

MATERIAL AND METHODS

During the baseline visit in 1985-86 (year 0), 5,115 black and white men and women were recruited into the CARDIA study. Of these, 3,950 participants were followed up in 1995-96 (year 10); 3,672 in 2000-2001 (year 15) and 3549 in 2005-2006 (year 20). Demographic characteristics, lifestyle habits (e.g., cigarette smoking), physical activity, and medical history were collected by self-report. The diagnosis of asthma was made if the subject was taking asthma medication (usually based on examination of medicine containers) or a self-reported doctor or nurse diagnosis of asthma that had been active in the past year or was “still active” at any of the study visits.

Spirometry at years 5 and 10 was performed using a Collins Survey 8-liter water sealed spirometer and an Eagle II Microprocessor (Warren E. Collins, Inc., Braintree, MA). At year 20, a dry rolling-seal OMI spirometer was used (Viasys Corp, Loma Linda, CA). A comparability study performed on 25 volunteers at the LDS Hospital (Salt Lake City, UT) demonstrated excellent consistency between the old and new machines; the average difference between the Collins Survey and OMI spirometer was 6 ml for FVC and 21 ml for FEV₁. Standard quality control and testing procedures¹⁻⁴ were followed at all examinations.

Overnight fasting blood samples were collected and processed within 90 minutes of blood collection and stored at -70°C. ICAM-1 levels were measured using serum samples diluted 1:400 fold and the ELISA assay was performed according to manufacturer's recommendation (R&D Systems; Cat No DY720). EDTA-plasma P-selectin levels were measured using an ELISA kit and plasma samples diluted 1:5 fold according to the manufacturer's recommendation (R&D systems, Cat No.BBC 6). The limit of sensitivity of the P-selectin and ICAM-1 assays was 125 pg/ml and 15 pg/ml respectively while the coefficient of variation was 9.4% for both assays.

RESULTS

Analysis of lung function and adhesion molecules among smokers and never smokers

Year 20 FEV₁ and FEV₁/FVC were significantly higher ($p \leq 0.01$) in never smokers as compared to smokers (current and ever smokers) (FVC: 3900 ml vs. 3858 ml ($p=0.53$); FEV₁: 3119 ml vs. 3035 ml; FEV₁/FVC: 79.37% vs. 77.61%). FVC was significantly lower in the highest vs. lowest ICAM-1 quartile in both smokers and never smokers (193 ml in smokers, p for trend = 0.003 and 163 ml in never smokers, p for trend = 0.003) (Table 1) as expected given that smoking induces oxidation and inflammation. The difference in FEV₁ from the lowest to highest ICAM-1 quartile in smokers was higher as compared to never smokers (168 ml in smokers ($p=0.002$) vs. 106 ml ($p=0.02$) in never smokers) but this difference was not statistically significant (p for the ICAM-1 and smoking interaction term >0.25 for both FVC and FEV₁) (Table 1). FEV₁/FVC was not associated with ICAM-1 levels in smokers or never smokers (Table 1). There were no significant interactions between ICAM-1 quartiles and smoking status in determining FVC, FEV₁ or FEV₁/FVC ($p > 0.70$). In addition, P-selectin levels were not associated with lung function in smokers and non smokers and the magnitude of difference in FVC, FEV₁, and FEV₁/FVC was similar in both subgroups (Table 1). There were no significant interactions between P-selectin quartiles and smoking status in determining FVC, FEV₁ or FEV₁/FVC ($p > 0.71$).

Analysis of lung function and endothelial markers among participants with and without asthma

Lung function values (FVC, FEV₁, and FEV₁/FVC) were higher ($p < 0.0001$) in participants without asthma as compared to participants with asthma (FVC: 4007 ml vs. 3619 ml;

FEV₁: 3156 ml vs. 2735 ml; FEV₁/FVC: 79.18% vs. 76.16%). The difference in FVC from highest to lowest ICAM-1 quartile was significant in both participants without asthma (154 ml, p=0.002) and participants with asthma (225 ml, p=0.05) (Table 2). FEV₁ was also significantly lower in the highest vs. lowest ICAM-1 quartiles among participants without asthma (103 ml, p for trend = 0.001) but was not significantly different among participants with asthma (182 ml, p for trend = 0.11). The greater estimated difference in those with asthma was as expected given that asthma represents an inflammatory state. However, there was no significant interaction between ICAM-1 quartiles and asthma status in determining FVC or FEV₁ (p for interaction > 0.25). Even though FEV₁/FVC was not significantly associated with ICAM-1 quartiles in either participants with or without asthma, FEV₁/FVC increased from lowest to highest ICAM-1 quartiles in participants without asthma as compared to a decrease in FEV₁/FVC across ICAM-1 quartiles among participants with asthma (p for ICAM-1 and asthma interaction = 0.03) indicating a relatively higher loss of FEV₁ as compared to FVC across ICAM-1 quartiles in participants with asthma as compared to those without asthma (Table 2). Since airway inflammation in participants with asthma involves both large and small airways, we hypothesize that the additional large-airway inflammation seen in those with asthma may contribute to the relatively higher FEV₁ loss across ICAM-1 quartiles. FVC, FEV₁ and FEV₁/FVC were not associated with P-selectin concentrations both in participants with and without asthma.

There were no significant interactions between P-selectin quartiles and asthma status in determining FVC, FEV₁ or FEV₁/FVC (p>0.13).

Table 1: Year 15 ICAM-1 and P-selectin concentrations and year 20 lung function (absolute values of FVC, FEV₁ and FEV₁/FVC) among non smokers and ever smokers at year 20.

	YEAR 15 ICAM-1 CONCENTRATIONS		Year 15 P-selectin	YEAR 15 P-SELECTIN CONCENTRATIONS	
	NON SMOKERS (n=1523)	SMOKERS (n = 932)		NON SMOKERS (n=1523)	SMOKERS (n = 932)
Year 15 ICAM-1	FVC (ml)	FVC (ml)	Year 15 P-selectin	FVC (ml)	FVC (ml)
Quartile 1 (≤125.47 ng/ml)	4004	4050	Quartile 1 (≤ 29.47 ng/ml)	3992	3982
Quartile 2 (125.48 ng/ml- 145.20 ng/ml)	3982	3967	Quartile 2 (29.48 ng/ml- 35.60 ng/ml)	3967	3925
Quartile 3 (145-21 ng/ml- 171.08 ng/ml)	3940	3918	Quartile 3 (36.61 ng/ml- 42.49 ng/ml)	3941	3971
Quartile 4 (≥ 171.09 ng/ml)	3841	3856	Quartile 4 (≥ 42.50 ng/ml)	3902	3860
Q1-Q4	163 (73-253)	193 (91-296)	Q1-Q4	89 (7-171)	122 (19-224)
	p for trend=0.003	p for trend=0.003		p for trend=0.18	p for trend=0.06
Year 15 ICAM	FEV ₁ (ml)	FEV ₁ (ml)	Year 15 P-selectin	FEV ₁ (ml)	FEV ₁ (ml)
Quartile 1 (≤125.47 ng/ml)	3139	3135	Quartile 1 (≤ 29.47 ng/ml)	3149	3083
Quartile 2 (125.48 ng/ml- 145.20 ng/ml)	3140	3082	Quartile 2 (29.48 ng/ml- 35.60 ng/ml)	3145	3035
Quartile 3 (145-21 ng/ml- 171.08 ng/ml)	3133	3033	Quartile 3 (36.61 ng/ml- 42.49 ng/ml)	3097	3069
Quartile 4 (≥ 171.09 ng/ml)	3033	2967	Quartile 4 (≥ 42.50 ng/ml)	3078	2980
Q1-Q4	106 (31-181)	168 (78-257)	Q1-Q4	71 (3-139)	103 (14-192)
	p for trend=0.02	p for trend=0.002		p for trend=0.29	p for trend=0.51
Year 15 ICAM	FEV ₁ /FVC (%)	FEV ₁ /FVC (%)	Year 15 P-selectin	FEV ₁ /FVC (%)	FEV ₁ /FVC (%)
Quartile 1 (≤125.47 ng/ml)	78.92	77.87	Quartile 1 (≤ 29.47 ng/ml)	79.25	77.83
Quartile 2 (125.48 ng/ml- 145.20 ng/ml)	79.13	77.98	Quartile 2 (29.48 ng/ml- 35.60 ng/ml)	79.75	77.83
Quartile 3 (145-21 ng/ml- 171.08 ng/ml)	79.90	77.53	Quartile 3 (36.61 ng/ml- 42.49 ng/ml)	79.13	77.49

Quartile 4 (≥ 171.09 ng/ml)	79.68	77.27	Quartile 4 (≥ 42.50 ng/ml)	79.32	77.30
Q1-Q4	-0.76 (-1.70 – 0.18)	0.60 (-0.69 – 1.89)	Q1-Q4	-0.08 (-0.93 – 0.77)	0.53 (-0.75 – 1.81)
	p for trend=0.08	p for trend=0.42		p for trend=0.45	p for trend=0.80

Tabulated values are estimates from models adjusting for race, sex, age, amount of physical activity, alcohol intake and BMI, all at year 15, asthma status at year 20, and height, height² measured at year 0.

Table 2: Year 15 ICAM-1, P-selectin concentrations and Year 20 lung function (FVC, FEV₁ and FEV₁/FVC) in participants with and without asthma at year 20

	YEAR 15 ICAM CONCENTRATIONS		Year 15 P-selectin	YEAR 15 P-SELECTIN CONCENTRATIONS	
	NON ASTHMATICS (n= 2043)	ASTHMATICS (PREVALENT+INCIDENT) (n=393)		NON ASTHMATICS (n=2043)	ASTHMATICS (PREVALENT+INCIDENT) (n=393)
Year 15 ICAM	FVC (ml)	FVC (ml)	Quartile 1 (≤ 29.47 ng/ml)	FVC (ml)	FVC (ml)
Quartile 1 (≤125.47 ng/ml)	4064	3762	Quartile 2 (29.48 ng/ml-35.60 ng/ml)	4050	3616
Quartile 2 (125.48 ng/ml-145.20 ng/ml)	4041	3651	Quartile 3 (36.61 ng/ml-42.49 ng/ml)	4003	3682
Quartile 3 (145-21 ng/ml-171.08 ng/ml)	3997	3566	Quartile 4 (≥ 42.50 ng/ml)	4011	3647
Quartile 4 (≥ 171.09 ng/ml)	3910	3536	Q1-Q4	3957	3505
Q1-Q4	154 (81-228)	225 (57-394)		93 (24-162)	111 (-58 - 280)
	p for trend=0.0002	p for trend=0.05		p for trend=0.07	p for trend=0.18
Year 15 ICAM	FEV ₁ (ml)	FEV ₁ (ml)	Year 15 P-selectin	FEV ₁ (ml)	FEV ₁ (ml)
Quartile 1 (≤125.47 ng/ml)	3182	2854	Quartile 1 (≤ 29.47 ng/ml)	3189	2743
Quartile 2 (125.48 ng/ml-145.20 ng/ml)	3184	2755	Quartile 2 (29.48 ng/ml-35.60 ng/ml)	3162	2792
Quartile 3 (145-21 ng/ml-171.08 ng/ml)	3173	2691	Quartile 3 (36.61 ng/ml-42.49 ng/ml)	3158	2744
Quartile 4 (≥ 171.09 ng/ml)	3079	2671	Quartile 4 (≥ 42.50 ng/ml)	3115	2645
Q1-Q4	103 (42-164)	182 (26-339)	Q1-Q4	73 (16-130)	98 (-59-254)
	p for trend=0.001	p for trend=0.11		p for trend=0.09	p for trend=0.31
Year 15 ICAM	FEV ₁ /FVC (%)	FEV ₁ /FVC (%)	Year 15 P-selectin	FEV ₁ /FVC (%)	FEV ₁ /FVC (%)
Quartile 1 (≤125.47 ng/ml)	78.75	76.67	Quartile 1 (≤ 29.47 ng/ml)	79.06	76.60
Quartile 2	79.04	75.99	Quartile 2	79.41	76.67

(125.48 ng/ml- 145.20 ng/ml)			(29.48 ng/ml-35.60 ng/ml)		
Quartile 3 (145-21 ng/ml- 171.08 ng/ml)	79.68	76.03	Quartile 3 (36.61 ng/ml-42.49 ng/ml)	79.20	75.67
Quartile 4 (≥ 171.09 ng/ml)	79.33	76.08	Quartile 4 (≥ 42.50 ng/ml)	79.11	75.86
Q1-Q4	-0.57 (-1.33 – 0.18)	0.59 (-1.97 – 3.15)	Q1-Q4	-0.04(-0.75 – 0.66)	0.74 (-1.81 – 3.29)
	p for trend=0.07	p for trend=0.95		p for trend=0.76	p for trend=0.79

Tabulated values are estimates from models adjusting for race, sex, age, amount of physical activity, alcohol intake and BMI, all at year 15, smoking status at year 20, and height, height² measured at year 0.

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