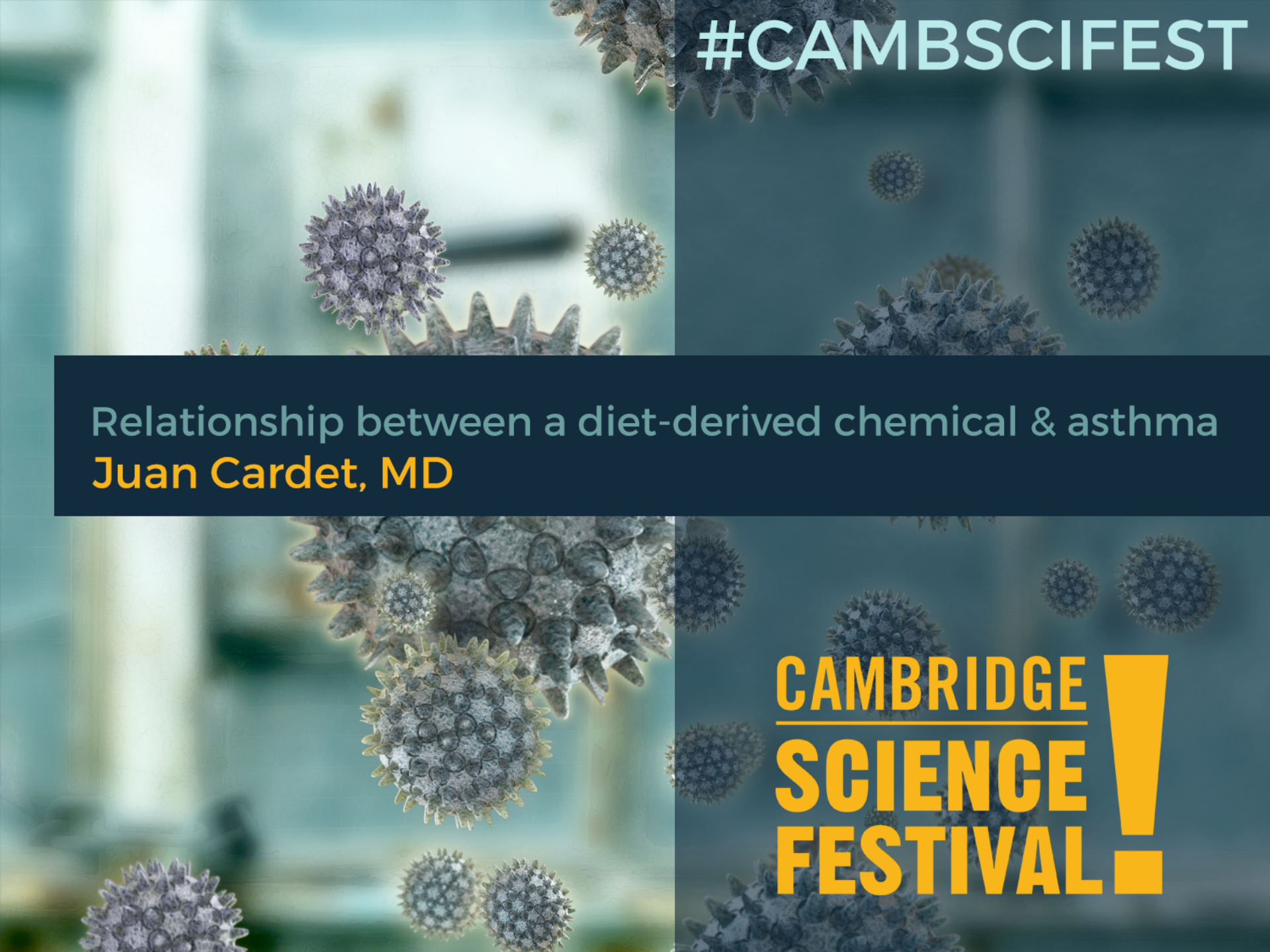
#CAMBSCIFEST
Relationship between a diet-derived chemical & asthma
Juan Cardet, MD
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Relationship between a diet-derived gut microbiomial metabolite and asthma

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Overview

- Research questions:
  - relationship between enterolactone and asthma?
  - nature of this relationship?

- Sources: diet, gut microbiome

- Inverse associations with chronic diseases

- Bioactivity: effects on inflammation, oxidation, and sex hormone receptors

- Inverse association with asthma in NHANES

Main research questions

Enterolactone is a diet-derived, human gut microbial metabolite.

-- Associated with asthma?

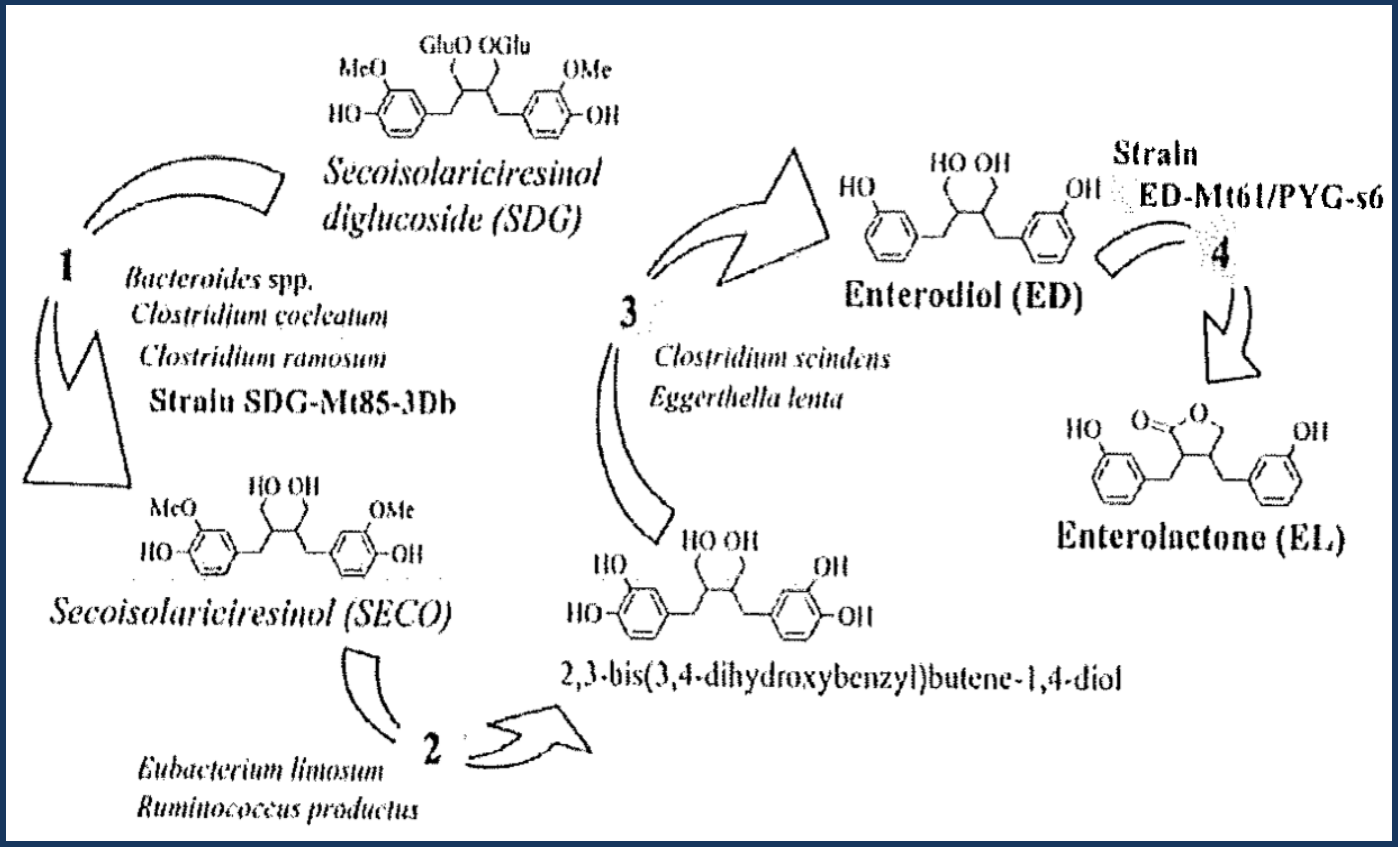
-- Causality?

Dietary sources

Fruits
Apricots, prunes, peaches dates, berries, apples, oranges
Vegetables
Squash, carrots, zucchini, broccoli, cabbage, Brussels sprouts, collards, kale, white potatoes
Breads, Cereals, Starches
Wheat, rye
Beverages
Red wine, coffee, tea
Nuts, Seeds, Miscellaneous
Flaxseed, sesame seed, sunflower seed, almonds, cashews, chestnuts, pistachios, soy, chick peas

French 2007, Lin 2013, Milder 2005, Thompson 2006

Human gut microbial metabolism, and distribution in the population



Antibiotics reduce excretion to zero; remains persistently zero in some

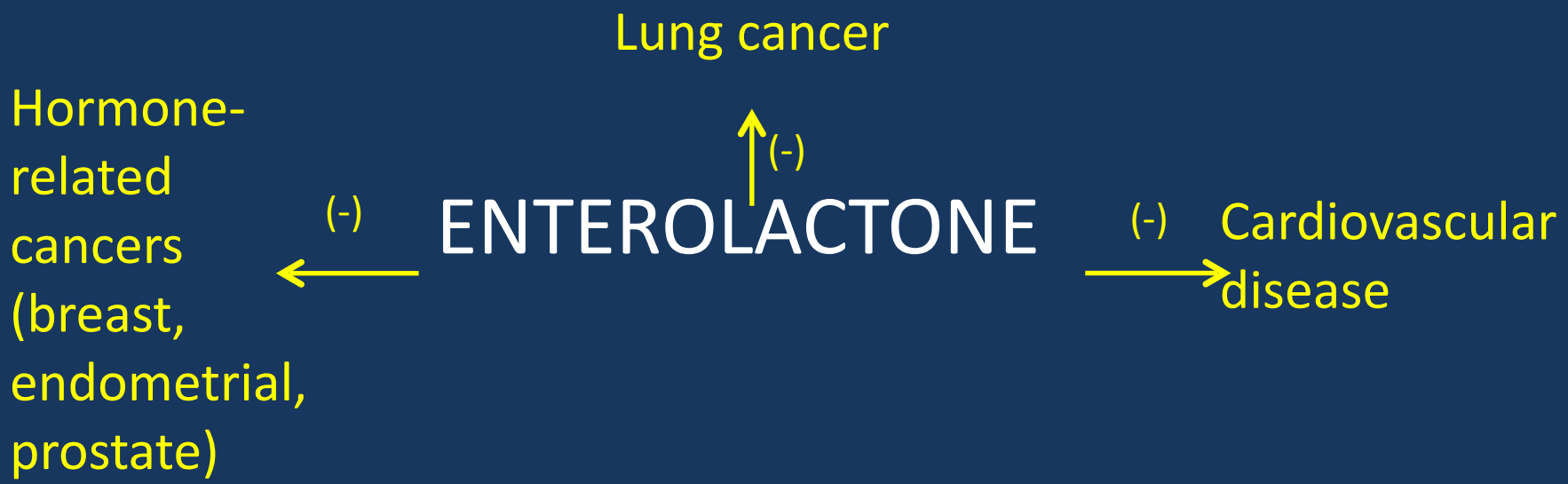
'Low' vs. 'High' enterolactone producers

TABLE E3. Urinary levels of bacterial metabolites by tertile (ng/mL)

Metabolite	Class	Tertile 1	Tertile 2	Tertile 3
Enterolactone	Lignan	0.1-173	174-640	641-122,000

Adlerkreutz 1986, Cardet 2015, Clavel 2007

Inverse associations with chronic diseases



Adlercreutz 1997, Hedelin 2006, Schabath 2005

Bioactivity

Effects on inflammation

In vitro

- Inhibits NFκB in human PBLs and TNF-a in THP-1 cells
  (Corsini 2010)

In vivo

- Reduction in pulmonary inflammation in ALI—hyperoxia, acid instillation, and radiation—in mice fed flaxseed diets
  (Christofidou-Solomidou 2011, Kinniry 2006, Lee 2009)

Cross-sectional observational human studies

- Inverse association with systemic CRP levels (NHANES database)
  - (Eichholzer 2014)

Bioactivity (cont.)

Effects on oxidation

In vitro

- Direct oxygen radical scavenger (Kitts 1999)
- Inhibitor of lipid peroxidation (Hu 2007)
- Inducer of the anti-oxidant protein heme-oxygenase 1 (HO1) (Kivela 2008)

In vivo

- Reduction in lung peroxidation levels (Kinniry 2006)
- Upregulation HO1 and NADPH quinone oxidoreductase-1 (NQO1) (Lee 2008)

Cross-sectional observational human studies

- Inverse association between serum ETL and isoprostane F2 (isoF2) (Vanharanta 2002)

Interventional pilot studies in humans

- Reduction in isoF2 in a subset of patients with CF (Turowski 2015)

Bioactivity (cont.)

Effects on sex hormone receptors

- Effects on estrogen receptors
  - Tissue-specific estrogen receptor (ER) modulator
    - Weaker agonist than estrogen
    - ERα > ERβ
    - Activates cell cycle regulators Cyclin D and Ki67 without inducing epithelial cell proliferation (Penttinen 2007)

Summary 1

- Enterolactone:
  - Dietary (flaxseed, sesame, others)
    + human gut microbiomial metabolism
  - Epi studies on inverse associations with chronic diseases
  - Bioactivity: unclear mechanism
    - Inflammation (NFκB, TNFa)
    - Oxidation (Anti-peroxidation, inducer anti-oxidant proteins, scavenger)
    - Tissue-selective estrogen receptor modulator

Microbiome and asthma

- Gut microbiome, antibiotics and asthma

  (Garn 2013)

- Microbial metabolomics and atopic diseases (e.g. short chain fatty acids)

  (Nicholson 2012, Tremaroli 2012)

NHANES database

- Nationally-representative dataset
- Free, publicly available
- 2003-2010
- 9,633 participants ages 6-85yo

Inverse association with asthma

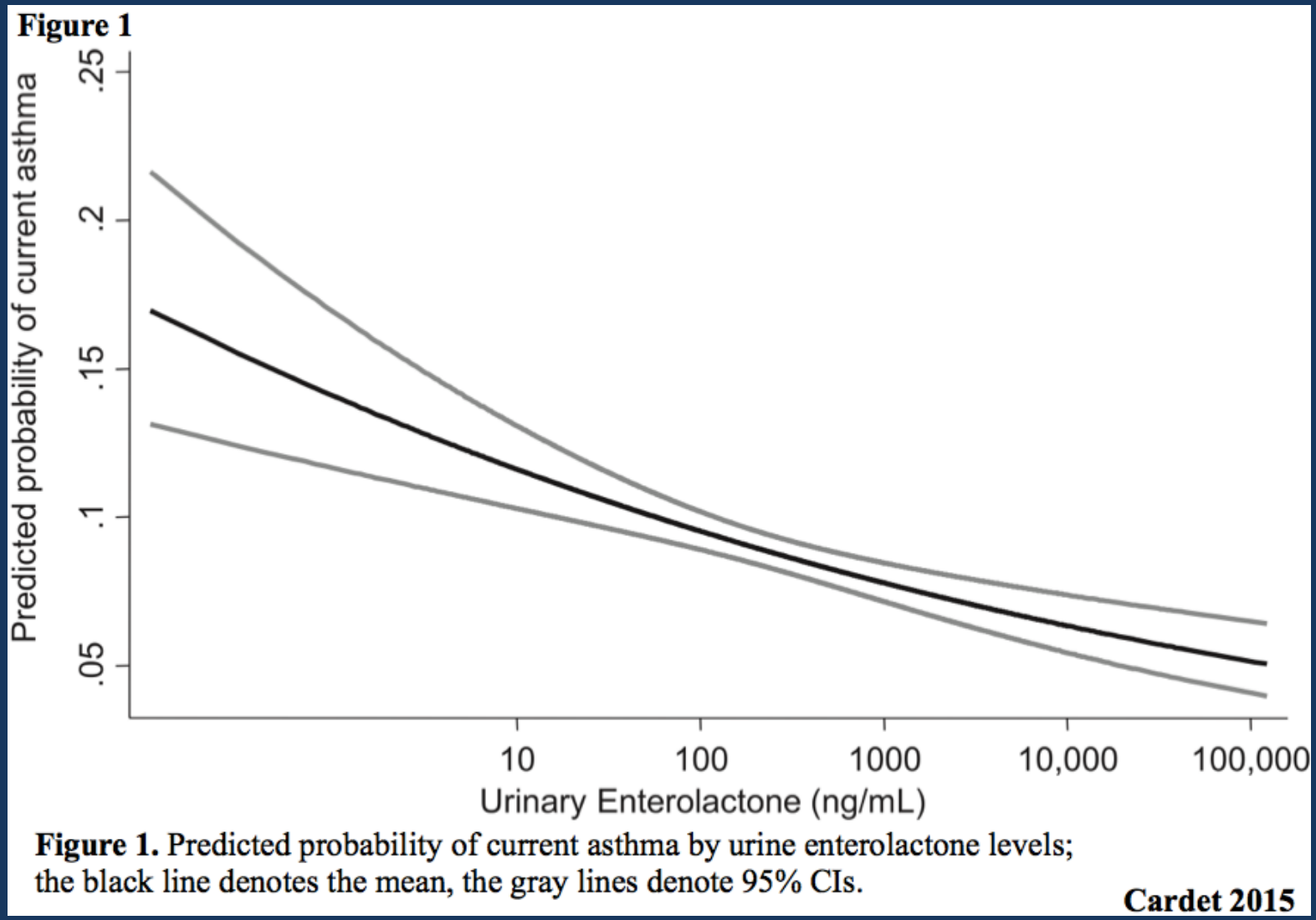


Figure 1. Predicted probability of current asthma by urine enterolactone levels; the black line denotes the mean, the gray lines denote 95% CIs.

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Inverse association with asthma (cont.)

TABLE I. ORs (and 95% CI) for current asthma and nonasthmatic wheeze by level of urinary metabolites of lignans and isoflavones

		Current asthma		Nonasthmatic wheeze	
Metabolite	**Tertile**	**Crude OR**	**Adjusted OR***	**Crude OR**	**Adjusted OR***
Enterolactone	1	1.0 [REF]	1.0 [REF]	1.0 [REF]	1.0 [REF]
	2	**0.59 (0.47-0.74)**	**0.61 (0.48-0.78)**	**0.64 (0.48-0.86)**	**0.67 (0.49-0.90)**
	3	**0.63 (0.52-0.76)**	**0.69 (0.56-0.85)**	**0.52 (0.34-0.65)**	**0.53 (0.42-0.67)**
	Test for trend (*P*)	**<.001**	**<.001**	**<.001**	**<.001**

Values in boldface are statistically significant ($P < .05$).

*Adjusted for age, sex, race/ethnicity, log-transformed urinary creatinine, PIR, and BMI.

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Inverse association with asthma (cont.)

TABLE E11. ORs (and 95% CI) for current asthma by level of enterolactone adjusted for smoke exposure, stratified by age

			Current asthma		
Age category (y)	**Metabolite**	**Tertile**	**OR, crude**	**OR, adjusted, model 1***	**OR, adjusted, model 2†**
≥20	Enterolactone	1	1.0 [REF]	1.0 [REF]	1.0 [REF]
		2	**0.56 (0.43-0.73)**	**0.57 (0.44-0.76)**	**0.59 (0.45-0.78)**
		3	**0.67 (0.54-0.84)**	**0.74 (0.58-0.94)**	**0.76 (0.59-0.97)**
		Test for trend (*P*)	**<.001**	**.008**	**.01**
<20	Enterolactone	1	1.0 [REF]	1.0 [REF]	1.0 [REF]
		2	**0.58 (0.39-0.86)**	**0.57 (0.38-0.86)**	**0.57 (0.38-0.86)**
		3	**0.50 (0.34-0.73)**	**0.50 (0.32-0.77)**	**0.50 (0.32-0.77)**
		Test for trend (*P*)	**.001**	**.002**	**.003**

Values in boldface are statistically significant ($P < .05$).

*Adjusted for age, sex, race/ethnicity, log-transformed urinary creatinine, PIR, and BMI.

†Model 1, additionally adjusted for smoking status (never, former, or current smoker), age ≥20 y, and household smoke exposure (present or absent) for age < 20 y.

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Summary 2

- Concentration-dependent association between a bacterial metabolite of diet-derived lignans and asthma and wheezing in a large, nationally representative population-based sample.

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