common with cognitive ability than FEV₁, with its slightly higher heritability potentially making this more likely.

Selection bias, due to study attrition and missing data, is an important source of bias in statistical estimates of relationships between variables derived from cohort studies. We conducted a complete-case analysis, which for an unbiased effect estimate, requires that data is either missing completely at random (MCAR i.e. no systematic missingness which could induce bias), or missing at random (MAR), i.e. missing dependent on
Lung function and cognitive ability in children: A UK birth cohort study

the outcome or exposure only via measured covariates. Given the social patterning of missingness in the ALSPAC dataset demonstrated in table 1 and discussed in the main text, it is safe to assume that the MCAR assumption is not satisfied. We have controlled for SES, but this was imperfectly measured by two proxy variables (maternal education and housing tenure). It is probable that a failure to control for the unmeasured component of SES, as well as for other unmeasured factors related to both outcome and selection, mean that the MAR assumption is also unsatisfied. Cornish et al. showed that FSIQ at age 15 in ALSPAC is likely to be missing not at random (MNAR) i.e. missing dependent on its own (unknown) value, with those with higher IQs more likely to remain in the sample. These findings are corroborated by the results of the logistic regression models we fitted using their method, to identify determinants of selection, which showed that not only is low maternal education negatively associated with inclusion, but that the odds of selection at each age are higher with increasing FSIQ scores, after adjustment for all other covariates. While it is not possible to demonstrate conclusively from the original dataset, these findings are strongly supportive of our outcomes being MNAR, a source of selection bias for which it is not possible to fully correct. According to the analysis of Cornish et al., selection bias might have been reduced, and precision increased, by the use of educational data to impute missing values. Due to time constraints relating to thesis submission deadlines, we did not apply for educational records via data linkage for the purpose of multiple imputation (MI), meaning that there may be greater bias in our estimate than if we had performed MI. However, due to the likelihood of the outcome being MNAR, bias would not have been completely eliminated by MI, and it seems reasonable to assume that any selection bias affecting our estimates would be towards the null. This is because if proportionately more participants with comparatively lower IQ and lung function are lost to follow-up (which seems plausible due to the socially patterned nature of missingness), without completely adjusting for the cause of their deselection, then the observed association would be weakened. There is some evidence for the assertion that selection bias due to missing data is toward the null, from the fact that coefficients from univariable analysis limited to participants with complete data were of smaller magnitude than those from analyses including the less selected group of participants with exposure and outcome, but not necessarily covariate, data.

Supplementary references

Lung function and cognitive ability in children: A UK birth cohort study


6. Williams PT. Spirometric traits show quantile-dependent heritability, which may contribute to their gene-environment interactions with smoking and pollution. PeerJ 2020;8:e9145-e45. doi: 10.7717/peerj.9145