Lung function trajectory and biomarkers in the Tasmanian Longitudinal Health Study

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In the general population, two circulating biomarkers (CRP and CC16) are associated with different lung function trajectories leading to COPD in adulthood https://bit.ly/3wqWfb3

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Abstract

Background and objective Different lung function trajectories through life can lead to COPD in adulthood. This study investigated whether circulating levels of biomarkers can differentiate those with accelerated (AD) from normal decline (ND) trajectories.

Methods The Tasmanian Longitudinal Health Study (TAHS) is a general population study that measured spirometry and followed up participants from ages 7 to 53 years. Based on their forced expiratory volume in 1 s (FEV_1) trajectories from age 7 to 53 years, this analysis included those with COPD at age 53 years (60 with AD and 94 with ND) and controls (n=720) defined as never-smokers with an average FEV_1 trajectory. Circulating levels of selected biomarkers determined at 53 and 45 years of age were compared between trajectories.

Results Results showed that CC16 levels (an anti-inflammatory protein) were lower and C-reactive protein (CRP) (a pro-inflammatory marker) higher in the AD than in the ND trajectory. Higher CC16 levels were associated with a decreased risk of belonging to the AD trajectory (OR=0.79 (0.63–0.98) per unit increase) relative to ND trajectory. Higher CRP levels were associated with an increased risk of belonging to the AD trajectory (OR=1.07, 95% CI: 1.00–1.13, per unit increase). Levels of CC16 (area under the curve (AUC) =0.69, 95% CI: 0.56–0.81, p=0.002), CRP (AUC=0.63, 95% CI: 0.53–0.72, p=0.01) and the combination of both (AUC=0.72, 95% CI: 0.60–0.83, p<0.001) were able to discriminate between the AD and ND trajectories. Other quantified biomarkers (interleukin (IL)-4, IL-5, IL-6, IL-10 and tumour necrosis factor-α (TNF-α)) were not significantly different between AD, ND and controls.

Conclusions Circulating levels of CRP and CC16 measured in late adulthood identify different lung function trajectories (AD *versus* ND) leading to COPD at age 53 years.

Introduction

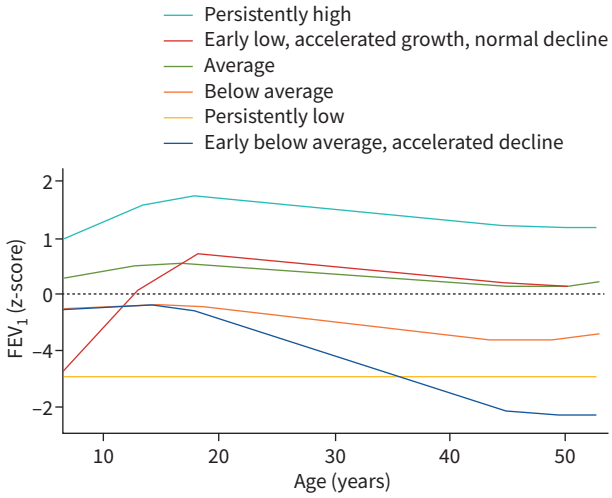
COPD has been traditionally considered a self-inflicted disease caused by tobacco smoking and characterised by an accelerated age-related decline (AD) of the forced expiratory volume in 1 s (FEV_1) [1]. Research over the past few years, however, has shown that only about half of adult COPD patients have followed this AD trajectory, whereas the other half never achieved normal peak lung function in early adulthood and develop COPD following a normal rate of FEV_1 decline (ND) [2–4]. Importantly, these latter patients suffer a higher prevalence and an earlier incidence of cardio-metabolic comorbidities and premature death [5], so identifying what trajectory a given COPD patient has followed when seen in the clinic for the first time in their fifties or sixties may have implications for prognosis and management [6, 7]. In real life, however, spirometry is rarely measured in childhood, adolescence or early adulthood [4], so circulating biomarkers associated with different life-long lung function trajectories leading to COPD may be potentially useful for the appropriate stratification of adult COPD patients.

The Tasmanian Longitudinal Health Study (TAHS) is a general population study that began in 1968 when 8583 Tasmanian children born in 1961 (7 years of age) were enrolled [8, 9]. Spirometry (and clinical assessment) were repeated at 13, 18, 45, 50 and 53 years [8, 9]. Previous analysis of the TAHS cohort have identified six distinct FEV_1 trajectories from age 7 to 53 years (figure 1) [3]. The prevalence of COPD at age 53 years increased exponentially between them (figure 1). Accordingly, TAHS offers a unique opportunity to explore the hypothesis that some circulating biomarkers may be differentially associated with the AD and ND trajectories leading to adult COPD. To test this hypothesis, we contrasted the serum levels of a panel of biomarkers determined in adulthood (45 and 53 years), including club cell secretory protein (CC16), C-reactive protein (CRP), interleukin (IL)-4, IL-5, IL-6, IL-10 and tumour necrosis factor (TNF)-α, in individuals with COPD at age 53 years who had followed a life-long AD *versus* ND trajectory in TAHS.

Methods

Study design, participants and ethics

The design and methods of TAHS have been summarised above and reported in detail elsewhere [8, 9]. In 1968, 8583 students (98.8% of all school students aged 7 years and born in Tasmania) were recruited. The children underwent a clinical examination including spirometry, and their parents completed a questionnaire. Follow-up studies were conducted at 13, 18, 45, 50 and 53 years with spirometry measured. In 2002, when the participants were 45 years old, we traced 7562 (88.1%) of the original 1968 cohort, and 5729 (78.4%) of those traced completed a postal survey. A subgroup of these respondents, enriched for cases of asthma or cough reported in childhood or adulthood, were invited to participate in another clinical study, which included spirometry and collection of blood samples (n=1405). In the most recent TAHS follow-up in 2012, all those from the original cohort who were alive (53 years) and had up-to-date contact



Trajectory	Prevalence %	% participants with FEV_1/FVC <0.7 at 53 years
Persistently high	12	0.2
Early low, accelerated growth, normal decline	8	0.5
Average	39	2.2
Below average	32	9.1
Persistently low	6	17.6
Early below average, accelerated decline	4	62.5

FIGURE 1 Six lung function trajectories from age 7 to 53 years identified in the Tasmanian Longitudinal Health Study (TAHS) [3]. Table shows the prevalence of each of these six trajectories as well as the proportion of participants in each trajectory with evidence of COPD at the age of 53 years. For further explanations, see text. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. Reproduced and modified from [3] with permission from the publisher.

details were invited to attend a clinical visit, where pre- and post-bronchodilator spirometry was measured again, and a new peripheral venous sample was obtained and processed [8]. The TAHS study was approved by ethics committees of all participating institutions, and all participants signed their written informed consent.

Biomarker quantification

The serum levels of CRP and CC16 were quantified by ELISA in blood samples obtained at both 45 and 53 years of age; and levels of IL-4, IL-5, IL-6, IL-10 and TNF-α were quantified for only blood samples at 45 years as published elsewhere [10–12].

Lung function trajectories over time and COPD at 53 years

In our previous analysis, we applied a group-based trajectory modelling technique to model FEV_1 trajectories from 7 to 53 years [3]. We identified six distinct trajectories three of which were associated with an increased risk of COPD (defined as post-bronchodilator FEV_1/forced vital capacity (FVC) <0.7) at 53 years (figure 1). Among these three "disadvantaged" trajectories, one (namely "early below average, accelerated decline") had accelerated lung function decline, while the other two (namely "below average" and "persistently low") had lower lung function from childhood and normal lung function decline in adulthood.

Data analysis

For the current analysis, we included 154 COPD cases at 53 years who had followed the three "disadvantaged" FEV_1 trajectories (figure 1). These COPD cases were classified into two COPD groups: (1) COPD cases included in the "early below average, accelerated decline" FEV_1 trajectory (n=60), labelled here as accelerated decline (AD); and (2) COPD cases included in the "below average" or "persistently low" FEV_1 trajectories, labelled here as normal decline (ND) (n=94). These two COPD groups (AD and ND) were primary comparison groups in this analysis. We additionally included a control group who were never-smoker participants in the "average" FEV_1 trajectory who had normal lung function at age 53 (n=702), labelled here as controls (C).

Results are summarised as n (%), mean±SD or median (interquartile range), as appropriate. Groups were compared using t-test, Kruskal–Wallis test and chi-squared test where appropriate. Levels of biomarkers were then associated with lung function trajectories using regression models, adjusted for age, sex, socioeconomic status, current asthma, smoking status, cumulative smoking exposure (pack-years) and childhood asthma and pneumonia. Receiver operating characteristic (ROC) analysis was used to assess the ability of biomarkers to discriminate among trajectories as indicated by the area under the curve (AUC) and 95% confidence intervals. All analyses were performed with STATA V.15.1 (Stata Corporation 2019, College Station, TX, USA).

Results

Table 1 presents the main characteristics of C, AD and ND participants at age 53 years. Main observations were that: the proportion of females was higher in C, intermediate in AD and lowest in ND; body mass index (BMI) was higher in AD than in ND; the prevalences of current smoking and parental smoking were similar in AD and in ND but cumulative smoking exposure was higher in AD; both AD and ND had more childhood pneumonia/pleurisy, and were diagnosed with asthma in childhood and adulthood more frequently than C; and finally, by definition, spirometry was normal in C, whereas airflow limitation at the age of 53 was generally more severe in AD than in ND.

Table 2 presents the biomarker levels determined in the three groups at 45 or 53 years of age. Compared with C, AD participants had higher CRP and lower CC16 levels, both at 45 and 53 years of age. They also showed reduced concentrations of the Th2-related cytokines IL-4 and IL-5, while IL-6, IL-10 and TNF-α levels were similar to C. By contrast, ND participants showed a biomarker pattern that resembled that of C, with normal CRP levels and mildly reduced CC16 concentrations and normal IL-4, IL-5, IL-6 and IL-10 values, although they had slightly increased TNF-α concentrations (table 2, supplementary figure S1). Finally, CC16 levels were significantly lower in the AD than in the ND trajectories, both at 45 and 53 years, and CRP levels were higher in the AD than in the ND trajectory at 53 years. The remaining measured biomarkers were not different between AD and ND (table 2). In the sensitivity analysis when smokers with normal lung function were added to the control group (C), we observed similar findings (supplementary table S1). Between 45 and 53 years, CC16 increased by 0.59 (95% CI: 0.38–0.81, SD=2.9) unit. CRP reduced by 0.77 (95% CI: 0.43–1.1; SD=4.6) unit.

TABLE 1 Main characteristics of controls, accelerated decline and normal decline at age 53 years

	Controls (C)		Accelerated decline (AD)		Normal decline (ND)		p-value		
	n	Mean±SD or %	n	Mean±SD or %	n	Mean±SD or %	C *versus* AD	C *versus* ND	AD *versus* ND
Demographics									
Age at last follow-up years	702	52.6±0.7	60	53.2±0.7	94	52.8±0.8	**<0.001**	0.41	**0.04**
Females %	702	55	60	45	94	35	0.15	**<0.001**	0.22
Height cm	702	169.3±9.1	60	169.5 ±9.1	94	172.1±10.1	0.99	**0.019**	0.24
Body mass index kg·m^{-2}	702	28.0±5.2	60	29.9 ±7.2	94	26.5±4.6	**0.028**	**0.026**	**<0.001**
SES at 53 years %	702		60		94				
1 (highest)		41.4		25		24.2	**0.013**	**0.002**	0.90
2		16.2		13.3		14.3			
3		29.6		40		32.9			
4		5.7		11.7		7.7			
5		7.1		10		20.9			
Smoking exposure									
Pack-years	702	0	60	21.9±19.5	94	16.7±16.8	**<0.001**	**<0.001**	**<0.001**
Smoking status %	702		60		94				
Never		100		10.0		29.8	-	-	**0.004**
Current		0		41.7		46.8			
Past		0		48.3		23.4			
Maternal smoking %	702	28.8	60	49.1	94	44.4	**0.001**	**0.003**	0.57
Paternal smoking %	702	49.7	60	64.9	94	65.2	**0.028**	**0.006**	0.90
Family history									
Maternal asthma %	702	9	60	14	94	12.2	0.21	0.32	0.70
Paternal asthma %	702	10	60	10.7	94	12.3	0.86	0.49	0.76
Previous personal history									
Low birthweight (<2.5 kg) %	450	5.8	39	7.7	62	6.4	0.60	0.80	0.80
Small gestational age (<37 weeks) %	450	15	39	12.8	62	18	0.70	0.59	0.50
Childhood pneumonia %	702	10.5	60	22	94	18.1	**0.008**	**0.030**	0.55
Childhood asthma %	702	14.7	60	41.7	94	24.5	**<0.001**	**0.015**	**0.025**
Asthma status %	702		60		94		**<0.001**	**<0.001**	0.10
Never		84.7		38.3		57.4			
Past		8.7		13.3		7.5			
Current		6.6		48.3		35.1			
Childhood hay fever %	702	11.5	60	26.3	94	17	**0.001**	0.13	0.17
Childhood eczema %	702	9.3	60	25	94	12.9	**<0.001**	0.28	0.055
Childhood food allergy %	702	6.3	60	11.8	94	10.6	0.10	0.12	0.81
Lung function at 53 years									
Post-BD FEV_1/FVC %	702	81.6±3.9	60	63.6±5.9	94	65.7±4.2	**<0.001**	**<0.001**	**0.005**
Post-BD FEV_1 % pred	702	109.7±8.8	60	72.4±8.7	94	86.1±8.6	**<0.001**	**<0.001**	**<0.001**
Post-BD FVC % pred	702	106.7±9.6	60	90.5±10.6	94	103.6±10.2	**<0.001**	**0.015**	**<0.001**

Bold indicates siginifcant differences (p<0.05). SES: socioeconomic status; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Regression analysis adjusted for age, sex, current asthma, smoking, pack-years and childhood factors, including childhood asthma and pneumonia, showed that higher CC16 levels at 53 years (OR=0.79, 95% CI: 0.63–0.98, per 1 unit increase in CC16 level) and 45 years (OR=0.69, 95% CI: 0.52–0.91, per 1 unit increase in CC16 level) were associated with a decreased risk of belonging to the AD trajectory relative to ND as the reference (table 3). Higher levels of CRP at 53 years were associated with an increased risk of AD (OR=1.07, 95% CI: 1.00–1.13, per 1 unit increase in CRP level) relative to ND as the reference. Although BMI has been associated with increased CRP levels, additional adjustment for BMI did not appreciably change our findings. ROC analysis showed that the combined consideration of CC16 and CRP levels had an AUC of 0.72 (95% CI: 0.60–0.83, p<0.001) to discriminate the AD from the ND trajectories (figure 2). The Youden method identified a cut-off point for CC16 is 5.11, which has a corresponding sensitivity of 60% and specificity of 71%. For CRP, the cut-off point is 4.72 with a sensitivity of 55% and specificity of 70%.

TABLE 2 Biomarker values (median (IQR)) in controls (C), accelerated decline (AD) and normal decline (ND) participants

	Controls (C)		Accelerated decline (AD)		Normal decline (ND)		p-value		
	n (%)	Median (IQR)	n	Median (IQR)	n	Median (IQR)	C *versus* AD	C *versus* ND	AD *versus* ND
Subjects n	702		60		94				
CRP									
45 years	232 (33.1)	2.3 (1.1–5.2)	37	3.2 (1.6–8.6)	45	2.6 (1.8–6.0)	**0.04**	0.17	0.36
53 years	648 (92.3)	2.1 (1.0–4.4)	55	5.1 (1.9–10.2)	84	2.6 (1.3–5.9)	**<0.001**	0.14	**0.01**
CC16									
45 years	217 (30.9)	6.7 (5.1–9.0)	33	3.9 (2.3–5.9)	43	5.6 (4.2–7.6)	**<0.001**	**0.02**	**0.003**
53 years	214 (30.5)	7.7 (5.5–9.8)	34	3.9 (2.6–5.5)	42	5.4 (3.7–8.6)	**<0.001**	**<0.001**	**0.005**
IL-4 (45 years)	212 (30.2)	194 (17–555)	37	15.3 (0.3–265)	40	37 (6–412)	**0.003**	0.08	0.21
IL-5 (45 years)	212 (30.2)	0.65 (0.14–1.8)	37	0.27 (0.1–0.0)	40	0.44 (0.15–1.1)	**0.02**	0.38	0.11
IL-6 (45 years)	212 (30.2)	21 (6.6–5.3)	37	9.3 (4.0–49)	40	17.4 (3.9–73)	0.19	0.78	0.49
IL-10 (45 years)	212 (30.2)	4.4 (0.3–11)	37	4.1 (0.6–9.1)	40	8.7 (1.7–30)	0.78	0.07	0.12
TNF-α (45 years)	212 (30.2)	6.1 (4.4–8.8)	37	7.2 (4.6–9.0)	40	7.7 (5.4–9.5)	0.53	**0.05**	0.39

CRP: C-reactive protein; IL: interleukin; TNF-α: tumour necrosis factor-α.

Discussion

In this study, we investigated biomarkers associated with different lung function trajectories leading to COPD in middle age. The main and novel observations of this analysis are that the AD trajectory was associated with significantly higher CRP and lower CC16 circulating levels than the ND one; and the combined assessment of these two biomarkers can effectively discriminate between the two trajectories among adults with COPD.

It is now well accepted that different lung function trajectories can lead to COPD in adulthood [2–4, 13, 14] albeit their relationship with circulating biomarkers is unclear. Guerra *et al.* [15] have recently shown using several cohorts with different, limited age ranges that low concentrations of CC16 in serum are associated with reduced lung function in childhood, accelerated lung function decline in adulthood, and development of moderate airflow limitation in adult populations [15]. In a subsequent publication, they showed that CC16 levels increased from birth to childhood to 32 years of age, likely related to increasing body/lung size with age, that there was intra-subject tracking of CC16 levels across all ages, and that several environmental (maternal age at delivery, maternal smoking and parental education) and genetic (sex and the single nucleotide polymorphism rs3741240) factors were associated with CC16 levels [16]. Our results confirm that CC16 is an important biomarker in this context, although two important differences with these previous studies are worth noting. First, Guerra *et al.* [15, 16] combined different cohorts followed during varying periods of time, whereas our cohort studied the same participants followed from infancy (7 years) to late adulthood (53 years) [8, 9]. Second, whereas Guerra *et al.* explored the predictive value of CC16 determined early in life, we used the reverse approach and explored the potential usefulness of quantifying CC16 (and other biomarkers) in late adulthood to estimate the trajectory that the individual with chronic airflow limitation in adulthood has already followed, a scenario which resembles much more current clinical practice. Finally, it is also important to acknowledge that, in patients with moderate to severe COPD recruited into the ECLIPSE study, Vestbo *et al.* [17] showed that CC16, CRP and

TABLE 3 Adjusted association between CC16 and C-reactive protein (CRP) levels and the two COPD groups

	COPD with accelerated lung function decline (AD) OR (95% CI)[#]
CC16 levels at 53 years, per unit increase	0.79 (0.63–0.98)*
CC16 levels at 45 years, per unit increase	0.69 (0.52–0.91)**
CRP levels at 53 years, per unit increase	1.07 (1.00–1.13)*
CRP levels at 45 years, per unit increase	1.08 (0.96–1.21)

Adjusted for age, sex, current asthma, smoking, pack-years, inhaled corticosteroid use and childhood factors, including childhood asthma and pneumonia. [#]: compared to COPD with early low-normal lung function decline (ND) as the "non-disease"/reference group; OR=odds ratio per unit increase in each biomarker. *p<0.05; **p<0.01.

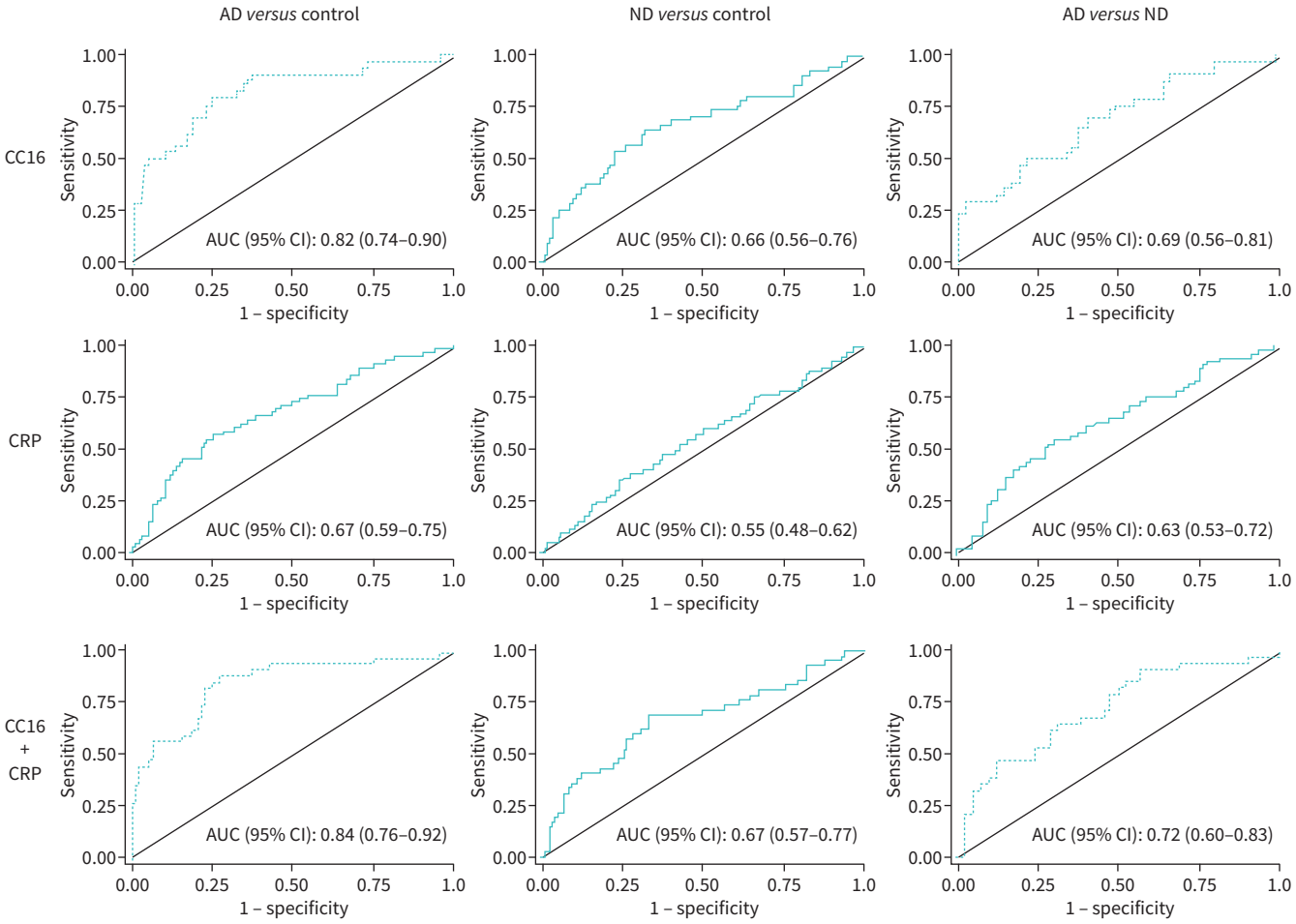


FIGURE 2 Receiver operating characteristic (ROC) curves (and corresponding area under the curve (AUC) values) of CC16 (top row), C-reactive protein (CRP) (middle row) and the combination of both biomarkers (bottom row) in the three-potential comparison in the Tasmanian Longitudinal Health Study. CRP and CC16 were measured at 53 years in this figure. AD: accelerated decline group. ND: early low–normal decline group. For further explanations, see text.

fibrinogen were significantly associated with the FEV_1 value determined at recruitment (63 years of age), and that the values of CC16 (p=0.04) and CRP (p=0.07) were related to the annual rate of FEV_1 change during 3 years follow-up, with no relationship observed for other biomarkers investigated (IL-6, IL-8, surfactant protein D and TNF-α) neither with basal FEV_1 or change over time.

We investigated the ability of CC16 and CRP to differentiate between the two COPD groups. CC16 was found to have better predictive ability. Although the combination of CRP and CC16 improved the predictive ability compared to CC16 alone, this improvement is relatively small and not statistically significant.

Our observation that the AD trajectory leading to COPD was associated with higher CRP and lower CC16 levels supports that an excessive inflammatory response may be an important endotype underlying this trajectory [18], whereas the fact that the ND trajectory was associated with a much more “normal” biomarker pattern suggests that inflammation is not the main endotype underlying this trajectory and that poor lung development mechanisms are likely to play a more relevant pathogenic role here [19]. If so, it is possible that individuals in the AD trajectory (identified by low CC16 and high CRP levels) may benefit most from treatment with anti-inflammatory drugs, whereas those in the ND trajectory (and no evidence of abnormal inflammatory response) are unlikely to do so. This hypothesis may be explored in previous randomised controlled trials, if blood samples are available for analysis, or considered in the design of future ones, thus helping to delineate more clearly any potential therapeutic effect or to repurpose existing drugs [20].

Our study has both strengths and limitations. The fact that participants in TAHS have been followed since childhood to late adulthood allows for lifetime trajectories that capture both lung growth and decline, which is a clear strength. Lack of replication is a limitation. Unfortunately, the uniqueness of TAHS makes it impossible to validate our observations in other cohorts. We acknowledge that our selection of biomarkers based on available data at the time the study was set up is a limitation, and exploration of other candidates using unbiased proteomics is warranted [21–26] and will occur with a future planned follow-up. As we only had data on biomarkers at 45 and 53 years, having such data over time from childhood would have provided more information on the longitudinal association with lung function trajectories leading to COPD. Although different spirometers were used in different follow-ups in TAHS, we used standardised measures (z-scores) to develop lung function trajectories, which reduces the impact of this limitation. As TAHS spans six decades, loss to follow-up is not unexpected. However, those participating at 53 years had similar baseline characteristics to those lost to follow-up, suggesting that the attrition is unlikely to explain our findings. We were able to control for smoking in this study; however, stratified analyses for smoking were not possible owing to small sample sizes. Finally, while we have assessed serum levels of the biomarkers, further studies measuring CC16 levels in the sputum and EBC are required to provide a direct measure of the airway pathology.

In conclusion this study shows that two circulating biomarkers (CC16 and CRP) are differentially associated with the AD and ND trajectories leading to COPD in adulthood and that their combined assessment can significantly discriminate between trajectories with potential implications both for clinical practice and future research.

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