Ozone and Health: Clinical Studies

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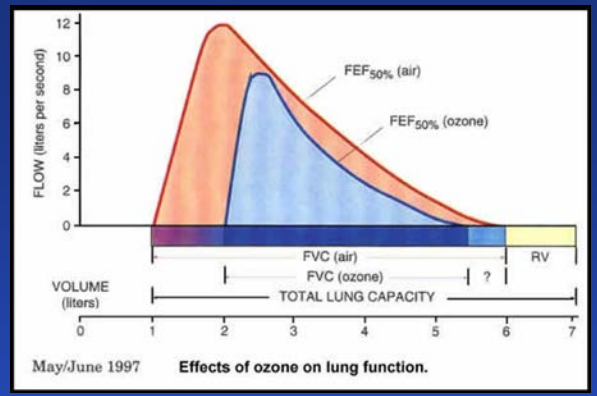
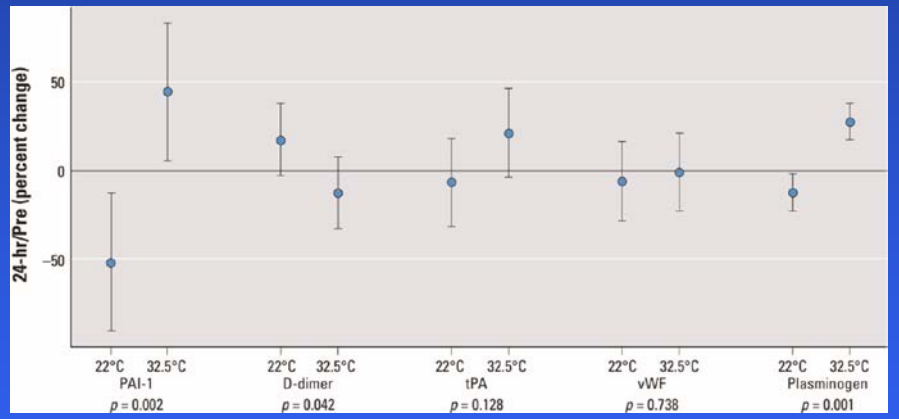
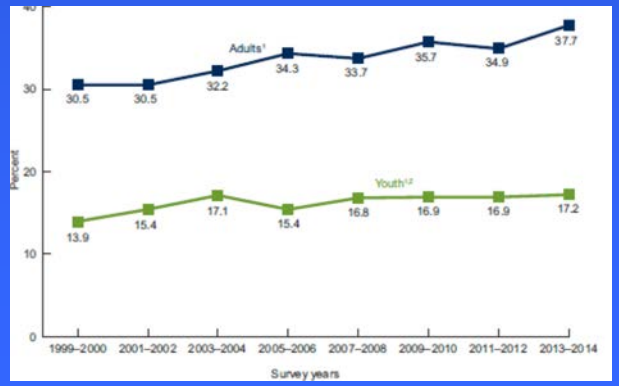
QUESTIONS

- **What do we know about respiratory effects of ozone?**
- **Are there acute cardiovascular effects of ozone?**
- **The obesity epidemic: ozone susceptibility?**
- **What's new since last ozone Integrated Science Assessment (ISA)?**



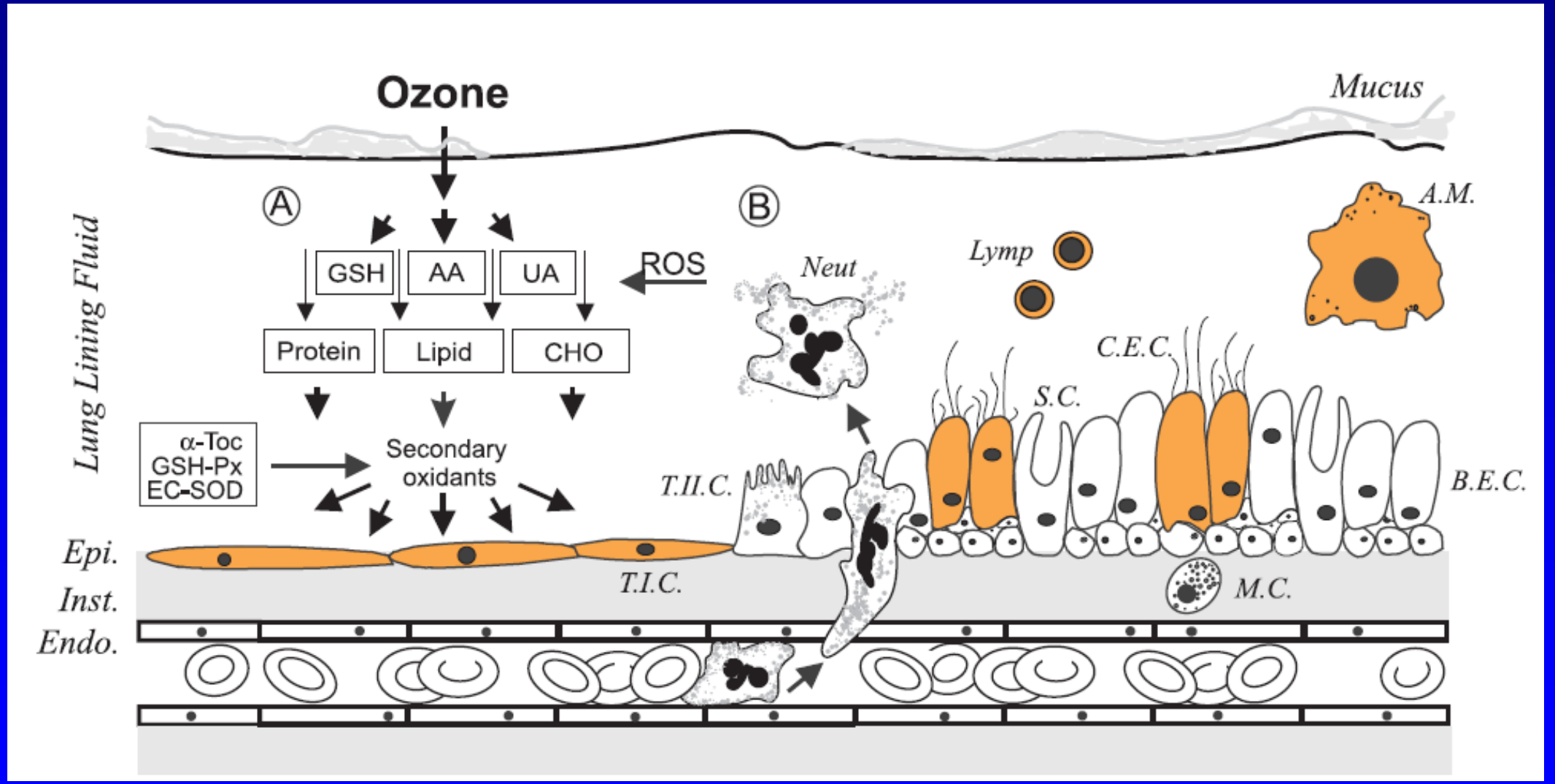




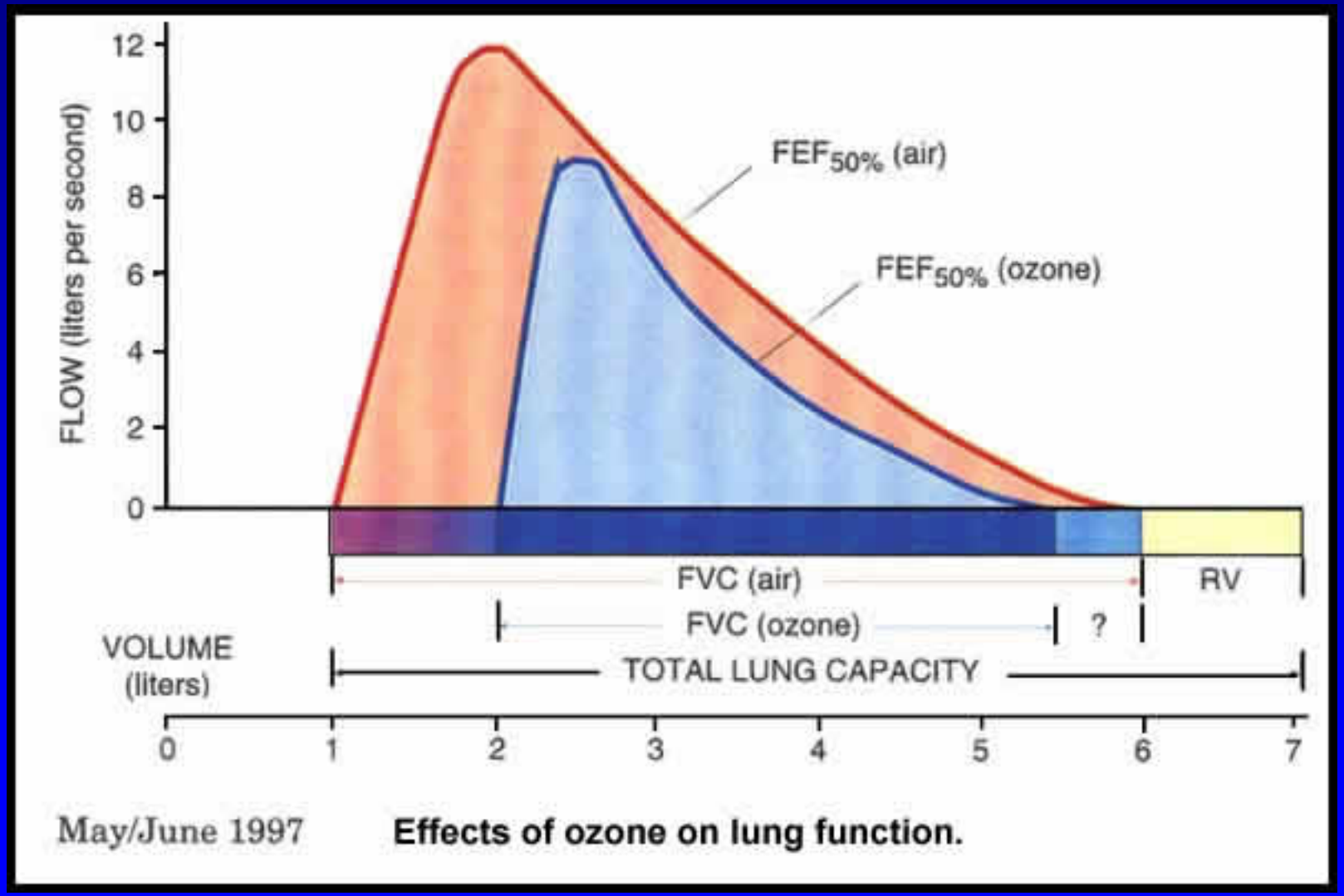
What do we know about respiratory effects of ozone?

OZONE AND THE AIRWAY

Mudway & Kelly, Molecular Aspects of Medicine 2000

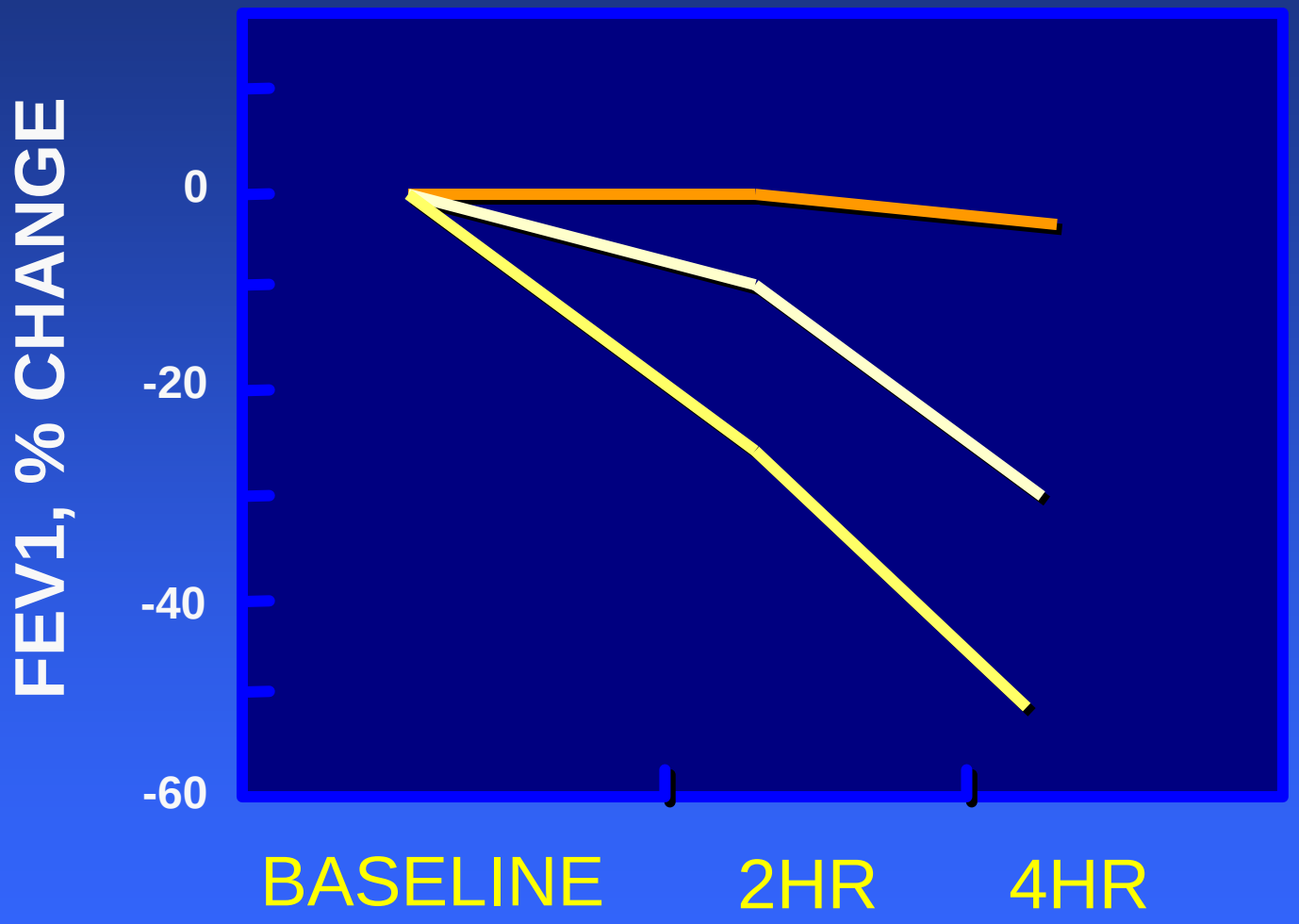


WHAT OZONE DOES TO THE FORCED VITAL CAPACITY



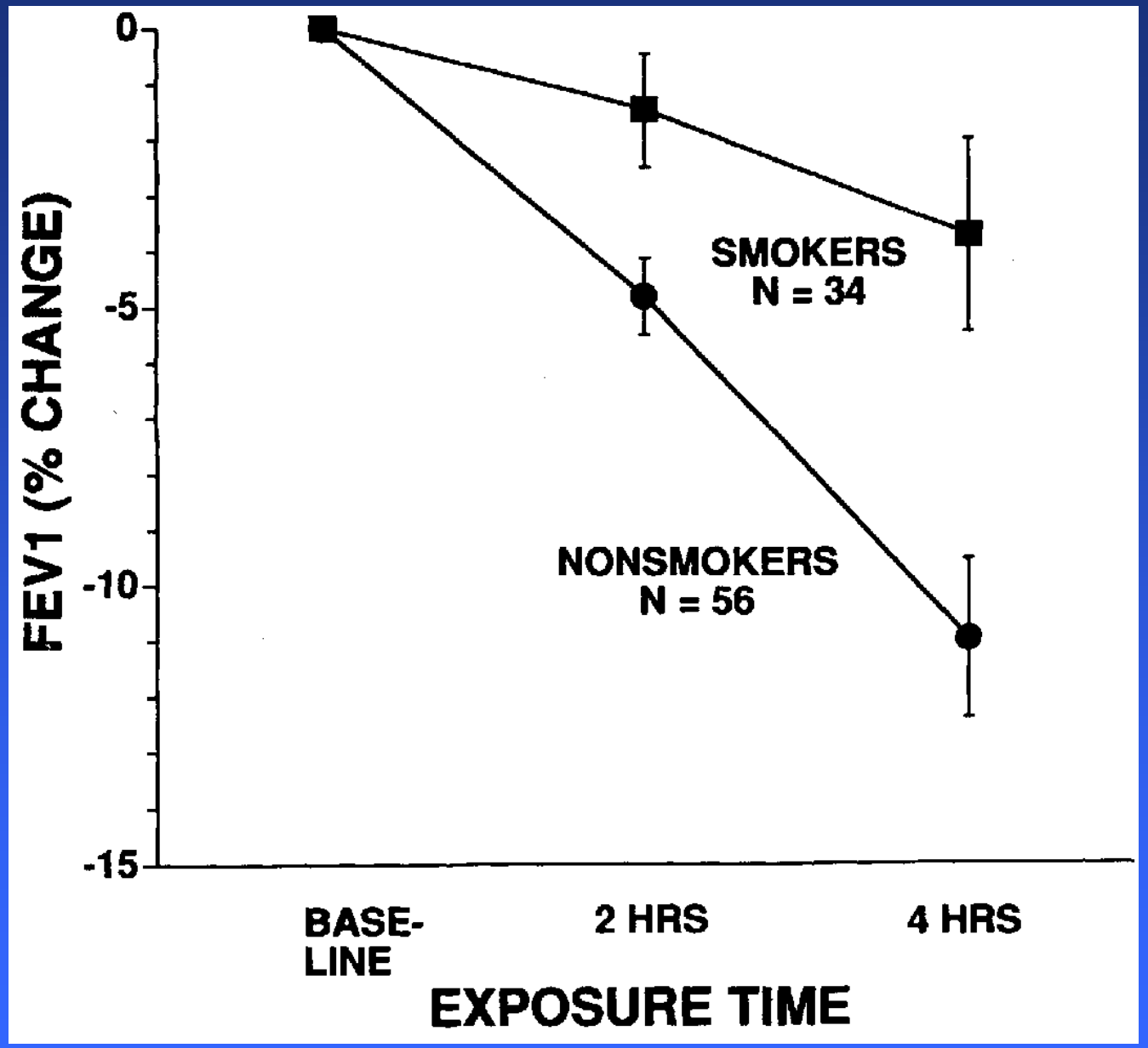
FEF = forced expiratory flow FVC = forced vital capacity RV = residual volume

Variability of Ozone Response



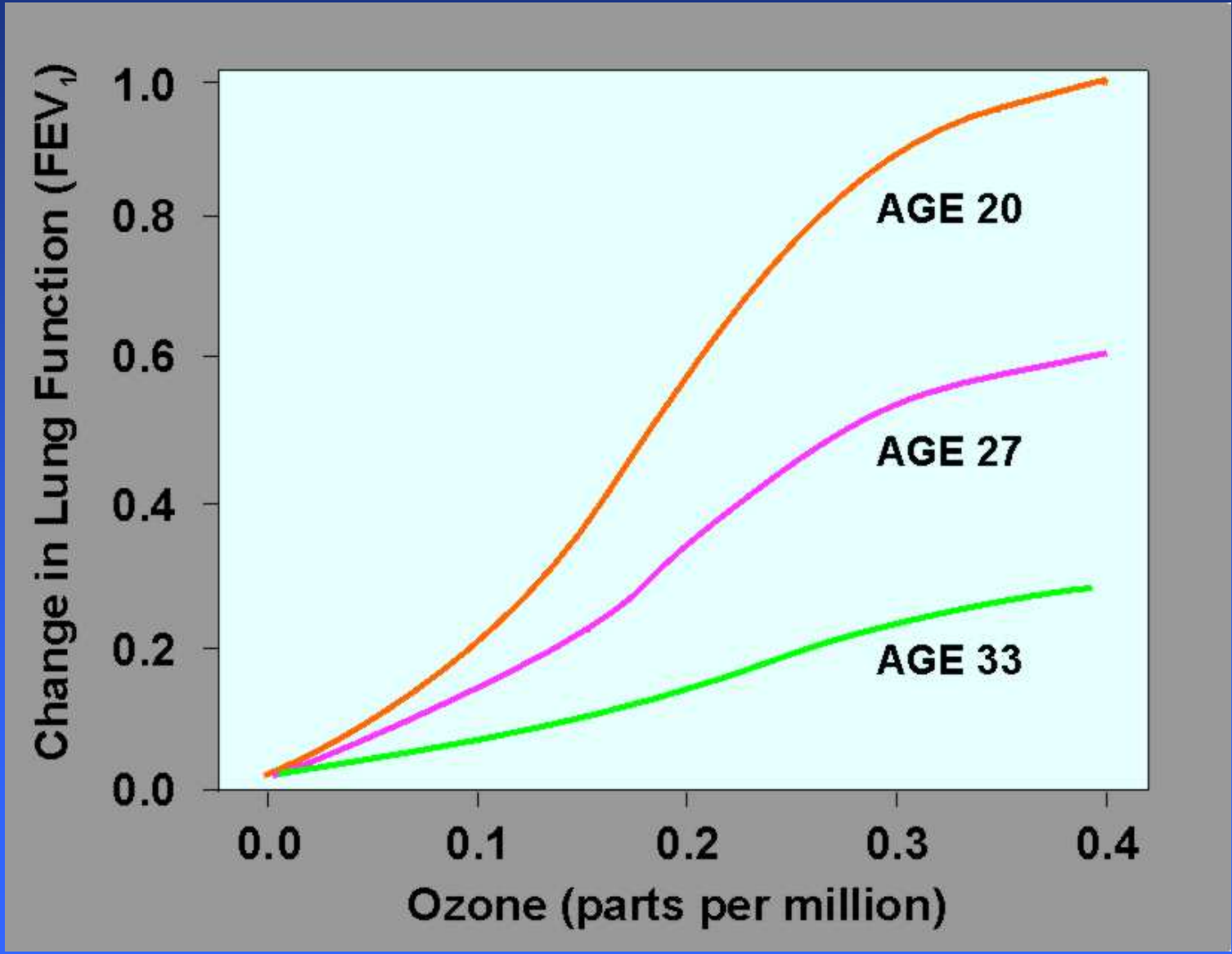
220 ppb 4 hours with exercise: Smokers are less responsive to Ozone

Frampton et al., AJRCCM 1997



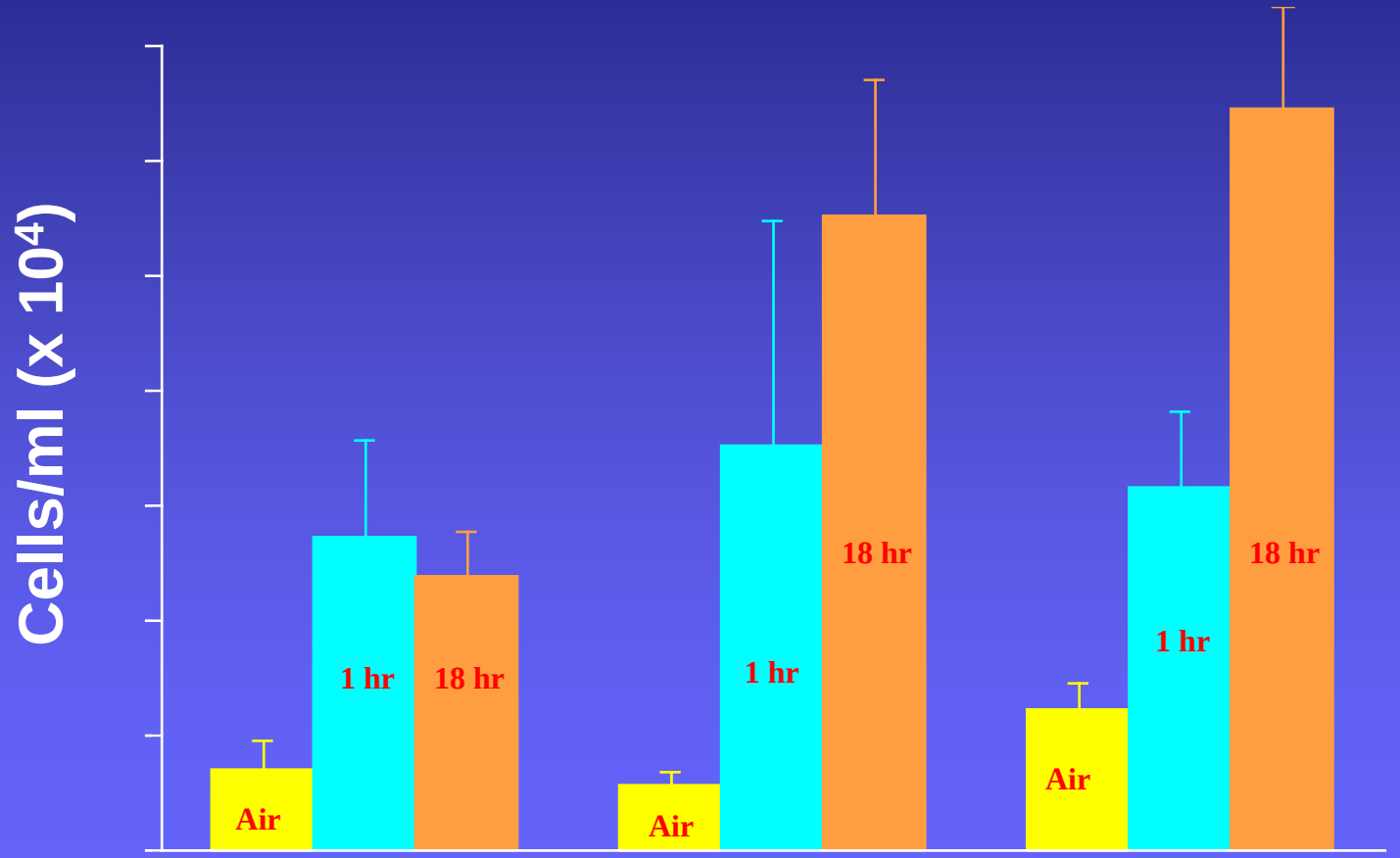
AJRCCM = American Journal of Respiratory and Critical Care Medicine

Age and Lung Function Effects of Ozone



PMN in Bronchial Lavage

220 ppb 4 hours **Torres et al., AJRCCM 1997**



PMN = polymorphonuclear neutrophils

Are there acute cardiovascular effects of ozone?

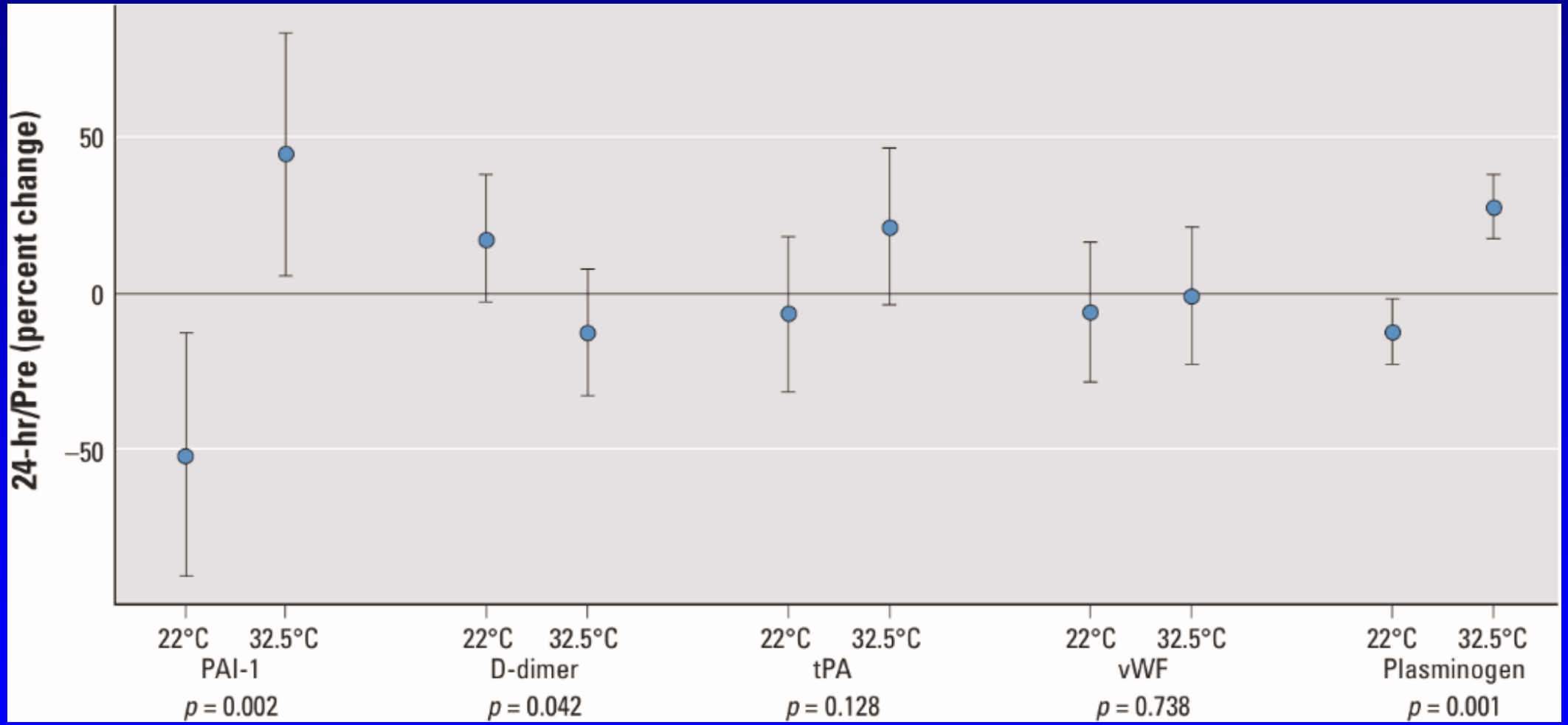
Human Clinical Studies of Ozone Cardiovascular Effects

Tank et al., PLoS One, 2011	14 ozone inflammation-responsive subjects, 250 ppb 3 hrs	No Δ BP, HR, HRV, cardiac output, PAI-1, muscle sympathetic activity
Devlin et al., Circulation, 2012	23 subjects, 300 ppb 2 hrs	↓ HRV (HF only), ↑IL-8 & CRP, ↓PAI-1 (fibrinolysis)
Barath et al., Toxicol Sci, 2013	36 men, 300 ppb 75 min	↑Vasodilation. No Δ BP, HR, HRV, fibrinolysis
Arjomandi et al., Am J Physiol, 2015	26 subjects (10 mild asthma), 100 & 200 ppb 4 hrs	↑CRP, ↓HRV (HF). No change PAI-1.
Frampton et al., Inhal Toxicol, 2015	24 subjects (12 GSTM1 null), 100 and 200 ppb 3 hrs	↓BP. No Δ HR, periph. art. tonometry, arterial and venous nitrite, cardiac output, platelet activation, microparticles. HRV not measured.

BP = blood pressure; CRP = C-reactive protein; GSTM1 = glutathione S-transferase mu 1; HF = high frequency; HR = heart rate; HRV = heart rate variability; IL-8 = interleukin 8; PAI-1 = plasminogen activator inhibitor type 1; ppb = parts per billion

OZONE, BLOOD CLOTTING, AND TEMPERATURE

300 ppb, 2 hours **Kahle et al., Environ Health Perspect 2015**



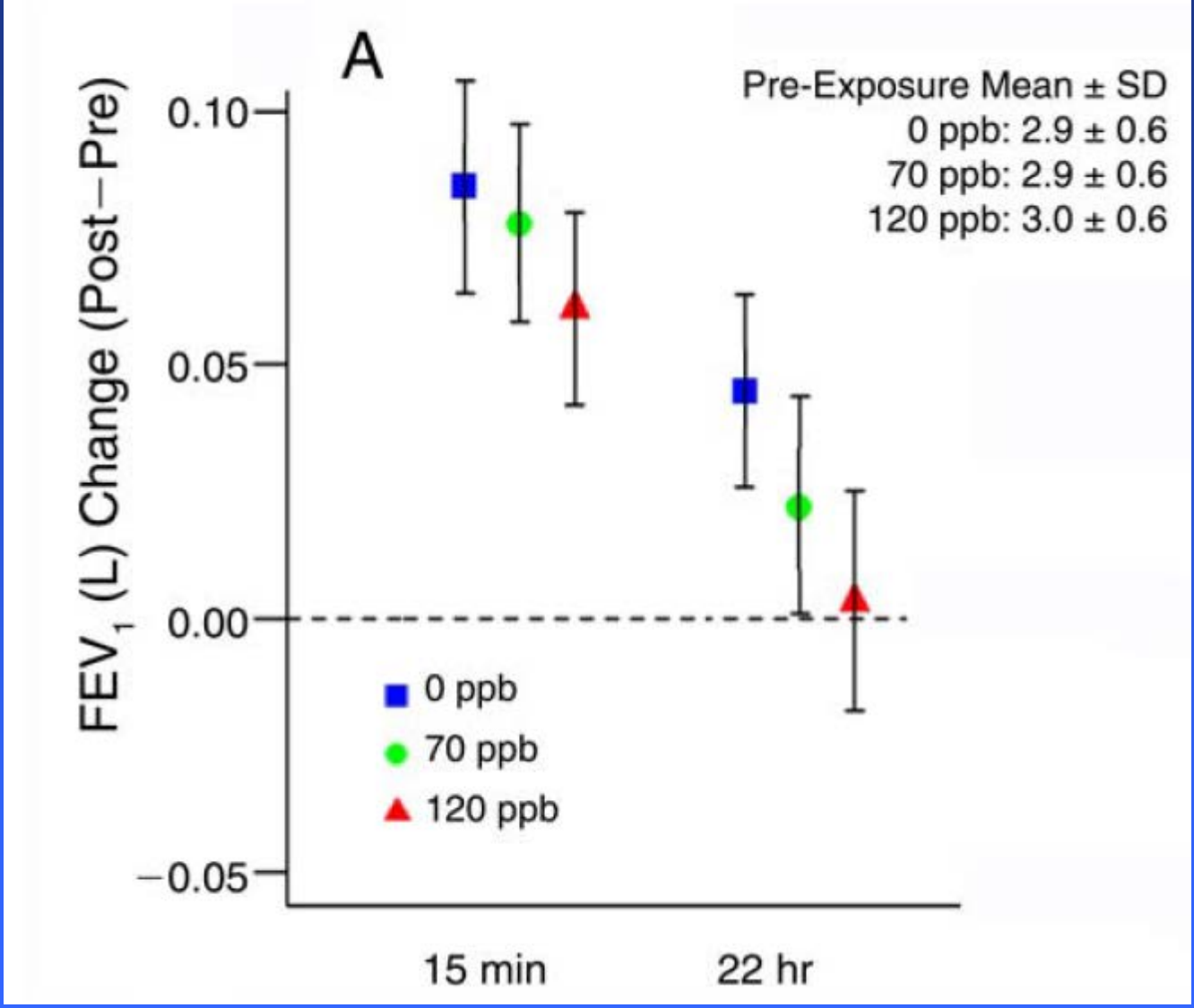
D-dimer = a fibrin degradation product; PAI-1 = plasminogen activator inhibitor type 1; tPA = tissue plasminogen activator; vWF = von Willebrand Factor

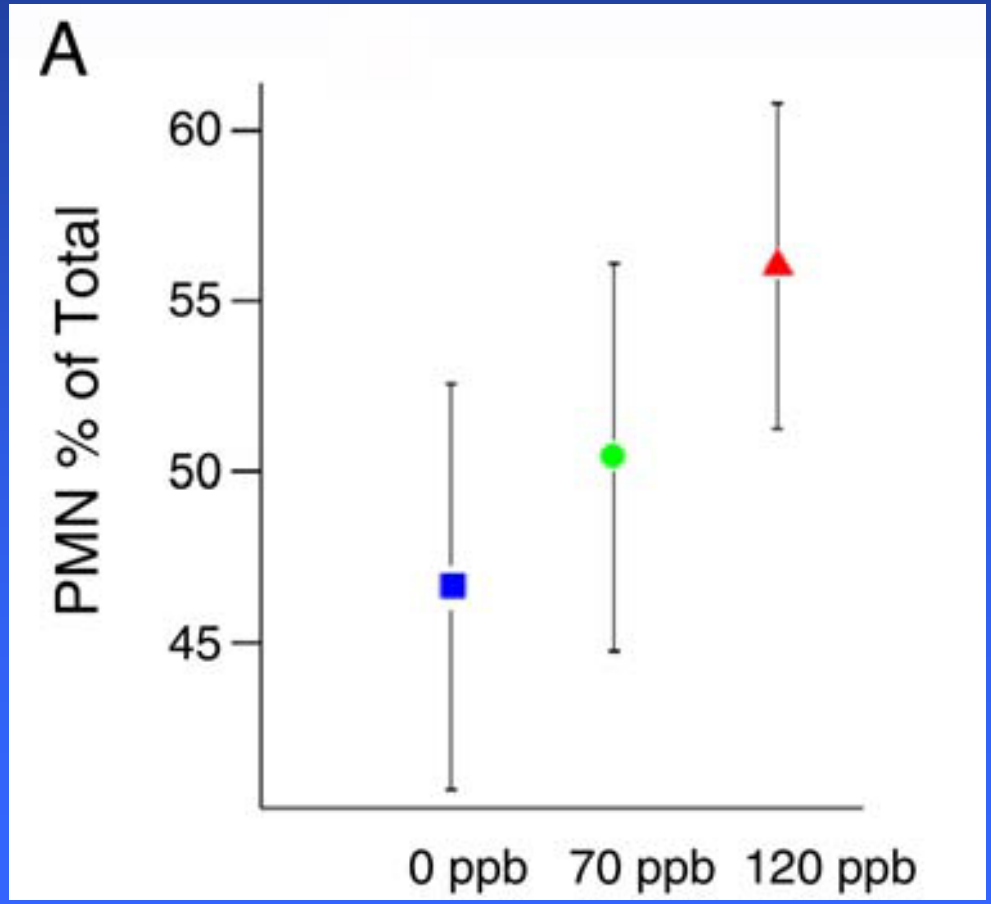
Multicenter Ozone Study of oldEr Subjects (MOSES)

- UCSF, UNC, URMC. Identical protocols. Central labs and data management.
- 87 healthy nonsmokers 55 to 70 years of age.
- 0, 70, 120 ppb ozone, intermittent moderate exercise.
- HRV, repolarization, ST segment, vascular function, platelet function, coagulation, oxidative stress, systemic inflammation, respiratory outcomes.
- GSTM1 genotyping.

UCSF = University of California–San Francisco; UNC = University of North Carolina–Chapel Hill; URMC = University of Rochester Medical Center
HRV = heart rate variability; GSTM1 = glutathione S-transferase mu 1

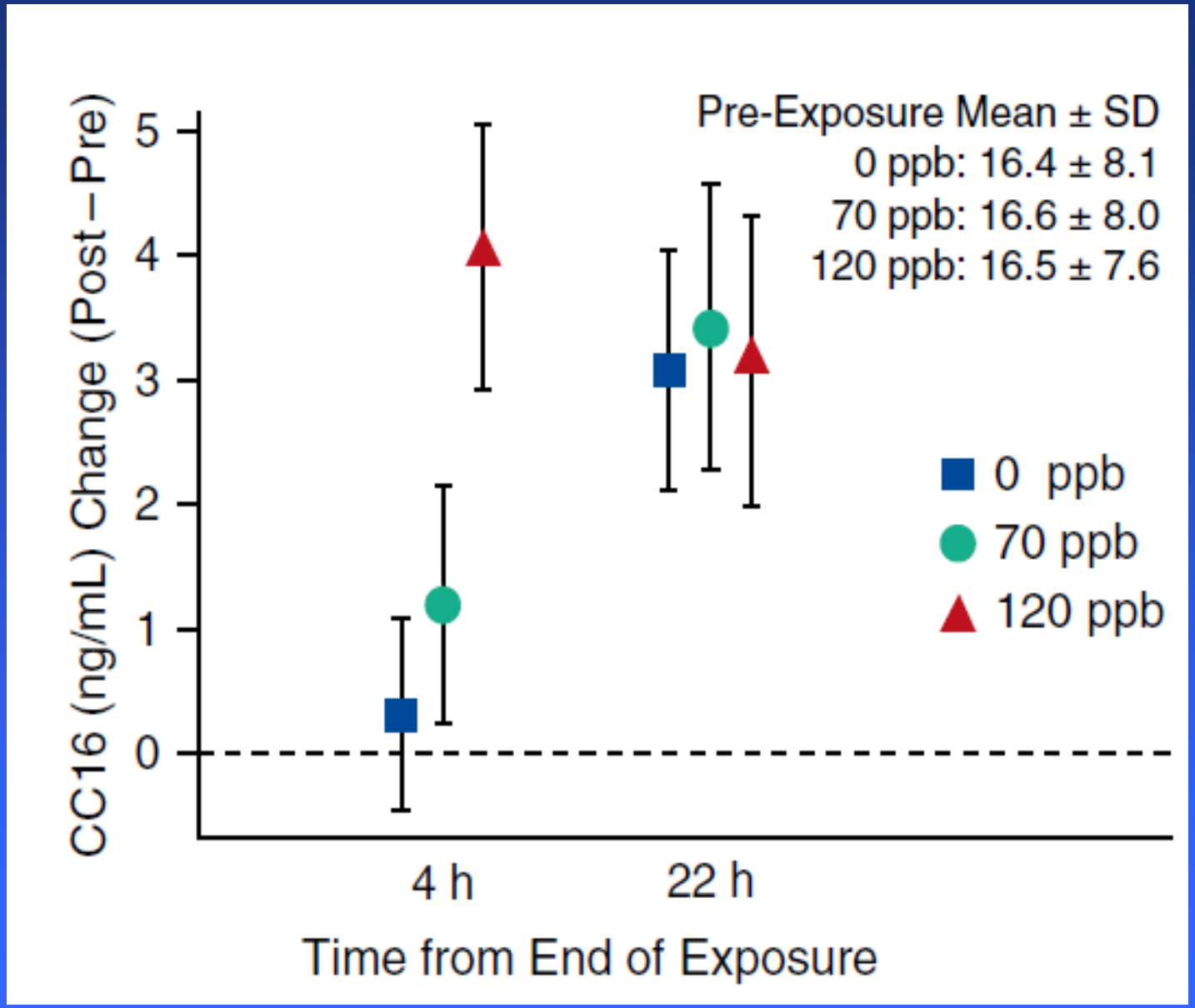
MOSES: Lung function and airway inflammation



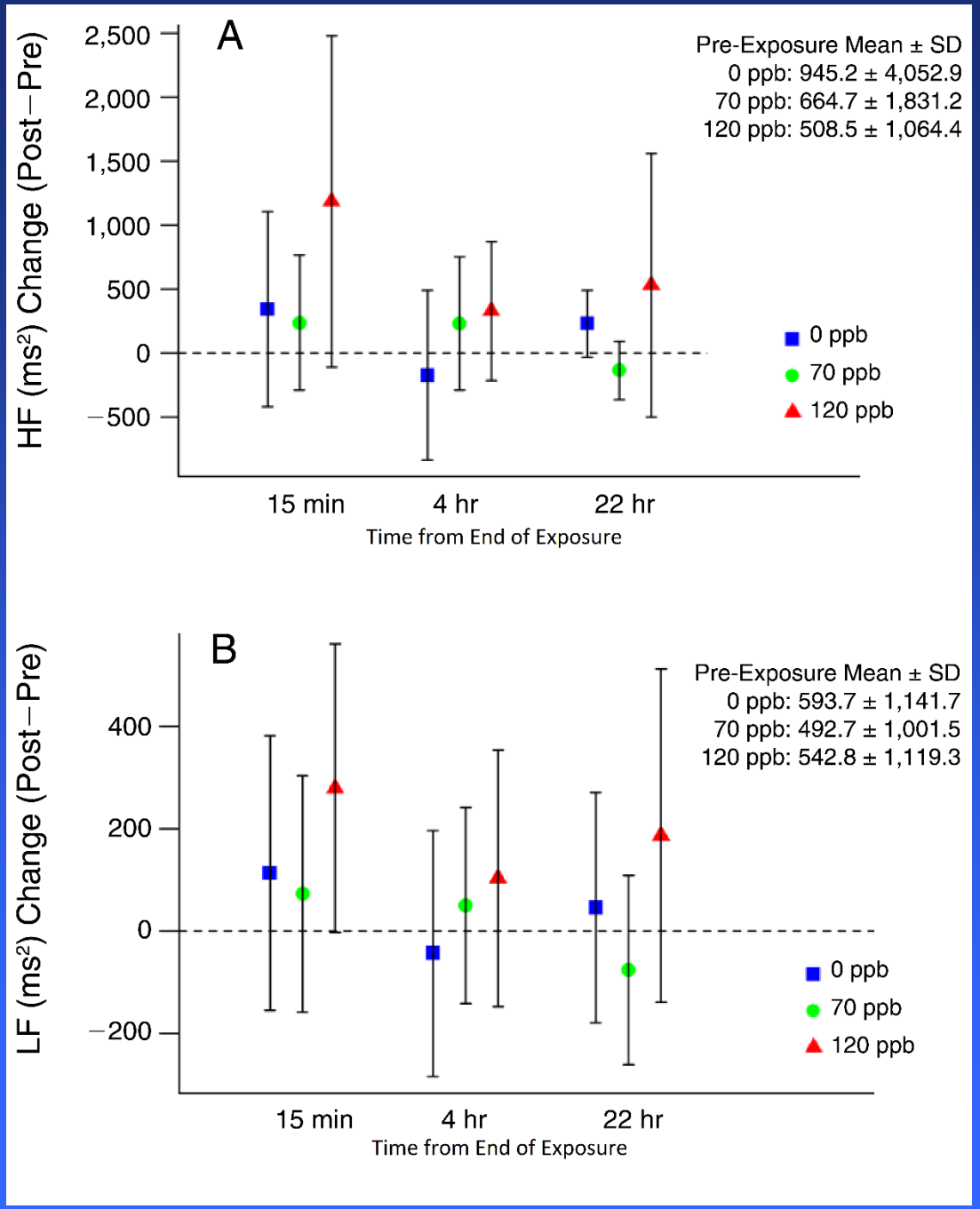


MOSES:

Evidence for lung injury (Club Cell 16)



MOSES: What about frequency-domain HRV?



LF = low frequency; HF = high frequency

MOSES Bottom Line:

- Subtle but clear respiratory effects.
- Not completely resolved 22 hours after exposure.
- No convincing evidence for cardiac or vascular effects.
- No interactions with GSTM1 genotype.

Could subjects' exposures to ambient ozone or other pollutants affect results of MOSES?

MOSES 2: Impacts of Personal and Ambient Pollutant Concentrations

- Personal ozone and NO_2 monitoring 72 hours before.
- Ambient pollutant concentrations up to 96 hours before.
- 3 Aims:
  1. Pollutant effects on pre-exposure biomarkers.
  2. Pollutant effects on pre to post change, independent of ozone.
  3. Pollutant modification of biomarker responses to controlled ozone.

Ambient Ozone Concentrations

Site	Lag Hrs	N	Mean	SD	Min	5th	25th	50th	75th	95th	Max
UCSF	0-23	73	23.1	8.9	4.4	8.9	17.3	23.3	28.6	37.6	44.9
	0-71	73	23.2	7.8	7.1	8.4	18.5	23.9	27.5	37.0	42.1
UNC	0-23	70	26.6	10.2	0	12.3	19.6	26.1	35.0	42.7	45.9
	0-71	70	28.2	9.3	0	14.3	21.9	28.6	36.0	41.2	45.7
URMC	0-23	92	27.0	9.1	10.6	13.4	20.7	26.0	32.9	43.5	52.4
	0-71	92	26.6	7.4	9.7	15.3	21.1	26.2	31.3	38.4	45.8

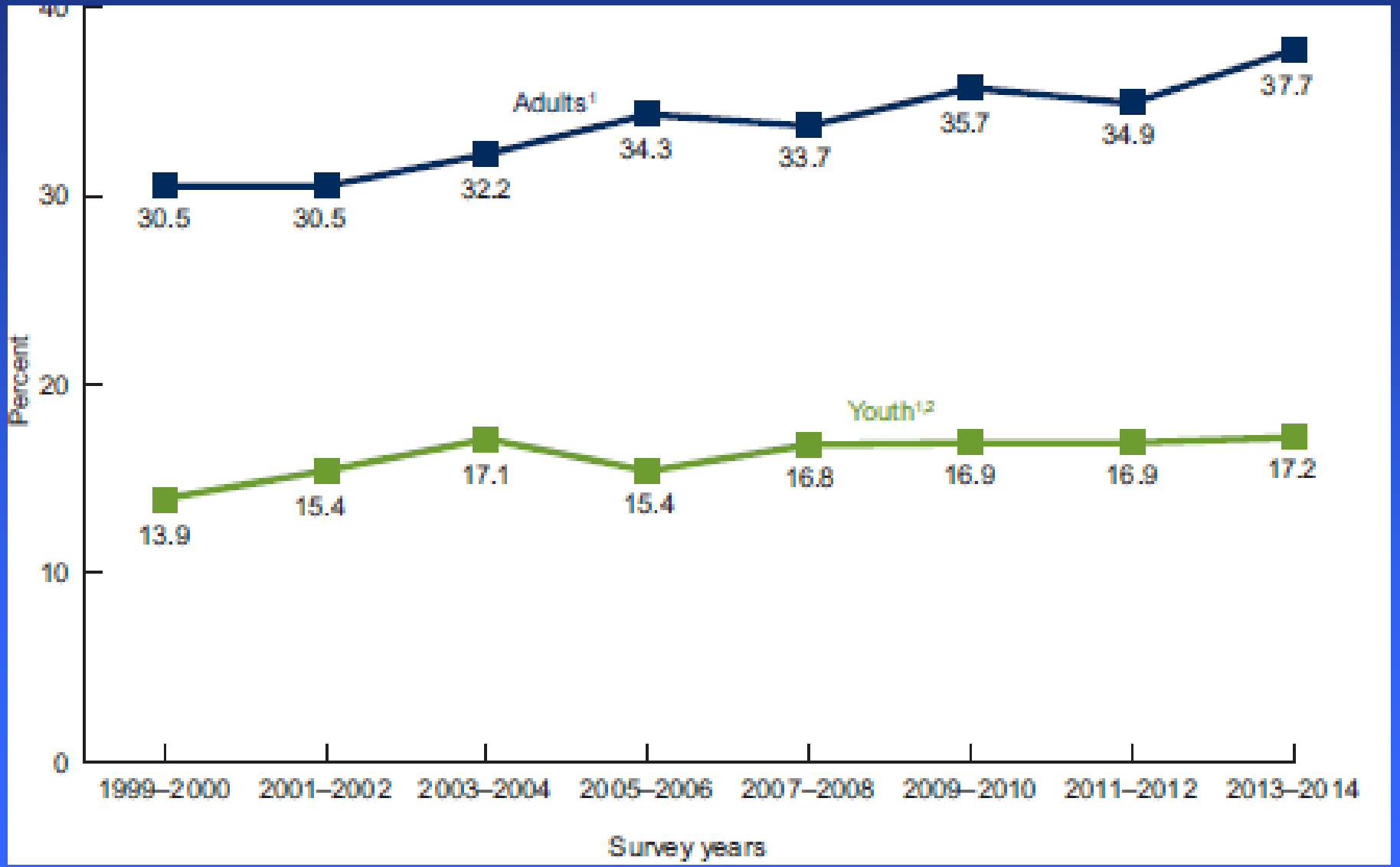
MOSES 2 Conclusions

- Ambient ozone reduced pre-exposure heart rate variability (HRV).
- Ambient $PM_{2.5}$, CO, NO_2, but not ozone, reduced forced expiratory volume in 1 second (FEV_1); recovers during exposure session.
- Ambient $PM_{2.5}$, CO, NO_2, but not ozone, increased lung function effect of experimental ozone.
- No evidence that prior pollutant exposures affected MOSES cardiovascular results.

The obesity epidemic: ozone susceptibility?

Obesity Prevalence Still Increasing

CDC 2015



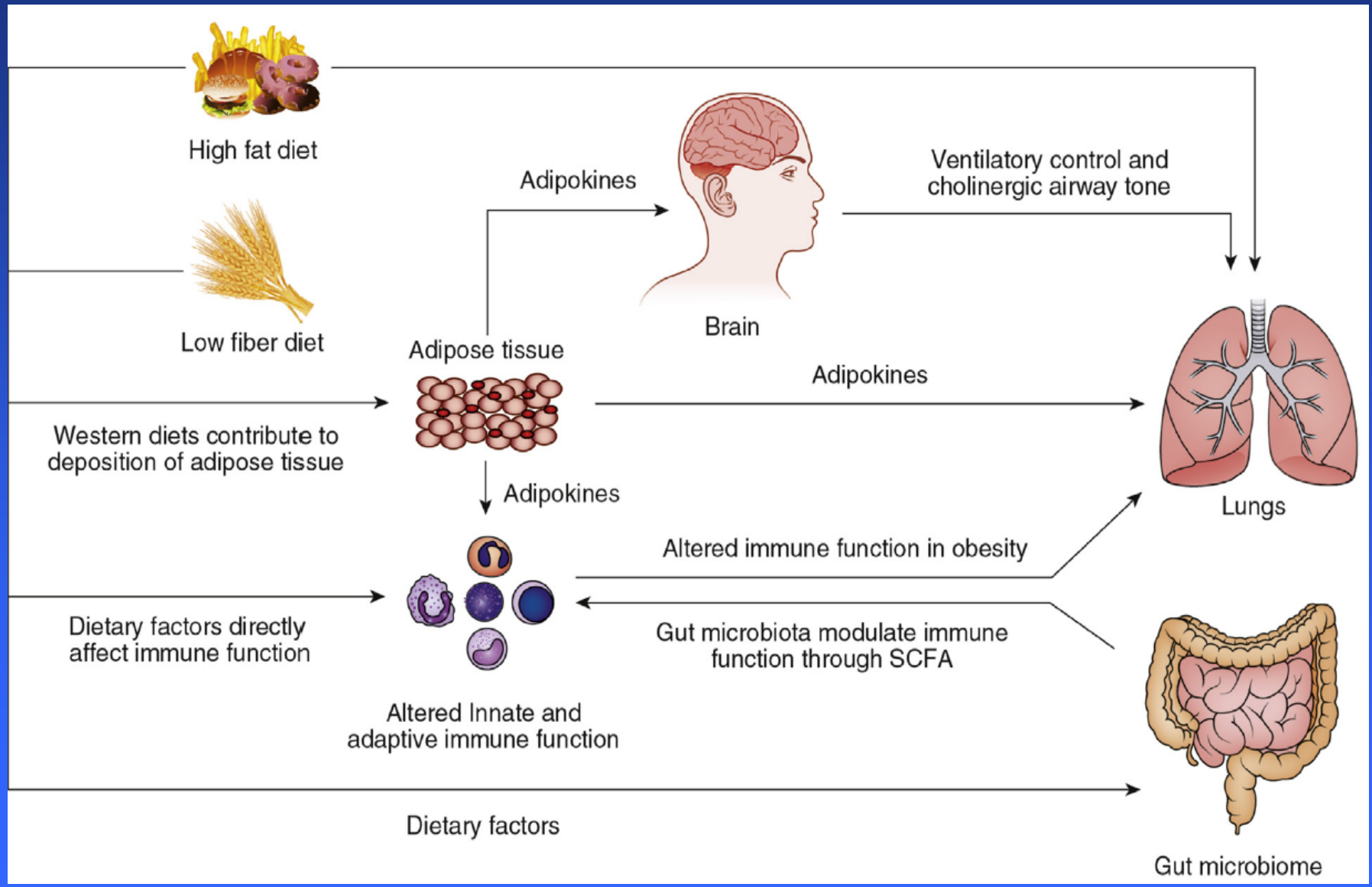
CDC = Centers for Disease Control and Prevention

Obesity and the Lung

- Lung restriction
- Increased work of breathing
- Increased oxygen demand
- Increased ventilation ⟶ increased ozone dose
- Increased systemic inflammation
- Altered gut microbiome

Obesity and the Lung

Peters et al., Chest 2018



Obesity & Ozone

- Increased lung function decrements in obese.
- Unclear whether gender difference.
- Obesity increases ozone effects on airway inflammation and responsiveness in mouse models—Stephanie Shore.
- Not clear in humans.

OBESITY AND RESPONSIVENESS TO OZONE

n=20 each group 400 ppb 2 hour Bennett et al. PloS One, 2016

Table 3. Mean (SD) decrements in lung function variables (delta % fall) expressed as ((Pre-Post Ozone)/Pre Ozone)–(Pre-Post Air)/Pre Air)) X 100.

	FVC	FEV1	IC	sGaw
Obese	12.5 (7.5)	15.9 (8.6)	16.7 (14.2)	12.6 (26.2)
Normal Wt	8.0 (5.8)	11.7 (7.1)	10.2 (13.2)	12.4 (21.0)
P	< 0.05	0.11	0.12	NS

Table 6. Sputum PMNs (concentration and %of recovered cells) and Sputum IL-6 concentration (pg/ml).

	Concentration cells/mg median (25th, 75th %ile)	% of total cells mean (SD)	IL-6 (pg/ml) median (25th, 75th %ile)
Obese Post Ozone	194.5 (25, 390.5)*	48 (28)*	13.1 (3.0, 24.4)
Obese Post Air	62.5 (7.5, 174)	22 (21)	7.9 (1.4, 10.8)
Obese Train	50 (16, 103.5)	19 (16)	2.2 (0.9, 10.1)
Normal Post Ozone	186.5 (15, 257.5)*	39 (25)^	15.9 (6.7, 33.3)^
Normal Post Air	64.5 (27, 100.5)	14 (10)	4.8 (2.6, 9.1)

IC = inspiratory capacity; IL-6 = Interleukin 6; NS = Not significant; sGAW = specific airway conductance

What's new since the last ozone ISA in 2013?

- Airway effects in older subjects at 120 ppb: lung function, inflammation, injury.
- Acute cardiovascular effects of brief exposures remain unclear.
- Ambient but not chamber ozone (120 ppb) reduces HRV. Delayed effect?
- Prior traffic exposures may enhance ozone response.
- Obesity confers increased susceptibility to lung function effects.

ISA = Integrated Science Assessment; HRV = heart rate variability