Circulating Biomarkers in Young Individuals with Low Peak FEV_1

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Circulating Biomarkers in Young Individuals with Low Peak FEV_1

To the Editor:

It is now well established that there is a range of lung function trajectories throughout the life course (1, 2). Specifically, 4–12% of young adults in the general population never achieve normal peak lung function, as determined by FEV_1 measurement (3). These individuals are at higher risk of developing chronic obstructive pulmonary disease (COPD) in adulthood (4), suffer a higher prevalence and a decade earlier incidence of cardiovascular and metabolic disorders, and die prematurely (3, 5). The biological mechanisms underlying these observations are unknown.

Older patients with COPD often present abnormal levels of circulatory inflammatory markers (IL-6, IL-8, CCL19 [C-C Motif Chemokine Ligand 19]) (6), pneumo-proteins (CC16 [Club cell secretory protein 16], SP-D [Surfactant Protein D], sRAGE [Soluble Receptor for Advanced Glycation End Products], CCL18) (6), and aging hallmarks (telomere attrition and mitochondrial damage/mitochondrial DNA copy number) (7). Whether or not these biological abnormalities also occur in young individuals with low peak lung function has not been investigated before. To explore this, we studied 300 individuals aged 25–35 years from the Lifelines Cohort Study (8) with $FEV_1 <$ lower limit of normal (LLN) ($n = 147$) or $FEV_1 \geqslant$ LLN ($n = 153$) for their age (according to the Global Lung Function Initiative [GLI] equations). Demographic and clinical factors had been recorded, as described elsewhere (8). Because groups were balanced by sex and smoking exposure, their potential effect could not be investigated here. The serum concentrations of IL-8, IL-6, sRAGE, SP-D, CCL2, CCL19, Pentraxin-3, TSLP (Thymic stromal lymphopoietin), CC16, CCL18, BNDF (Brain-derived neurotrophic factor), Leptin, vWFA-2 (von Willebrand Factor 2), and Collagen I α1, all previously associated with COPD (6), were quantified using the Luminex MAGPIX platform (R&D systems). Because IL-6 and TSLP concentrations were below the detection level of the assay in >80% of samples, they were excluded from analysis. For the included biomarkers, determinations below the detection limit were imputed with one-fourth of that value. The maximum number of imputed samples was 11 (out of 300 measured, i.e., 3.7%) for both IL-8 and Pentraxin-3. Telomere length and the ratio of mitochondrial to nuclear DNA (i.e. mitochondrial DNA copy number measured as 12S rRNA/RNAseP), two well-stablished aging hallmarks (7), were measured by quantitative PCR in whole-blood DNA. Differences between groups were compared using the Mann-Whitney *U* test. A stepwise multivariate logistic regression model that included clinical factors associated with low peak FEV_1 (Table 1) (3, 9–11) and the biomarkers measured here was used to identify variables independently associated with $FEV_1 <$ LLN.

Table 1 compares selected clinical characteristics and biomarker levels in participants with $FEV_1 \geqslant$ LLN or $FEV_1 <$ LLN. A diagnosis of asthma was similarly prevalent in both groups, but ever-wheezing and eosinophil counts were higher in participants with $FEV_1 <$ LLN, so we cannot exclude asthma underdiagnoses. Triglycerides were higher in participants with $FEV_1 <$ LLN, who also showed a tendency toward shorter pregnancy duration and breathing problems. The serum level of most measured biomarkers was similar in both groups, except for lower CC16 and higher CCL19 and leptin levels in individuals with $FEV_1 <$ LLN. Telomere length and the mitochondrial DNA copy number were similar in both groups.

Multivariate logistic regression showed that triglycerides, HbA1c, ever-wheezing, CC16, CCL2, sRAGE, CCL19, and Leptin were independently related to low lung function in this young population (Figure 1). In a sensitivity analysis in the population in which information on eosinophils was available ($n = 291$), we found that they did not have a significant effect (odds ratio, 1.18; 95% confidence interval, 0.90–1.55; $P = 0.222$), whereas the other variables preserved the direction of effect and significance.

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Data sharing statement: Lifelines data can be requested following the procedures described in: https://www.lifelines.nl/researcher/how-to-apply.

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Table 1. Selected Characteristics and Biomarkers in Young Individuals (25–35 yr) with $FEV_1 \geq$ Lower Limit of Normal or $FEV_1 <$ Lower Limit of Normal

	$FEV_1 <$ LLN		$FEV_1 \geq$ LLN		
	N	**Mean ± SD or *n* (%)**	***N***	**Mean ± SD or *n* (%)**	***P* Value**
Demographics and exposures					
Sex female*	147	88 (59.86)	153	88 (57.52)	0.725
Age, yr*	147	29.37 ± 3.22	153	29.84 ± 2.97	0.149
Body mass index, kg/m^2*	147	25.15 ± 4.46	153	24.65 ± 3.43	0.68
Smoking status > or <5 pack-years*					
Ever-smoker with >5 pack-years	147	0 (0)	153	0 (0)	1.00
Ever-smoker with ≤5 pack-years		98 (66.67)		102 (66.67)	
Never-smoker		49 (33.33)		51 (33.33)	
Tobacco exposure*					
Secondhand, exposed and more hours than the average (40 min)	141	18 (12.77)	149	18 (12.08)	0.977
Secondhand, exposed but fewer hours than the average (40 min)		12 (8.51)		12 (8.05)	
Not exposed		111 (78.72)		119 (79.87)	
Age of starting smoking and smoking status > or <5 pack-years*					
Ever-smoker with ≤5 pack-years and age of starting above average (15.8 yr)	146	57 (39.04)	152	60 (39.47)	1.00
Ever-smoker with ≤5 pack-years and age of starting below average (15.8 yr)		40 (27.4)		41 (26.97)	
Never-smoker		49 (33.56)		51 (33.55)	
Early life events					
Pregnancy duration, wk*	144	33.82 ± 13.32	152	34.36 ± 13.41	0.079
Mother ever smoked regularly during your childhood?*	146	65 (44.52)	153	59 (38.56)	0.348
Education level*					
Low education	147	8 (5.44)	152	3 (1.97)	0.331
Medium education		72 (48.98)		71 (46.71)	
High education		66 (44.9)		77 (50.66)	
Respiratory diagnoses and symptoms					
Ever asthma diagnosed by doctor*	138	13 (9.42)	145	16 (11.03)	0.699
Asthma onset*					
Asthma and onset above the average (9.7 yr)	136	<10	143	<10	0.723
Asthma and onset below the average (9.7 yr)		<10		<10	
No asthma		125 (91.91)		129 (90.21)	
Have you ever suffered from wheezing?*	147	38 (25.85)	153	21 (13.73)	**0.009**
Do you at times have breathing problems?*	145	39 (26.9)	152	28 (18.42)	0.096
Do you usually cough in winter during daytime or at night?*	147	18 (12.24)	153	21 (13.73)	0.734
Respiratory medicines*	147	21 (14.29)	152	19 (12.5)	0.735
Allergies					
Known allergies*	147	65 (44.22)	153	71 (46.41)	0.914
Nasal allergy (including hay fever)*	147	42 (28.57)	153	42 (27.45)	0.898
Spirometry					
FEV_1% reference	147	74.71 ± 4.96	153	101.33 ± 8.13	**0**
FVC % reference	147	83.61 ± 8.76	153	103.64 ± 8.56	**0**
FEV_1/FVC, L	147	0.75 ± 0.07	153	0.81 ± 0.06	**0**
Analytics					
Leukocytes, 10^9/L*	147	6.15 ± 1.6	153	5.87 ± 1.51	0.099
Lymphocytes, 10^9/L	141	2.12 ± 0.61	150	2.04 ± 0.55	0.249
Neutrophil granulocytes, 10^9/L	141	3.24 ± 1.03	150	3.16 ± 1.12	0.351
Monocytes, 10^9/L	141	0.46 ± 0.12	150	0.45 ± 0.14	0.217
Eosinophil granulocytes, 10^9/L	141	0.19 ± 0.12	150	0.16 ± 0.12	**0.035**
Triglycerides, mmol/L*	147	1.11 ± 0.56	152	0.96 ± 0.51	**0.002**
Creatinine, μmol/L	147	71.29 ± 11.44	152	73.63 ± 10.76	**0.046**
HbA1c, %*	147	5.41 ± 0.35	153	5.35 ± 0.28	0.224
Hematocrit, v/v*	147	0.42 ± 0.03	153	0.42 ± 0.04	0.534
HDL cholesterol, mmol/L*	147	1.43 ± 0.35	152	1.48 ± 0.32	**0.047**
LDL cholesterol, mmol/L*	147	2.81 ± 0.76	152	2.75 ± 0.84	0.345
Cardiovascular					
Heart rate*	147	68.16 ± 12.91	153	66.28 ± 9.95	0.309
Systolic blood pressure, mm Hg*	147	120.64 ± 12.9	153	120.3 ± 10.41	0.964
Diastolic blood pressure, mm Hg*	147	69.86 ± 8.13	153	69.71 ± 6.31	0.714

Table 1. (*Continued*)

	$FEV_1 < LLN$		$FEV_1 \geq LLN$		
	N	**Mean ± SD or *n* (%)**	***N***	**Mean ± SD or *n* (%)**	***P* Value**
Nonrespiratory health problems					
Diabetes mellitus*	146	<10	153	0 (0)	0.238
Heart valve problems*	147	<10	153	<10	1.000
Rheumatoid arthritis (joint inflammation)*	147	<10	153	<10	1.000
Hypertension*	147	<10	153	<10	0.614
Biomarkers					
BNDF, pg/ml*	147	26.56 ± 17.91	153	27.62 ± 21.81	0.521
CCL18, pg/ml*	147	49.33 ± 44.07	153	45.92 ± 38.34	0.766
Collagen-1α, pg/ml*	147	10.86 ± 16.99	153	12.1 ± 20.99	0.157
CCL19, pg/ml*	147	0.05 ± 0.05	153	0.04 ± 0.04	**0.045**
CCL2, pg/ml*	147	0.27 ± 0.3	153	0.23 ± 0.3	0.219
IL-8, pg/ml*	147	0.59 ± 1.26	153	0.90 ± 1.93	0.223
Leptin, pg/ml*	147	17.41 ± 32.4	153	10.09 ± 20.95	**0.01**
Pentraxin 3, pg/ml*	147	0.62 ± 1.38	153	0.74 ± 1.32	0.528
sRAGE, pg/ml*	147	2.53 ± 1.72	153	2.79 ± 1.49	0.246
SP-D, pg/ml*	147	10.76 ± 8.25	153	10.70 ± 8.77	0.609
vWFA-2, pg/ml*	147	0.03 ± 0.05	153	0.03 ± 0.06	0.263
CC16, pg/ml*	147	13.51 ± 21.85	153	22.06 ± 25.62	**0.003**
Aging biomarkers					
Telomere length, R/S ratio	143	67.05 ± 42.04	152	70.1 ± 33.61	0.358
Mitochondrial DNA qPCR, 12s/RNAsa P	141	8.67 ± 3.65	151	8.53 ± 3.43	0.438

Definition of abbreviations: 12s/RNAsa P = Mitochondrial 12S ribosomal RNA gene and to nuclear-encoded RNAse P gene ratio of copies; BNDF = Brain-derived neurotrophic factor; CC16 = Club cell secretory protein 16; CCL = C-C Motif Chemokine Ligand; HDL = high-density lipoprotein; LDL = low-density lipoproteins; LLN = lower limit of normal; qPCR = quantitative PCR; R/S = relative telomere to single copy gene ratio; SP-D = Surfactant Protein D; sRAGE = Soluble Receptor for Advanced Glycation End Products; vWFA-2 = von Willebrand Factor 2.
Bold font indicates a *P* value < 0.05.
*Indicates that the variable was included in the step-wise selection for logistic regression (Figure 1).

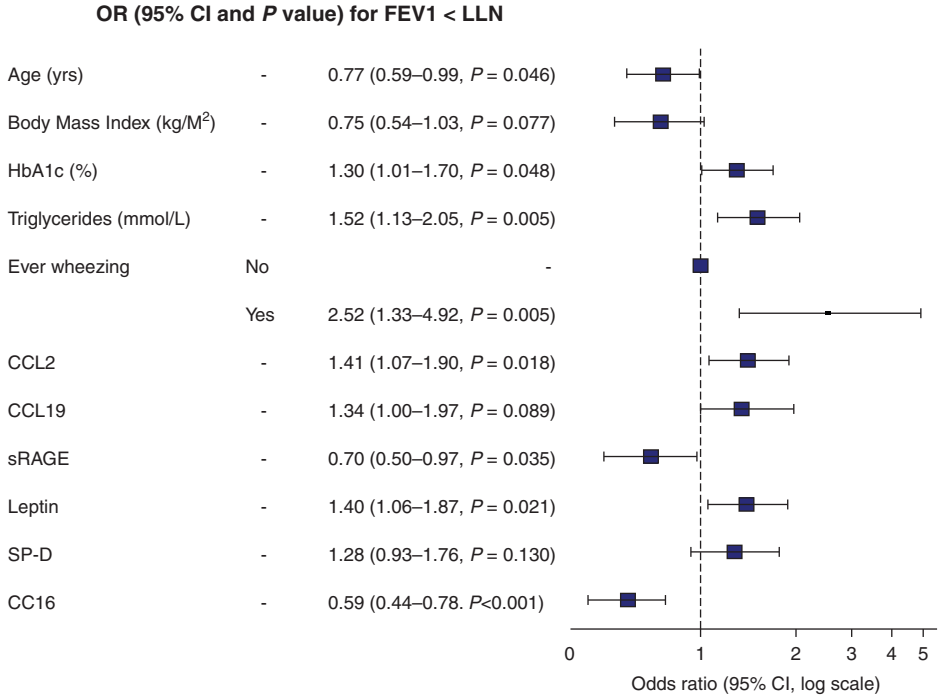

Figure 1. Forest plot showing factors independently associated with $FEV_1 <$ lower limit of normal (LLN) identified by the multivariate logistic regression in 299 individuals (152 $FEV_1 >$ LLN and 147 $FEV_1 <$ LLN). The C-index of the logistic regression was (0.722). The variables included in the model were the ones that minimized the AIC, which indicates a better goodness-of-fit. Odds ratio (OR) are per increase of 1 SD in the values of the log-scaled biochemical and biomarker measurements. For instance, the OR for CC16 (Club cell secretory protein 16) (0.59) indicates that for every 1 SD increase in CC16 levels, there is about a 41% decrease in the odds of having $FEV_1 <$ LLN. AIC = Akaike information criterion; CCL = C-C Motif Chemokine Ligand; CI = confidence interval; SP-D = Surfactant Protein D; sRAGE = soluble Receptor for Advanced Glycation End Products.

To explore if the biomarkers associated here with low peak lung function were also related to early lung function decline, we calculated FEV_1 changes during 5 years of follow-up in 70 of the 300 individuals in whom this information was available. In this admittedly small population, we observed that FEV_1 changed a median of −1.85 ml/yr (interquartile range [IQR], 63.8 ml/yr) in those with baseline $FEV_1 < LLN$ ($n = 32$) and −18.7 ml/yr (IQR 58.8 ml/yr) in those with baseline $FEV_1 > LLN$ ($n = 38$; $P = 0.02$), suggesting that low peak lung function is not associated with early lung function decline in the studied population.

CC16 is a homodimer protein with antiinflammatory properties secreted mostly by nonciliated bronchiolar club cells (10). Previous studies have reported lower circulating CC16 levels in relation to low lung function in childhood, smoking, increased airway inflammation, airflow limitation in the general population, accelerated FEV_1 decline, and asthma (10, 12, 13). In line with these reports, we observed that systemic CC16 levels were lower in individuals with $FEV_1 < LLN$, supporting that CC16 is a biomarker of abnormal lung development (14). This can be the consequence of early-life respiratory infections (11), but this information was not available in this cohort. CCL19 is a chemokine involved in cell trafficking that activates dendritic and B cells to produce proinflammatory cytokines (15). Increased levels of CCL19 have been described in smoking mice models of COPD, in the airway smooth muscle of patients with asthma (16), and in severe COPD related to B cell responses (17). Our observations here suggest that activation of dendritic and B cells in young individuals can drive an inflammatory response. Interestingly, the levels of CCL2, a monocyte homing cytokine, and those of surfactant protein D, also an innate immune response protein (6), were also associated with reduced FEV_1 levels in the multivariate analysis. This further supports a role of inflammation in this young population that goes beyond smoking according to our study design.

We observed that low peak FEV_1 in early adulthood was associated with biomarkers of extrapulmonary organ dysfunction, such as of the metabolic system (HbA1c) and leptin. This supports that low lung function in early adulthood is a marker of poor development of the lungs and also other organ systems, which may contribute to multimorbidity later in life (3, 4).

We did not find differences in telomere length and mitochondrial DNA copy number between groups, suggesting that abnormal aging does not play a significant role in young adults with low peak lung function. This is at variance with what has been reported in both old and young patients with severe COPD (7), albeit it may be too early in the disease course to observe these abnormalities.

In conclusion, we showed that low peak lung function in early adulthood is associated with some circulating biomarkers (CC16, CCL19, CCL2, SP-D, and sRAGE) previously associated with airflow limitation in older patients with COPD, as well as with markers of systemic organ dysfunction (HbA1c and Leptin), but not with abnormal aging. These observations are partly in line with the Dutch hypothesis (18), because some of these individuals present asthma features and are likely to develop COPD later in life, particularly if exposed to noxious stimuli. Also, these observations point toward still poorly known mechanisms linking abnormal lung and other systemic organ development. Understanding them better may open novel opportunities for prevention and early intervention with the long-term aim of promoting healthier aging. ■

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Critical Illness Myopathy Alters Diaphragm Neuromuscular Junction Protein and Gene Expression

To the Editor:

Mechanical ventilation (MV) is a lifesaving intervention for patients in respiratory failure. However, MV is associated with the development of critical illness–associated diaphragm weakness. This condition occurs because of a rapid loss of diaphragm muscle fiber contractility and atrophy and is a serious complication to weaning patients from the ventilator. Failure to wean prolongs time spent in the ICU, dramatically increasing healthcare costs and the risk of morbidity and mortality (1). Although clinical techniques exist to diagnose respiratory muscle dysfunction in critical care patients, there are currently no approved therapies to prevent diaphragm weakness in mechanically ventilated patients.

Critical illness–associated diaphragm weakness contributes to difficult weaning because of an inability of the diaphragm to support the load necessary for independent respiration. Failure to wean can be attributed to inactivity-induced wasting of the diaphragm, contractile weakness, and/or insufficient signaling from the central nervous system to the diaphragm (2, 3). Indeed, liberation from MV requires the resumption of diaphragm neuromuscular activity, which necessitates adequate signaling from the central nervous system to the respiratory muscles via signal transduction through the neuromuscular junction (NMJ). Limited evidence from preclinical models suggests that critical illness–induced diaphragm weakness may be associated with impaired postsynaptic membrane depolarization and altered postsynaptic protein expression (4). However, the contribution of neuromuscular dysfunction is currently unknown. This is the first study to show that prolonged MV results in modification of postsynaptic diaphragm NMJ proteins in patients.

Intraoperative biopsy specimens were obtained from the costal diaphragm of seven brain-dead organ donors (case subjects) and seven patients undergoing surgery for either benign lesions or stage 1 lung cancer (control subjects). Case subjects with diaphragm inactivity underwent MV for 18–69 hours. In control subjects, the combination of diaphragm inactivity and MV was limited to

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