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Mid-childhood fat mass and airflow limitation at 15 years: The mediating role of insulin resistance and C-reactive protein

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Abstract

Background: We previously reported an association of high fat mass levels from age 9 to 15 years with lower forced expiratory flow in 1 s (FEV_1)/forced vital capacity (FVC) ratio (i.e., increased risk of airflow limitation) at 15 years. Here, we aimed to assess whether insulin resistance and C-reactive protein (CRP) at 15 years partially mediate this association.

Methods: We included 2263 children from the UK Avon Longitudinal Study of Parents and Children population-based cohort (ALSPAC). Four fat mass index (FMI) trajectories ("low," "medium-low," "medium-high," "high") from 9 to 15 years were previously identified using Group-Based Trajectory Modeling. Data on CRP, glucose, insulin, and post-bronchodilator FEV_1/FVC were available at 15 years. We defined insulin resistance by the homeostasis model assessment-estimated insulin resistance index (HOMA-IR). We used adjusted linear regression models and a causal mediation analysis to assess the mediating role of HOMA-IR and CRP.

Results: Compared to children in the "low" FMI trajectory, children in the "medium-high" and "high" FMI trajectories had lower FEV_1/FVC at 15 years. The percentage of the total effect explained by HOMA-IR was 19.8% [−114.1 to 170.0] and 20.4% [1.6 to 69.0] for the "medium-high" and "high" trajectories, respectively. In contrast, there was little evidence for a mediating role of CRP.

Conclusion: The association between mid-childhood fat mass and FEV_1/FVC ratio at 15 years may be partially mediated by insulin resistance.

KEYWORDS
airflow limitation, ALSPAC, C-reactive protein, epidemiology, insulin resistance, mediation, obesity

1 | BACKGROUND

Childhood obesity is a major public health problem associated with adverse health outcomes including increased risk of cardiovascular and metabolic diseases along the life course.[1,2] Obesity during childhood and adolescence has also been associated with poor respiratory health, specifically asthma,[3] but also reduced lung function levels.[4] The effects of obesity are especially impactful in the long run, as the level of lung function achieved by early adulthood is a strong determinant of chronic respiratory conditions and other non-communicable diseases in later life.[5,6]

Research on the effects of obesity (as measured by body mass index, waist circumference, or fat mass) on lung function levels (forced expiratory volume in 1 s [FEV_1], forced vital capacity [FVC]) in children and adolescents is still limited and to some extent controversial mostly due to the cross-sectional design of existing studies and poor obesity measurements. However, an association between obesity and the FEV_1/FVC ratio, the primary index of airflow limitation, has been consistently reported.[4,7,8] Systemic inflammation, induced by fat mass, has been proposed as a potential mechanism underlying this association. Several studies have reported positive associations between body fat mass and levels of C-reactive protein levels (CRP), a commonly systemic inflammation marker, in children and adolescents.[9,10] Higher CRP levels have also been associated with impaired lung function in adults[11,12] and children.[13] In addition, in recent years, several studies have suggested that obesity may impair lung function by means of metabolic derangements.[14] There is growing evidence that insulin resistance, a common consequence of childhood obesity,[15] is associated with reduced lung function levels and asthma-like symptoms in children.[16–18] However, despite this evidence, no previous study has explicitly assessed whether childhood obesity leads to a lower FEV_1/FVC ratio due to increased CRP levels or insulin resistance. Identifying the biological mechanisms underlying the association between obesity and airway limitation in adolescents is relevant to confirming a true causal relationship. Ultimately this is important for the development of public health strategies aiming to reduce respiratory morbidity.

In this study, we aimed to assess whether insulin resistance and CRP levels at 15 years partially mediate the association of fat mass from age 9 to 15 years and FEV_1/FVC at 15 years (Figure 1), using a causal mediation analysis approach in children participating in the UK Avon Longitudinal study of Parents and Children (ALSPAC) population-based birth cohort.

Key Message

Although obesity measures have been consistently associated with a lower FEV_1/FVC ratio in adolescents, no previous study has assessed the underlying mechanisms of this association This population-based study assessed whether insulin resistance and CRP levels at 15 years partially mediate the association between fat mass and FEV_1/FVC using a causal mediation analysis approach. The findings suggest that insulin resistance at 15 years may mediate over 20% of this association, but no evidence of a mediating role of CRP was found. Further, longitudinal studies that evaluate other biomarkers of systemic inflammation and examine other potential mechanisms are needed to better understand the pathways linking obesity and respiratory health in adolescence. This is key for public health interventions and targeting clinical interventions.

2 | METHODS

Complete details are provided in the supplement.

2.1 | Study population

We used data from the UK ALSPAC birth cohort previously described.[19,20] Briefly, ALSPAC recruited 14,541 pregnant women residing in Avon, UK, with expected dates of delivery between April 1, 1991, and December 31, 1992. Since age 7, surviving offspring have attended regular follow-up visits. The present analysis was restricted to children from singleton births with available information for the identification of fat mass index trajectories from 9 to 15 years and with lung function, CRP, and insulin resistance data at 15 years (Figure S1). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires

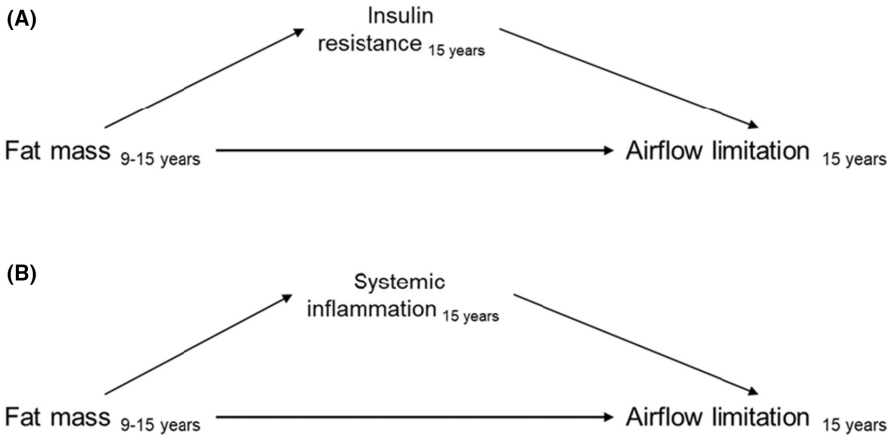

FIGURE 1 How insulin resistance (A) and systemic inflammation here measured as CRP (B) affect the association between fat mass and airflow limitation (i.e., FEV_1/FVC).

and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

2.2 | Fat mass index trajectories

Body composition and height were measured at clinic visits at ages 9, 11, 13, and 15 years. Total fat mass was derived using a Lunar Prodigy DXA scanner (GE Medical Systems Lunar) following standardized procedures. We calculated fat mass index (FMI) by dividing total body fat mass (kg) by height squared (m). We previously identified four FMI trajectories from 9 to 15 years ("low," "medium-low," "medium-high," and "high") using a Group-Based Trajectory Modeling approach (Figure S2).[4] We used the assigned trajectory as the exposure variable.

2.3 | Lung function

Lung function was measured by spirometry at 8 and 15 years (Vitalograph 2120; Vitalograph) according to American Thoracic Society standards, as described previously.[21] At 15 years, lung function was measured before and after bronchodilation with salbutamol. FVC and FEV_1 were obtained and FEV_1/FVC ratios were calculated and expressed as percentages. We used post-bronchodilation FEV_1/FVC at 15 years as the main outcome variable. We also calculated FEV_1/FVC standard deviation scores (*z*-scores) using the Global Lung Initiative equation references.[22]

2.4 | CRP and insulin resistance

Fasting blood samples were obtained during the 15 years' clinic visit. High-sensitivity CRP was measured by automated particle-enhanced immunoturbidimetric assay (Roche UK). Insulin was measured with an enzyme-linked immunosorbent assay (ELISA) (Mercodia) that does not cross-react with proinsulin. Plasma glucose was measured with an auto-mated assay. Insulin resistance was calculated as a continuous measure from insulin and glucose by using the homeostasis model assessment-estimated insulin resistance (HOMA-IR). As CRP and HOMA-IR data did not follow a normal distribution, we applied the natural log-transformation to these variables and used log-transformed CRP and HOMA-IR in the mediation analysis.

2.5 | Covariates

We collected information at different time points on maternal social class, maternal smoking, child's sex, birthweight, gestational age, breastfeeding, total dietary energy intake, environmental tobacco exposure, physical activity, asthma ever diagnosed by a doctor and pubertal status.

2.6 | Statistical analysis

To assess the potential mediating role of HOMA-IR and CRP on the association of FMI trajectories with FEV_1/FVC at 15 years, we used a causal inference analysis approach.[23] We hypothesized that accumulated fat mass from 9 to 15 years, as measured by the FMI trajectories, may affect insulin resistance and CRP levels at 15 years and that these factors in turn can affect the risk of airflow limitation at the same age. Although our data do not fulfill the assumption of temporality (by which the mediator should precede the outcome), we assumed that both insulin resistance and CRP levels at 15 years are good proxies of these same factors in early adolescence and that it is unlikely that lung function can affect them.

We performed the mediation analysis following several steps. First, we fit two mediator models, where HOMA-IR and CRP levels were modeled as a function of FMI trajectories in separate models, after adjusting for relevant confounders (maternal social class and smoking during pregnancy, and child's sex, age, height, and pubertal status at 15 years). Then, we built the outcome model, which modeled FEV_1/FVC as a function of HOMA-IR and CRP, in separate models, including FMI trajectories and the same covariates used in the mediator models plus FEV_1/FVC at 8 years to reduce potential reverse causality. We used linear regression models to estimate both the mediator and outcome models.

The mediator and outcome models were then incorporated into the "mediation" package[24] in the statistical program "R," which estimates the amount of the association between FMI trajectories and FEV_1/FVC that can be explained by changes in HOMA-IR or CRP. The "mediation" package provides three effect estimates: the indirect effect (the population average causal mediation effect that is occurring through the mediator, that is, through changing HOMA-IR or CRP levels), the direct effect (the remaining population average effect that is not occurring through changes in HOMA-IR or CRP) and the total effect (the sum of the indirect and direct effects). Confidence intervals (CI) around these effect estimates are calculated using a quasi-Bayesian Monte Carlo method based on normal approximation.

We performed several sensitivity analyses: (i) excluding children with lifetime doctor-diagnosed asthma; (ii) additionally adjusting models for child's energy intake at 7 years, environmental tobacco exposure at 8 years and wear-time spent in moderate to vigorous physical activity at 11 years; (iii) additionally adjusting models for fasting time; (iv) using pre-bronchodilator FEV_1/FVC ratio as the outcome; (v) using FEV_1/FVC z-scores as the outcome; (vi) categorizing CRP in tertiles to test for a potential non-linear relationship with FEV_1/FVC; (vii) after implementing multiple imputations by chained equations for missing values for CRP, HOMA-IR and the covariates (generating 25 complete datasets), and finally, (viii) testing for potential exposure-mediator interaction by inserting an interaction term between HOMA-IR/CRP (as continuous variables) and FMI trajectories in the outcome model.

3 | RESULTS

3.1 | Sample description

We included 2263 children in the present study. Mothers of these children were older at pregnancy, had higher social class (professional and intermediate), were less likely to smoke during pregnancy and more likely to breastfeed than mothers of children not included in the analysis (Table S1). In addition, children included had higher birth weights and gestational ages and slightly lower FEV_1/FVC at 8 years than children not included. Table 1 shows the main characteristics of the study sample. Approximately 24% of children reported lifetime doctor-diagnosed asthma at 15 years and 19% were classified in the "low" FMI trajectory.

3.2 | Mediating role of HOMA-IR and CRP in the association between FMI trajectories and FEV_1/FVC

Fat mass index trajectories were associated with higher CRP and HOMA-IR levels at 15 years (Table S2). There was little evidence of an association between CRP and FEV_1/FVC (%) at 15 years (mean difference [95% CI]: −0.16 [−0.46 to 0.14] per one unit increase in log-CRP), while higher HOMA-IR levels were associated with lower FEV_1/FVC (−0.74 [−1.40 to −0.08], per one unit increase in log-HOMA-IR).

Compared to children in the "low" FMI trajectory, children in the "medium-high" and "high" FMI trajectories had lower FEV_1/FVC (%) at 15 years (−0.81 [−1.74 to 0.07] and −1.85 [−2.96 to −0.62], respectively). The effect mediated via HOMA-IR in this association was −0.17 [−0.35 to −0.01] and −0.38 [−0.72 to −0.04] for the "medium-high" and "high" trajectories, respectively (Figure 2; Table S3). These indirect effects corresponded to 19.8% [−114.1 to 170.0] and 20.4% [1.6 to 69.0] of the total effect, respectively. In contrast, there was little evidence for a mediating role of CRP levels in the association between fat mass and FEV_1/FVC (Figure 3; Table S4).

Sensitivity analyses yielded similar findings for a mediating role of HOMA-IR (Tables S5–S8) and a null mediating role of CRP (Tables S9–S13). However, the magnitude of the effect mediated via HOMA-IR was reduced in models additionally adjusted for child's energy intake, environmental tobacco exposure and physical activity, as well as in models using pre-bronchodilator FEV_1/FVC. The interaction between FMI trajectories and both HOMA-IR and CRP in the mediation analysis was not statistically significant.

4 | DISCUSSION

To our knowledge, this population-based study is the first to examine the potential mediating role of insulin resistance and CRP on the association between fat mass and airflow limitation (i.e., reduced FEV_1/FVC ratio) in adolescence. Our study suggests that insulin resistance at 15 years may mediate part of this association, but not CRP.

Our finding related to insulin resistance is biologically plausible. Obesity is one of the most important risk factors for insulin resistance in childhood.[15] Insulin receptors are expressed in the lung and there is evidence that insulin can influence lung structure and function at different stages of life.[25] Previous research has suggested that insulin has a direct effect on human airways by influencing airway smooth muscle and airway epithelial cells.[14] Results from a 3-year randomized control trial on the safety and direct effects of inhaled human insulin showed that those receiving the drug were more likely to exhibit respiratory symptoms and reduced lung function.[26] In addition, a previous cross-sectional study found that insulin resistance (measured using the HOMA-IR index) was associated with lower FVC and FEV_1 levels in adolescents with and without asthma.[18] Similarly, a recent longitudinal study reported that high insulin levels at 6 and 10 years tended to be associated with lower FVC.[13] However, in contrast with our findings, these two previous studies did not report an association of insulin resistance or levels with FEV_1/FVC. The results of the several sensitivity analyses that we performed yielded similar findings for a mediating role of HOMA-IR, however, the effect mediated via HOMA-IR was reduced in models additionally adjusted for child's energy intake, environmental tobacco exposure, and physical activity and in models using

TABLE 1 Characteristics of the study sample ($n = 2263$)[a]

	n (%), mean (SD) or median (P_{25}; P_{75})
Maternal characteristics	
Age at delivery (years)	29.2 (4.5)
Social class	
Professional and intermediate	815 (45.6)
Skilled nonmanual	672 (37.6)
Skilled manual, partly skilled and unskilled	299 (16.7)
Smoking during pregnancy: yes	343 (16.6)
Child characteristics	
Sex: girl	1144 (50.6)
Birth weight (g)	3466 (515)
Gestation (weeks)	39.6 (1.7)
Pre-term delivery (<37 weeks gestation)	80 (3.7)
Breastfeeding for 3 months or more	1310 (64.1)
Total energy intake (kcal) at 7 years	1733 (306)
Environmental tobacco exposure at 8 years	408 (20.6)
Wear-time in MVPA (min) at 11 years	19.5 (11.7–30.7)
Lifetime doctor-diagnosed asthma at 15 years: yes	534 (23.6)
Age at the 15 years visit (years)	15.4 (0.3)
Height the 15 years visit (m)	1.7 (0.1)
Pubertal status 15 years: Tanner stage for pubic hair	
Stage 1–3	105 (5.2)
Stage 4	918 (45.4)
Stage 5	1001 (49.4)
FMI trajectories from 9 to 15 years	
Low (Reference)	422 (18.7)
Medium-low	835 (36.9)
Medium-high	686 (30.3)
High	320 (14.1)
CRP (mg/L) 15 years	0.4 (0.2–0.9)
Log CRP 15 years	−0.7 (1.1)
HOMA-IR 15 years	2.1 (1.5–2.8)
Log HOMA-IR 15 years	0.7 (0.5)
Lung function measures	
8 years (pre-bronchodilation)	
FVC (L)	1.9 (0.3)
FEV_1 (L)	1.7 (0.3)
FEV_1/FVC (%)	88.1 (6.5)
15 years (post-bronchodilation)	
FVC (L)	3.8 (0.9)
FEV_1 (L)	3.5 (0.8)
FEV_1/FVC (%)	92.1 (6.5)

Abbreviations: CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FMI, fat mass index; FVC, forced vital capacity; HOMA-IR, homeostasis model assessment-estimated insulin resistance; MVPA, moderate to vigorous physical activity; P_{25}-P_{75}, 25th and 75th percentiles; SD, standard deviation.

[a]Some variables had missing values: Maternal characteristics: 93 in age at delivery, 477 in maternal social class, 191 in smoking during pregnancy; Child characteristics: 93 in gestational age, 121 in birthweight, 221 in breastfeeding, 348 in total energy intake at 7 years, 280 in environmental tobacco exposure at 8 years, 376 in wear-time in MVPA at 11 years, 20 in height at 15 years, 239 in pubertal status, 307 in FVC at 8 years, 328 in FEV1 at 8 years and 328 in FEV_1/FVC at 8 years.

pre-bronchodilator FEV_1/FVC as outcome. This could indicate that the associations of fat mass and HOMA-IR with FEV_1/FVC could be affected by residual confounding due to lifestyle factors. Moreover, the reduction of the effect when using pre-bronchodilator measures could be attributed to an alteration of the ratio in participants with asthma or reversible obstruction of the airways, which is eliminated when using post-bronchodilator measures. Further research is needed to replicate our findings in other populations.

Despite previous evidence of an association between high CRP levels and decreased lung function,[11–13] we found no evidence of a mediating role of CRP in the association between mid-childhood fat mass and FEV_1/FVC at 15 years in this British population. There are some potential explanations for this finding. First, it is possible that CRP affects FVC and FEV_1 to the same extent, leading to a mathematically null effect on the ratio of these two parameters. This is consistent with a previous study in children reporting an association of high CRP levels with FEV_1 and FVC, but not with FEV_1/FVC.[13] Second, there may be low variation in CRP levels in our study sample, so that even children with higher levels do not have levels high enough to affect lung function and lead to airflow limitation. This is plausible because adolescents have been reported to have lower CRP levels than adults[27] and most previous research on the association of CRP with lung function has been conducted in adults. Finally, there is evidence that insulin resistance may precede the elevation of CPR levels in the evolution of the metabolic syndrome in adolescents.[28] This could explain why we observed a mediating role for insulin resistance in the association of fat mass and airflow limitation in 15-year-olds, but not for CRP. Finally, it cannot be discarded that there may be an unknown factor that could causally relate to both CRP and lung function and is responsible for the previously reported associations between them.

This work has important implications for future research. Our study suggests that the association of high-fat mass with airflow limitation at 15 years is only partly mediated by insulin resistance (just over 20% of the total effect). Therefore, other potential mechanisms should be examined, such as the mechanical effects of fat mass on lungs.[29] In addition, since the adipose tissue is involved in the secretion of several proinflammatory markers other than CRP,[30] future research should consider other biomarkers of systemic inflammation such as interleukin-6 (IL-6) or tumor necrosis factor alpha (TNF-α), which have been linked to lower lung function.[31,32] Understanding how fat mass affects lung function in adolescence may help the identification of intermediate treatment targets for clinical interventions aiming to reduce respiratory morbidity. Accordingly, our study suggests that clinical interventions targeting insulin resistance in adolescents may reduce part of the deleterious effects of obesity on respiratory health, especially the effects on airflow limitation.

Important strengths of this study are the population-based nature of the ALSPAC birth cohort and the availability of metabolic and inflammatory biomarkers, which allowed us to examine two potential mechanisms for the association between fat mass and FEV_1/FVC.

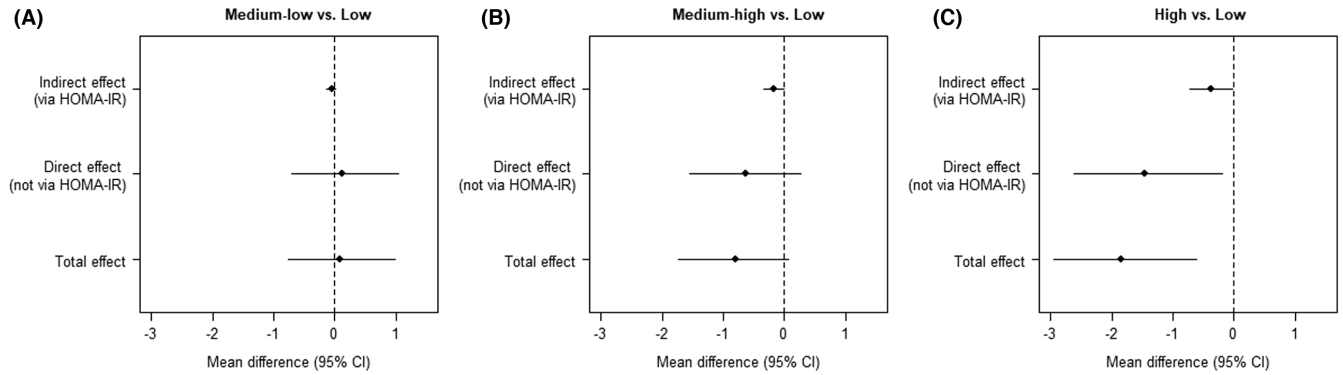

FIGURE 2 Mediating role of log-HOMA-IR index on the association between FMI trajectories and FEV_1/FVC (%) at 15 years. The figure shows the indirect, direct and total effects for the "medium-low" (A), "medium-high" (B) and "high" (C) FMI trajectories, using the "low" trajectory as reference category. Mediator and outcome models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height, and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years. The percentage of the total effect explained by HOMA-IR [95% CI] was 19.8% [−114% to 170%] and 20.4% [1.6% to 69%] for the "medium-high" and "high" trajectories, respectively. CI, confidence intervals; FEV_1, forced expiratory volume in 1 s; FMI, fat mass index; FVC, forced vital capacity; HOMA-IR, homeostasis model assessment-estimated insulin resistance.

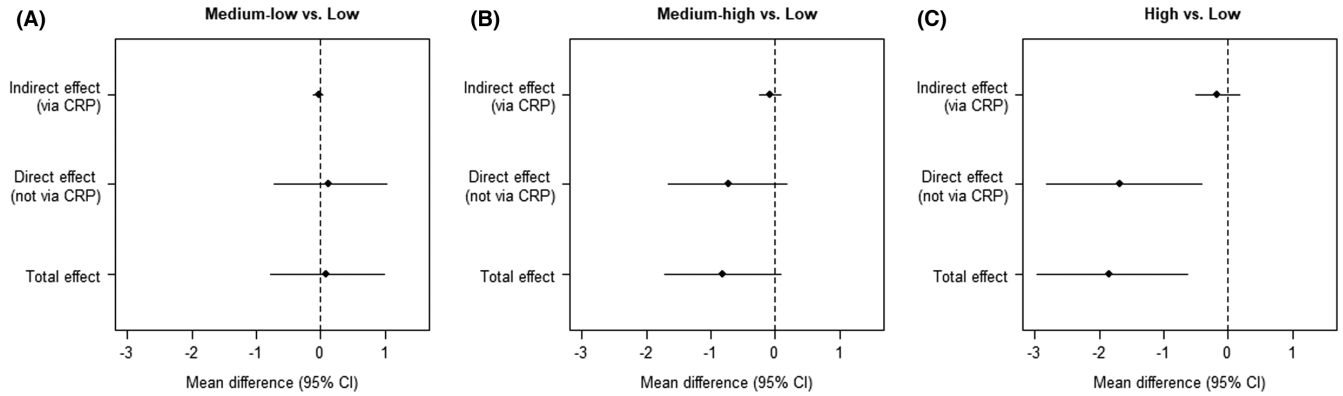

FIGURE 3 Mediating role of log-CRP on the association between FMI trajectories and FEV_1/FVC (%) at 15 years. The figure shows the indirect, direct and total effects for the "medium-low" (A), "medium-high" (B) and "high" (C) FMI trajectories, using the "low" trajectory as reference category. Mediator and outcome models are adjusted for maternal social class and smoking during pregnancy, and child's sex, age, height, and pubertal status at 15 years. The outcome model is additionally adjusted for FEV_1/FVC at 8 years. CI, confidence intervals; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FMI, fat mass index; FVC, forced vital capacity.

A limitation is that the associations of CRP and insulin resistance with FEV_1/FVC were assessed cross-sectionally and therefore are subject to potential reverse causation. However, it is unlikely that lung function levels affect CRP levels or insulin resistance. Another limitation is potential selection bias as children included had a higher socioeconomic status, a higher birth weight, a higher gestational age, a higher proportion of breastfeeding and lower maternal smoking exposure than those excluded, which could underestimate the true associations in the general population. In addition, the regional basis of the ALSPAC cohort may prevents the generalization of our results to populations with more ethnic variability and with different environmental and lifestyle factors. Finally, although we accounted for a wide range of potential confounders, we cannot exclude residual confounding by unmeasured confounders (e.g., genetic factors).

In conclusion, in this population-based study, we found that insulin resistance may partially mediate the association between mid-childhood fat mass and the FEV_1/FVC ratio in adolescence, but we found little evidence of a mediating role of CRP. Further, longitudinal studies that evaluate other biomarkers of systemic inflammation and examine other potential mechanisms are needed to better understand the pathways linking obesity and respiratory health in adolescence.

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CONFLICT OF INTEREST

The authors declared no conflict of interest related to this work.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The informed consent obtained from 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.

REFERENCES

1. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;350:2362-2374.
2. Weihrauch-Blüher S, Schwarz P, Klusmann JH. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. *Metabolism*. 2019;92:147-152.
3. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. *BMC Pediatr*. 2013;13:1-13.
4. Peralta GP, Fuertes E, Granell R, et al. Childhood body composition trajectories and adolescent lung function. Findings from the ALSPAC study. *Am J Respir Crit Care Med*. 2019;200:75-83.
5. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med*. 2017;5:935-945.
6. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373:111-122.
7. Forno E, Han Y-Y, Mullen J, Celedón JC. Overweight, obesity, and lung function in children and adults—a meta-analysis. *J Allergy Clin Immunol Pract*. 2018;6:570-581.e10.
8. Mensink-Bout SM, Santos S, van Meel ER, et al. General and organ fat assessed by magnetic resonance imaging and respiratory outcomes in childhood. *Am J Respir Crit Care Med*. 2020;201:348-355.
9. Tam CS, Clément K, Baur LA, Tordjman J. Obesity and low-grade inflammation: a paediatric perspective. *Obes Rev*. 2010;11:118-126.
10. Singer K, Eng DS, Lumeng CN, Gebremariam A, Lee JM. The relationship between body fat mass percentiles and inflammation in children. *Obesity*. 2014;22:1332-1336.
11. Rasmussen F, Mikkelsen D, Hancox RJ, et al. High-sensitive C-reactive protein is associated with reduced lung function in young adults. *Eur Respir J*. 2008;33:382-388.
12. Ahmadi-Abhari S, Kaptoge S, Luben RN, Wareham NJ, Khaw KT. Longitudinal association of C-reactive protein and lung function over 13 years. *Am J Epidemiol*. 2014;179:48-56.
13. Mensink-Bout SM, Santos S, de Jongste JC, Jaddoe VWV, Duijts L. Cardio-metabolic risk factors during childhood in relation to lung function and asthma. *Pediatr Allergy Immunol*. 2021;32:945-952.
14. Baffi CW, Wood L, Winnica D, et al. Metabolic syndrome and the lung. *Chest*. 2016;149:1525-1534.
15. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among U.S. adolescents: a population-based study. *Diabetes Care*. 2006;29:2427-2432.
16. Arshi M, Cardinal J, Hill RJ, Davies PSW, Wainwright C. Asthma and insulin resistance in children. *Respirology*. 2010;15:779-784.
17. Cottrell L, Neal WA, Ice C, Perez MK, Piedimonte G. Metabolic abnormalities in children with asthma. *Am J Respir Crit Care Med*. 2011;183:441-448.
18. Forno E, Han YY, Muzumdar RH, Celedón JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. *J Allergy Clin Immunol*. 2015;136:304-311.e8.
19. Boyd A, Golding J, Macleod J, et al. Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol*. 2013;42:111-127.
20. Fraser A, Macdonald-Wallis C, Tilling K, et al. Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol*. 2013;42:97-110.
21. Sonnenschein-Van Der Voort AMM, Howe LD, Granell R, et al. Influence of childhood growth on asthma and lung function in adolescence. *J Allergy Clin Immunol*. 2015;135:1435-1443.e7.
22. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324-1343.
23. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15:309-334.
24. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *J Stat Softw*. 2014;59:1-38.
25. Singh S, Prakash YS, Linneberg A, Agrawal A. Insulin and the lung: connecting asthma and metabolic syndrome. *J Allergy*. 2013;2013:1-8.
26. Rosenstock J, Cefalu WT, Hollander PA, Klioze SS, Reis J, Duggan WT. Safety and efficacy of inhaled human insulin (Exubera) during discontinuation and readministration of therapy in adults with type 2 diabetes: a 3-year randomized controlled trial. *Diabetes Technol Ther*. 2009;11:697-705.
27. Schlenz H, Intemann T, Wolters M, et al. C-reactive protein reference percentiles among pre-adolescent children in Europe based on the IDEFICS study population. *Int J Obes (Lond)*. 2014;38:S26-S31.
28. Moran A, Steffen LM, Jacobs DR, et al. Relation of C-reactive protein to insulin resistance and cardiovascular risk factors in youth. *Diabetes Care*. 2005;28:1763-1768.
29. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol*. 2010;108:206-211.

30. Ferrante AW. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med*. 2007;262:408-414.
31. Mukhopadhyay S, Hoidal JR, Mukherjee TK. Role of TNFα in pulmonary pathophysiology. *Respir Res*. 2006;7:125.
32. Thorleifsson SJ, Margretardottir OB, Gudmundsson G, et al. Chronic airflow obstruction and markers of systemic inflammation: results from the BOLD study in Iceland. *Respir Med*. 2009;103:1548-1553.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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