World Cancer Research Fund International
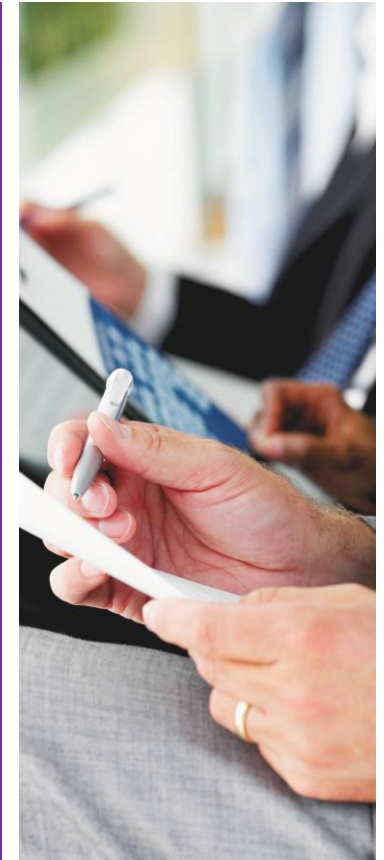
Recent Findings on Diet, Nutrition, Physical Activity and Cancer: the WCRF/AICR Continuous Update Project

IARC 50th Anniversary Scientific Conference, June 7-10, 2016
Global Cancer, Occurrence, Causes and Avenues to Prevention

Michael Leitzmann, Continuous Update Project Panel member

Outline

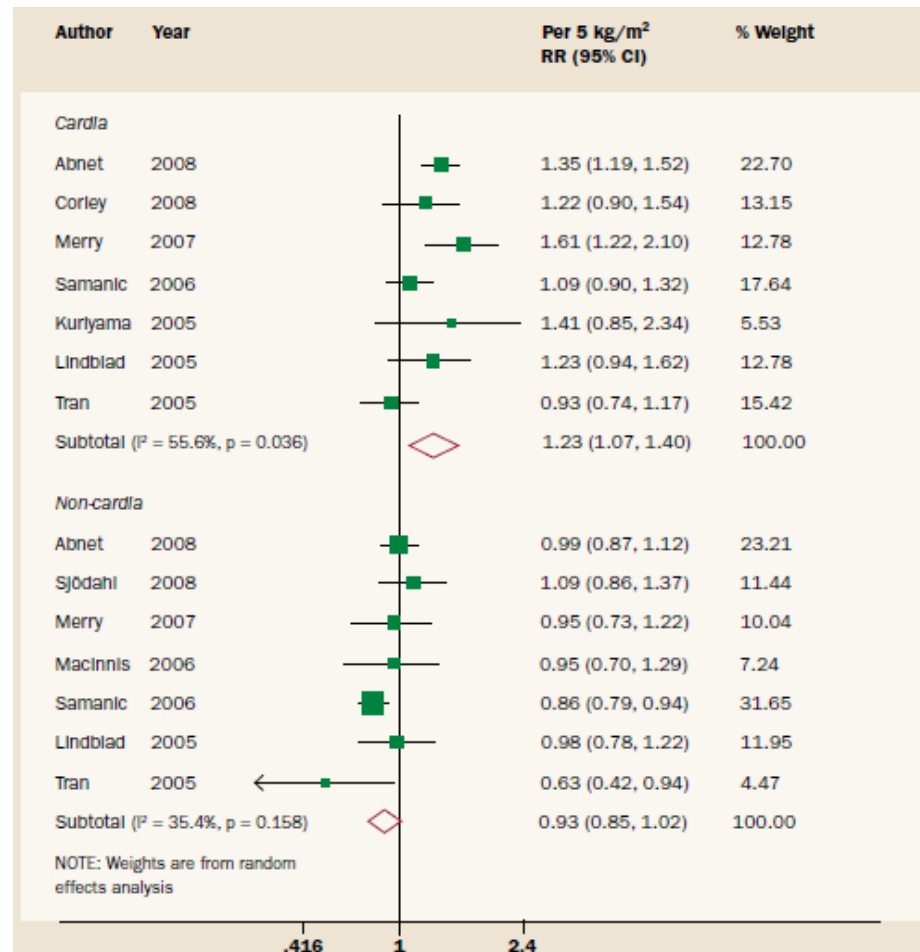**Epidemiologic studies of diet, nutrition, physical activity and cancer**

- **Stomach cancer**

- **Liver cancer**

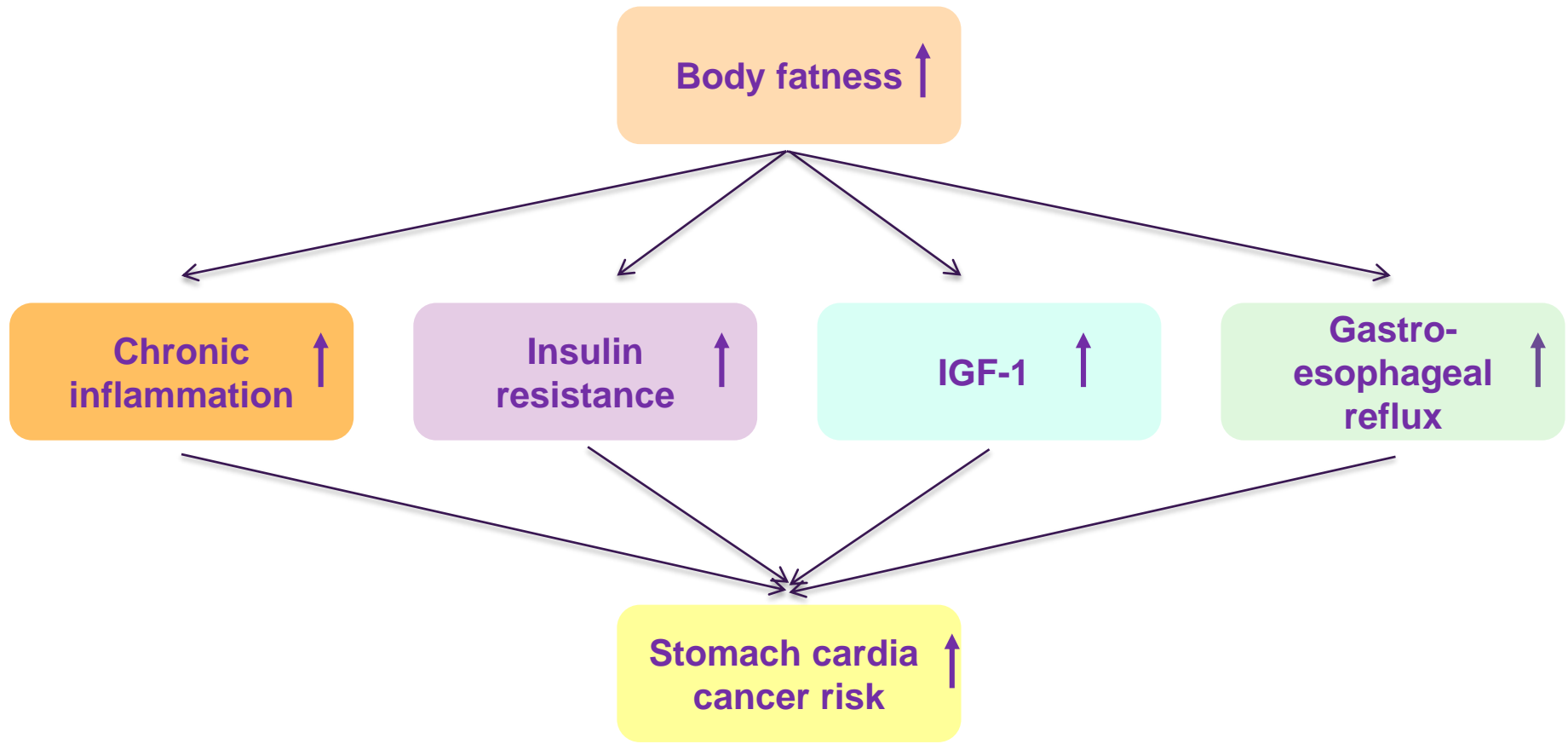- **Gallbladder cancer**

- **Prostate cancer**

- **Breast cancer survivors**

DIET, NUTRITION, PHYSICAL ACTIVITY AND STOMACH CANCER

|		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	**Convincing**		
	Probable		Body fatness (cardia)[1] Alcoholic drinks[2] Foods preserved by salting[3] Processed meat (non-cardia)
LIMITED EVIDENCE	**Limited – suggestive**	Citrus fruit (cardia)	Grilled (broiled) or barbecued (charbroiled) meat and fish Low fruit intake

Dose-response meta-analysis of BMI and stomach cancer, per 5 kg/m²

Author	Year	Per 5 kg/m² RR (95% CI)	% Weight
Cardia			
Abnet	2008	1.35 (1.19, 1.52)	22.70
Corley	2008	1.22 (0.90, 1.54)	13.15
Merry	2007	1.61 (1.22, 2.10)	12.78
Samanic	2006	1.09 (0.90, 1.32)	17.64
Kuriyama	2005	1.41 (0.85, 2.34)	5.53
Lindblad	2005	1.23 (0.94, 1.62)	12.78
Tran	2005	0.93 (0.74, 1.17)	15.42
Subtotal (I² = 55.6%, p = 0.036)		1.23 (1.07, 1.40)	100.00
Non-cardia			
Abnet	2008	0.99 (0.87, 1.12)	23.21
Sjödahl	2008	1.09 (0.86, 1.37)	11.44
Merry	2007	0.95 (0.73, 1.22)	10.04
MacInnis	2006	0.95 (0.70, 1.29)	7.24
Samanic	2006	0.86 (0.79, 0.94)	31.65
Lindblad	2005	0.98 (0.78, 1.22)	11.95
Tran	2005	0.63 (0.42, 0.94)	4.47
Subtotal (I² = 35.4%, p = 0.158)		0.93 (0.85, 1.02)	100.00

NOTE: Weights are from random effects analysis

Potential biologic mechanisms linking body fatness to stomach cardia cancer

Renehan et al., Nat Rev Cancer 2015;15:484-98
Hampel et al., Ann Int Med 2005;143:199-211

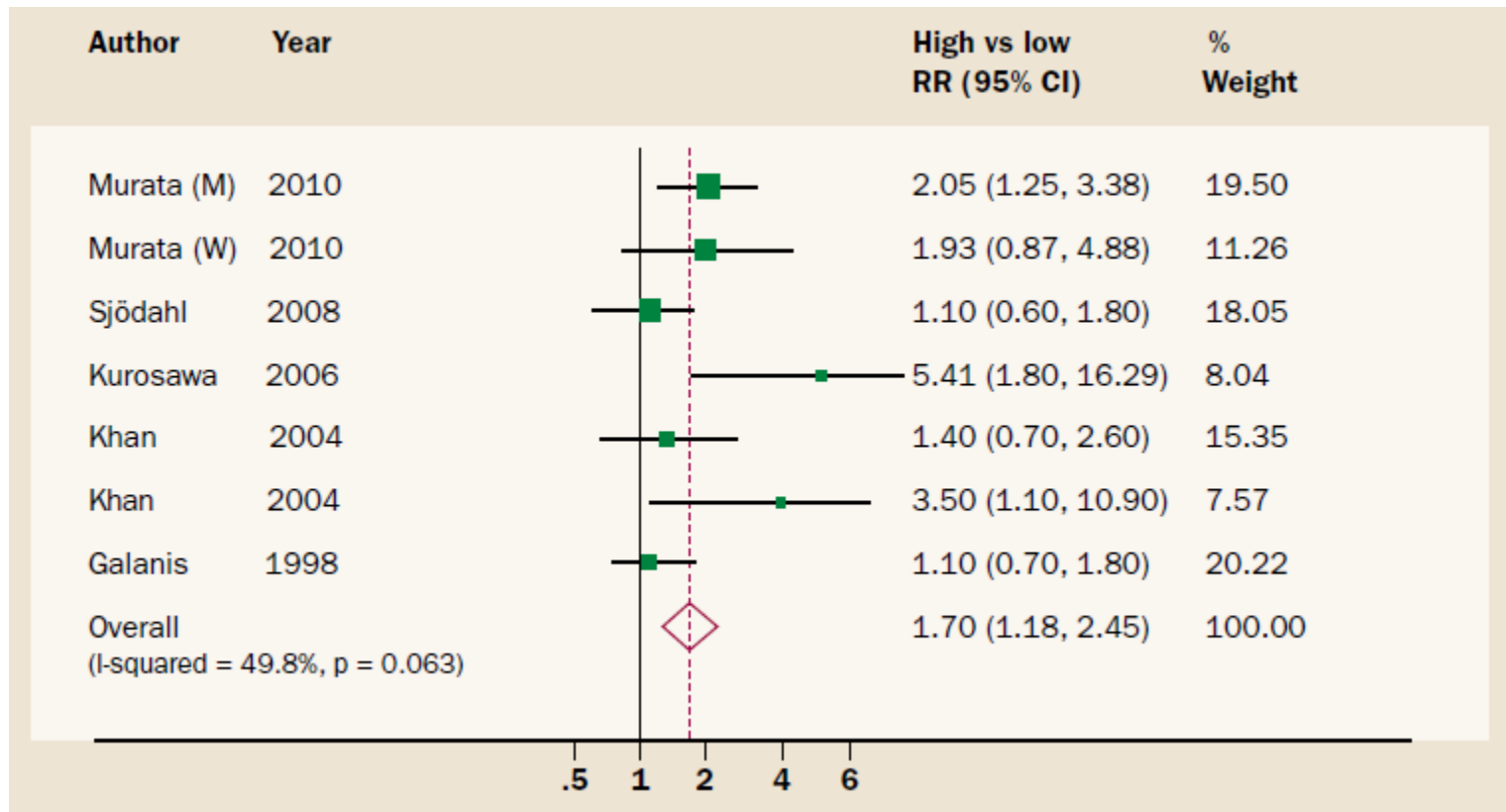# Non-linear dose-response association of alcohol and stomach cancer
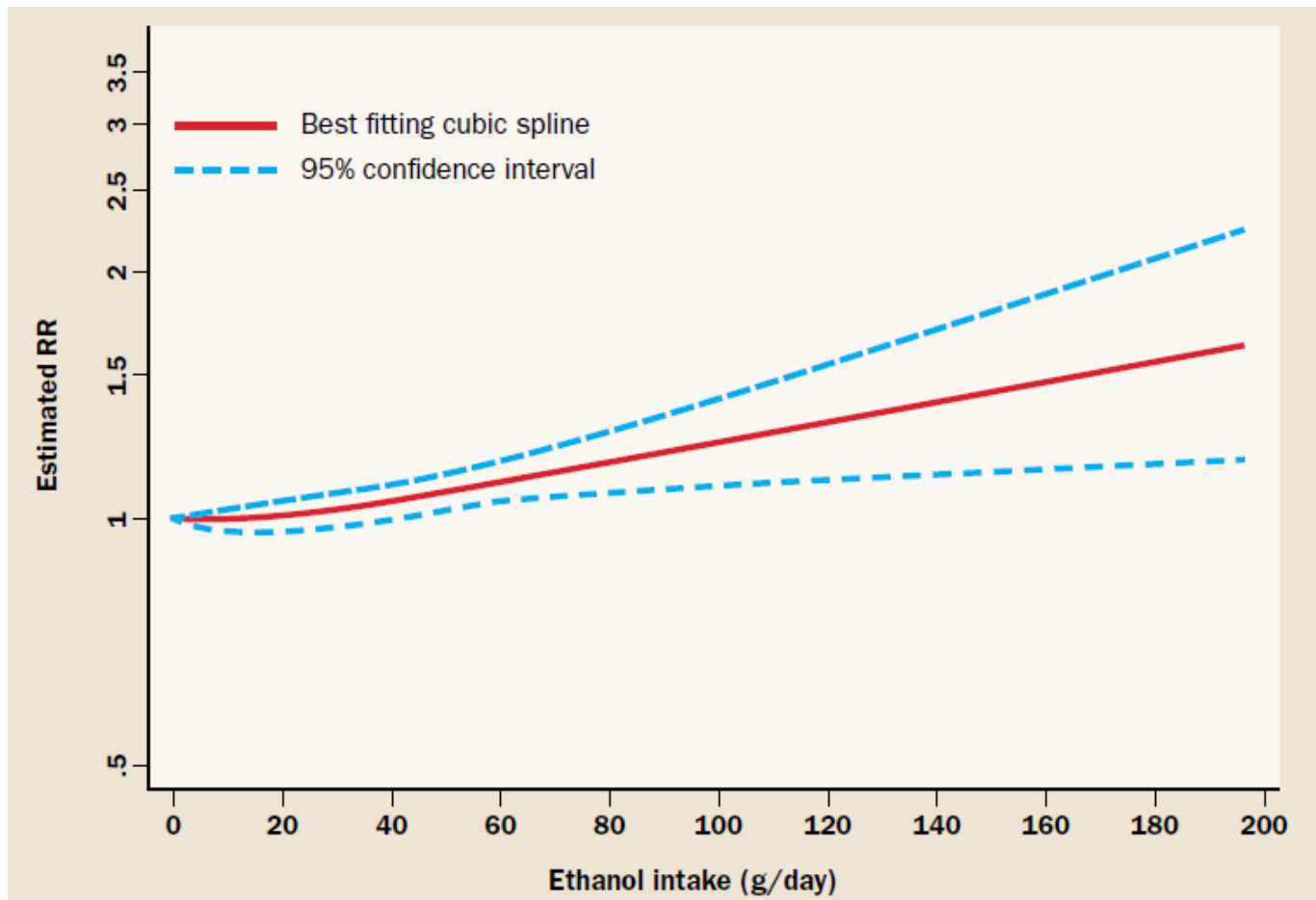
Potential biologic mechanisms linking alcohol to stomach cancer

- **Carcinogenic effect of acetaldehyde**

- **Oxidative stress and impaired antioxidant defense**

- **Chronic inflammation**

- **Direct DNA damage and inhibition of DNA repair**

- **Interference with methyl group transfer, thereby altering gene expression**

- **Ability to act as a solvent, facilitating enhanced penetration of carcinogens**

High versus low intake of salt-preserved foods in relation to stomach cancer

Author	Year	High vs low RR (95% CI)	% Weight
Murata (M)	2010	2.05 (1.25, 3.38)	19.50
Murata (W)	2010	1.93 (0.87, 4.88)	11.26
Sjödahl	2008	1.10 (0.60, 1.80)	18.05
Kurosawa	2006	5.41 (1.80, 16.29)	8.04
Khan	2004	1.40 (0.70, 2.60)	15.35
Khan	2004	3.50 (1.10, 10.90)	7.57
Galanis	1998	1.10 (0.70, 1.80)	20.22
Overall (I-squared = 49.8%, p = 0.063)		1.70 (1.18, 2.45)	100.00

Mechanisms linking salt-preserved foods to stomach cancer

Potential confounding factors

Salt preservation may be used where refrigeration is unavailable

Potential confounding by socio-economic status/ H. pylori infection status

Salt-preserved vegetables contain fewer nutrients

Potential biological mechanisms
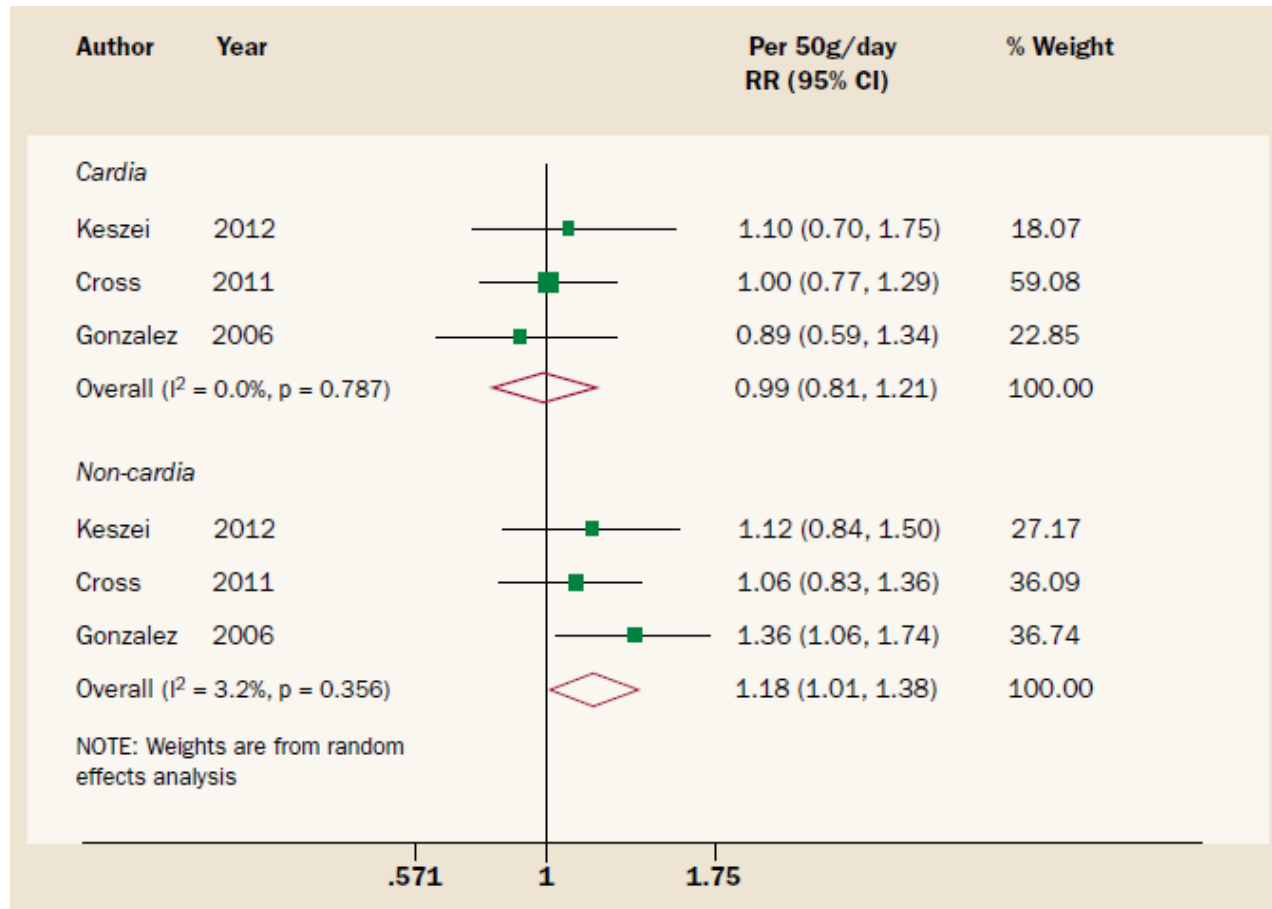
Mucosal damage causes chronic inflammation and atrophy
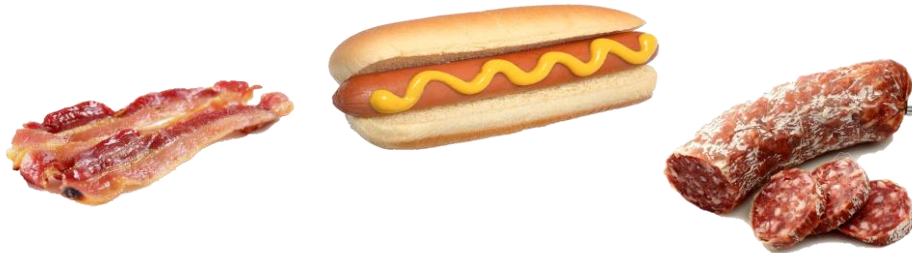
Increased *H. pylori* colonization

Endogenous N-nitroso compound formation

Dose-response meta-analysis of processed meat intake and stomach cancer, per 50 grams per day

Potential biologic mechanisms linking processed meat to stomach cancer

High levels of salt	Nitrates and nitrite	Smoked meat	Haem iron
↓	↓	↓	↓
Damage to stomach lining[1]	N-nitroso compounds[2]	Polycyclic aromatic hydrocarbons[3]	Endogenous intestinal N-nitrosation[4]

1. Bergin et al., Dig Dis Sci 2003;48:475-85
2. Takahashi et al., Carcinogenesis 1994;15:1429-32
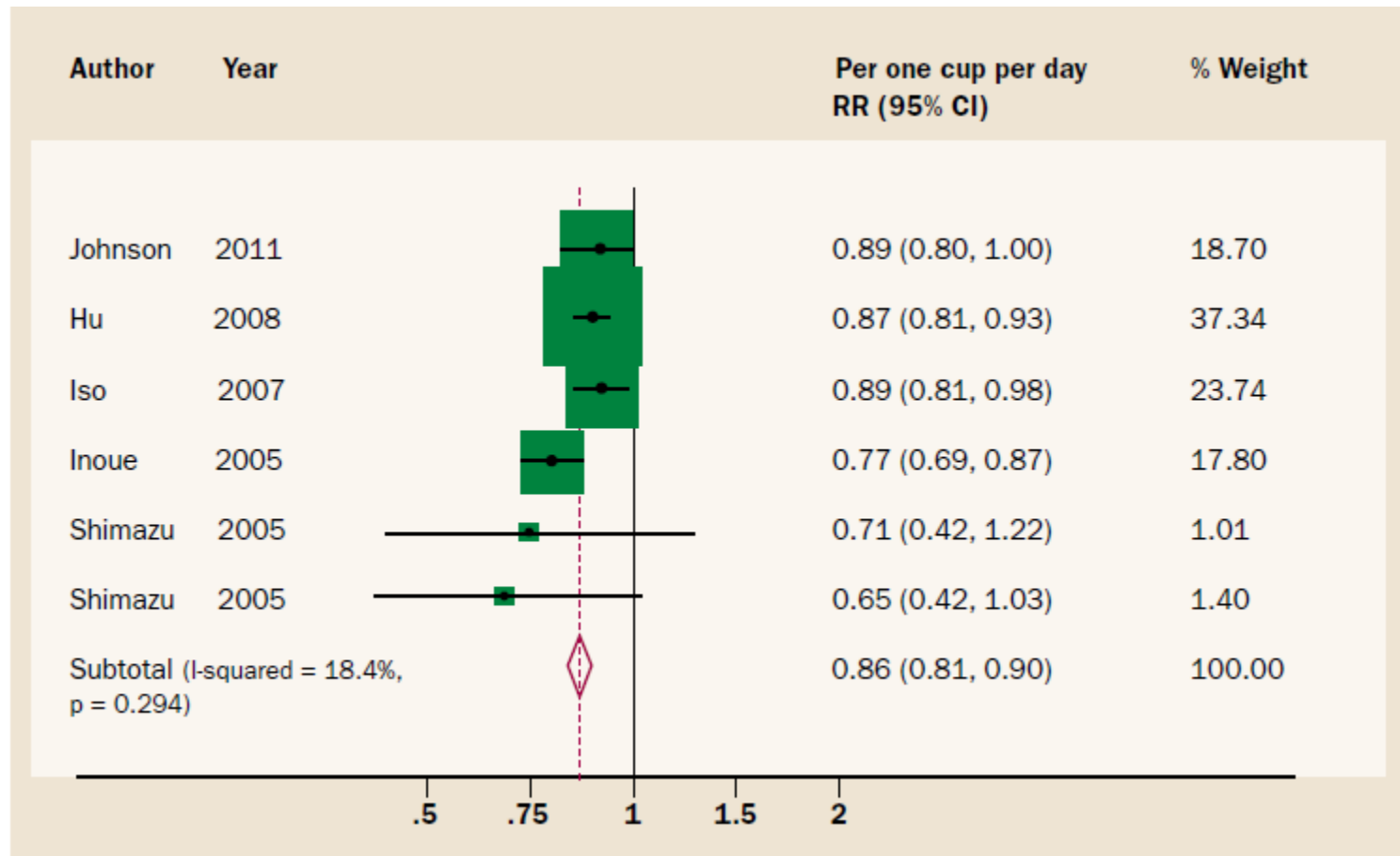3. Lijinski, Mutat Res 1991;259:251-61
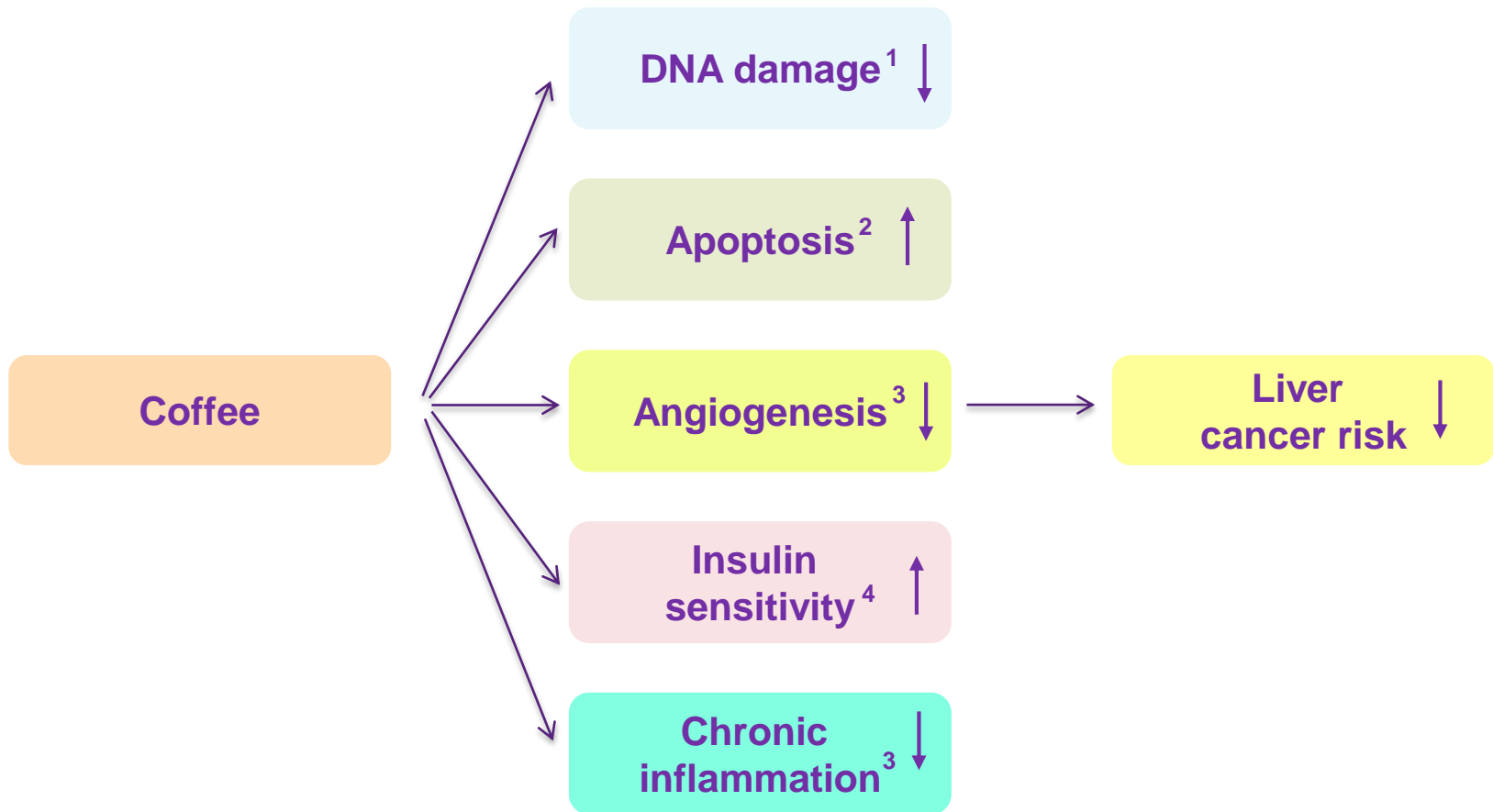4. Cross et al., Cancer Research 2003;63:2358-60

DIET, NUTRITION, PHYSICAL ACTIVITY AND LIVER CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	**Convincing**		**Aflatoxins**[1] **Alcoholic drinks**[2] **Body fatness**[3]
	Probable	**Coffee**	
LIMITED EVIDENCE	**Limited - suggestive**	Fish Physical activity[4]	
	Limited - no conclusion	Cereals (grains) and their products, non-starchy vegetables, fruits, peanuts (groundnuts), meat and poultry, salted fish, tea, green tea, glycaemic index, calcium and vitamin D supplements, vitamin C, water source, low fat diet	
STRONG EVIDENCE	**Substantial effect on risk unlikely**		

Dose-response meta-analysis of coffee and liver cancer, per one cup per day

Author	Year		Per one cup per day RR (95% CI)	% Weight
Johnson	2011		0.89 (0.80, 1.00)	18.70
Hu	2008		0.87 (0.81, 0.93)	37.34
Iso	2007		0.89 (0.81, 0.98)	23.74
Inoue	2005		0.77 (0.69, 0.87)	17.80
Shimazu	2005		0.71 (0.42, 1.22)	1.01
Shimazu	2005		0.65 (0.42, 1.03)	1.40
Subtotal (I-squared = 18.4%, p = 0.294)			0.86 (0.81, 0.90)	100.00

Potential biologic mechanisms linking coffee to decreased liver cancer risk

DNA damage[1] ↓

Apoptosis[2] ↑

Coffee → Angiogenesis[3] ↓ → Liver cancer risk ↓

Insulin sensitivity[4] ↑

Chronic inflammation[3] ↓

1. Majer et al., Food Chem Toxicol 2005;43:433-41
2. Cardin et al., Dig Liver Dis 2013;45:499-504
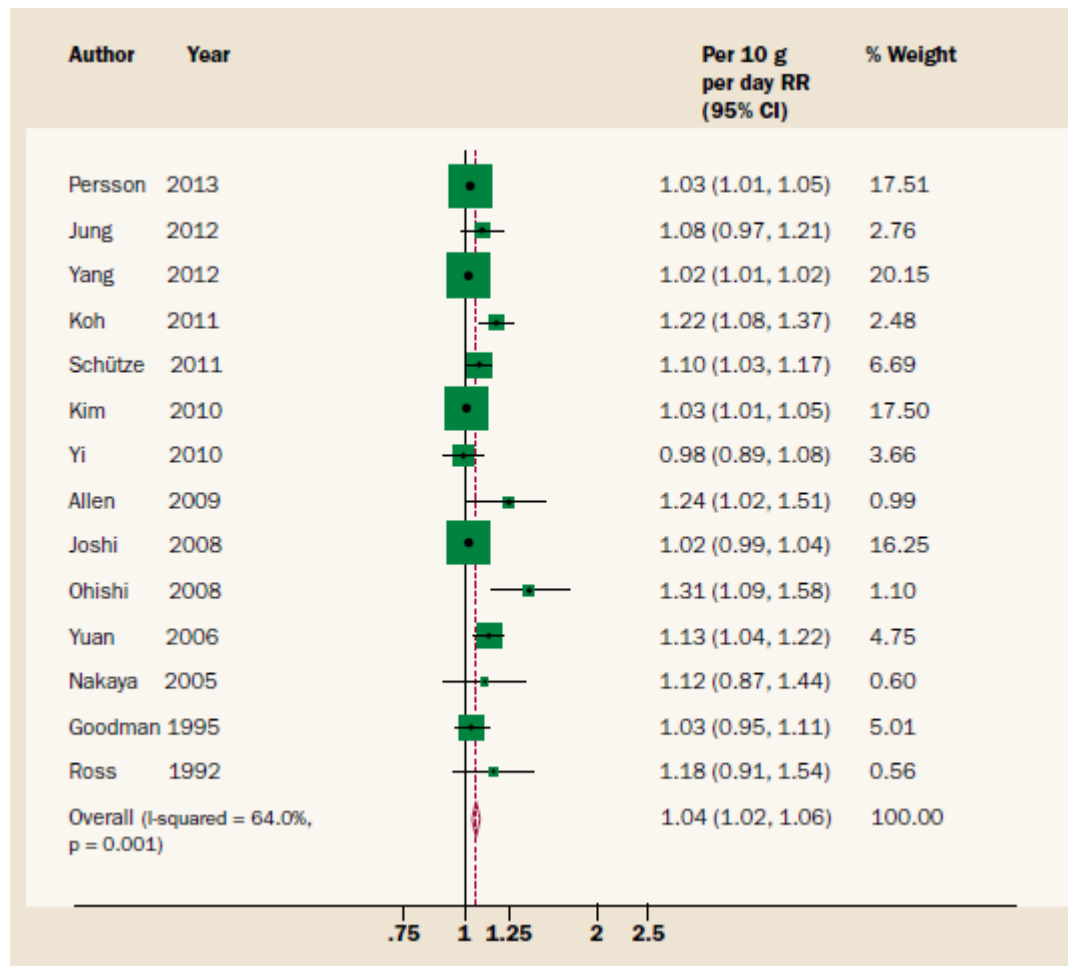3. Bohn et al., Mol Nutr Food Res 2014;58:915-30
4. Tunnicliffe & Shearer, Appl Physiol Nutr Metab 2008;33:1290-300

Aflatoxins and liver cancer

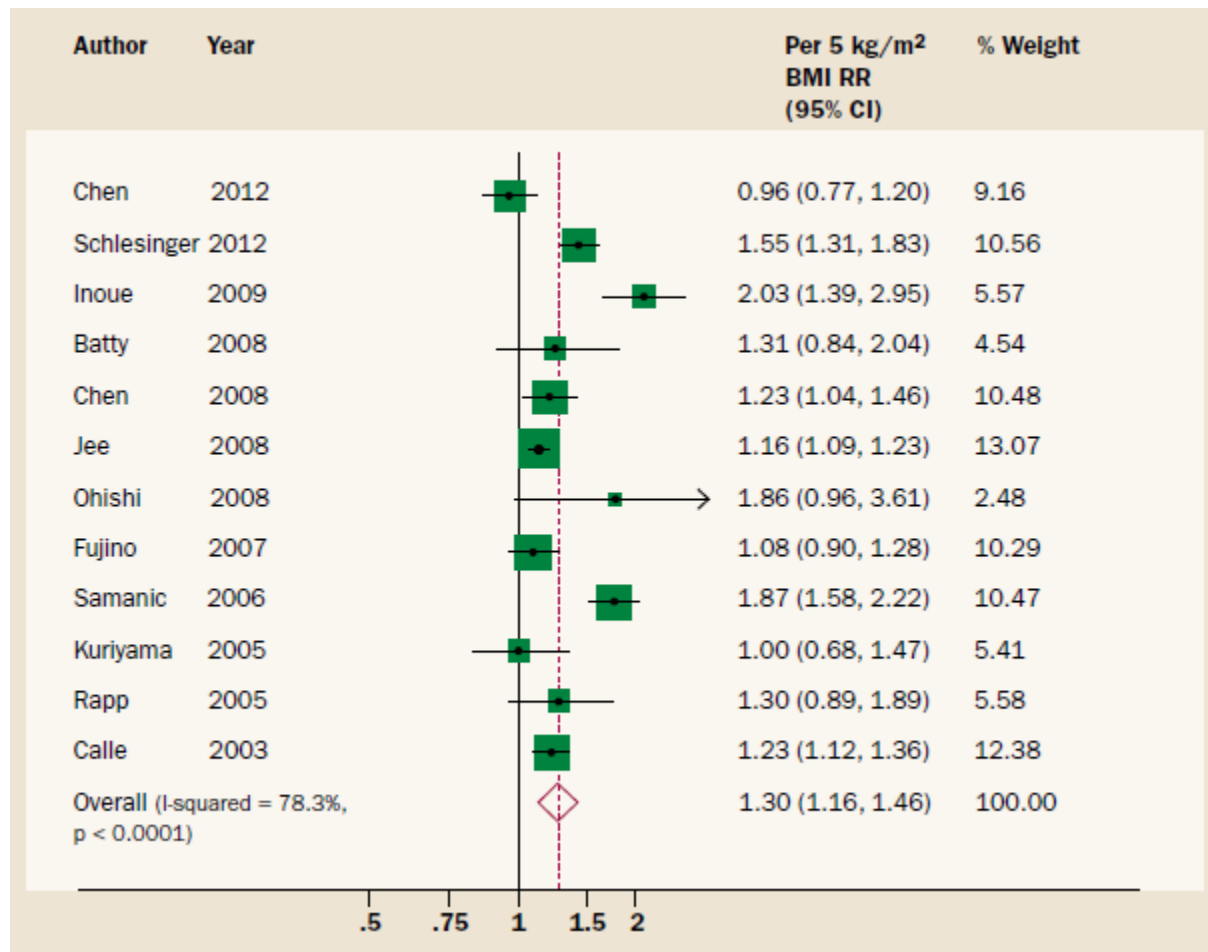| PUBLICATION	NO.CASES/ CONTROLS	RR (95% CI)	CONTRAST
Wu 2009 [18]	241 HCC 1052 controls	1.54 (1.01–2.36)	AFB$_1$-albumin adducts above vs. below mean (59.8 fmol/mg)
		1.76 (1.18–2.58)	Urinary AFB$_1$ above vs. below mean (55.2 fmol/mL)
Sun 2001 [19]	HBsAg carriers 75 HCC 140 controls	2.0 (1.1–3.7)	AFB$_1$-albumin adducts detectable vs. non-detectable
Wang 1996 [20]	56 HCC 220 controls	1.6 (0.4–5.5)	Serum level aflatoxin-albumin detectable vs. non-detectable
		3.8 (1.1–12.8)	Urinary levels of aflatoxin high vs. low

PUBLICATION	NO.CASES/ CONTROLS	RR (95% CI)	CONTRAST
Yuan 2006 [21]	213 HCC 1087 controls	3.25 (1.63–6.48)	Urinary aflatoxin biomarker positive vs. negative
Qian 1994 [22]	55 HCC 267 controls	5.0 (2.1–11.8)	Any urinary aflatoxin biomarker vs. none
Ross 1992 [23]	22 HCC 110 controls	2.4 (1.0–5.9)	Any urinary aflatoxin biomarker vs. none
Sun 1999 [24]	22 HCC 149 controls	3.3 (1.2–8.7)	Urinary AFM$_1$ detectable (above 3.6 ng/L) vs. non-detectable
Yu 1997 [25]	HBsAg carriers 21 HCC 63 controls	12.0 (1.2–117.4)	Both markers (urinary AFM$_1$ and AFB$_1$-N7-guanine adducts) vs. none
Chen 1996 [26]	HBsAg carriers 32 HCC 73 controls	3.8 (1.0–14.5)	AFB$_1$-albumin adducts high vs. undetectable

Dose-response meta-analysis of alcohol and liver cancer, per 10 g per day

Author	Year	Per 10 g per day RR (95% CI)	% Weight
Persson	2013	1.03 (1.01, 1.05)	17.51
Jung	2012	1.08 (0.97, 1.21)	2.76
Yang	2012	1.02 (1.01, 1.02)	20.15
Koh	2011	1.22 (1.08, 1.37)	2.48
Schütze	2011	1.10 (1.03, 1.17)	6.69
Kim	2010	1.03 (1.01, 1.05)	17.50
Yi	2010	0.98 (0.89, 1.08)	3.66
Allen	2009	1.24 (1.02, 1.51)	0.99
Joshi	2008	1.02 (0.99, 1.04)	16.25
Ohishi	2008	1.31 (1.09, 1.58)	1.10
Yuan	2006	1.13 (1.04, 1.22)	4.75
Nakaya	2005	1.12 (0.87, 1.44)	0.60
Goodman	1995	1.03 (0.95, 1.11)	5.01
Ross	1992	1.18 (0.91, 1.54)	0.56
Overall (I-squared = 64.0%, p = 0.001)		1.04 (1.02, 1.06)	100.00

.75 1 1.25 2 2.5

Dose-response meta-analysis of BMI and liver cancer, per 5 kg/m^2

Author	Year		Per 5 kg/m^2 BMI RR (95% CI)	% Weight
Chen	2012		0.96 (0.77, 1.20)	9.16
Schlesinger	2012		1.55 (1.31, 1.83)	10.56
Inoue	2009		2.03 (1.39, 2.95)	5.57
Batty	2008		1.31 (0.84, 2.04)	4.54
Chen	2008		1.23 (1.04, 1.46)	10.48
Jee	2008		1.16 (1.09, 1.23)	13.07
Ohishi	2008		1.86 (0.96, 3.61)	2.48
Fujino	2007		1.08 (0.90, 1.28)	10.29
Samanic	2006		1.87 (1.58, 2.22)	10.47
Kuriyama	2005		1.00 (0.68, 1.47)	5.41
Rapp	2005		1.30 (0.89, 1.89)	5.58
Calle	2003		1.23 (1.12, 1.36)	12.38
Overall (I-squared = 78.3%, p < 0.0001)			1.30 (1.16, 1.46)	100.00

DIET, NUTRITION, PHYSICAL ACTIVITY AND GALLBLADDER CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	**Convincing**		
	Probable		Body fatness[1]
LIMITED EVIDENCE	**Limited – suggestive**		
	Limited – no conclusion	Peppers (capsicums), fish, coffee, tea, alcohol, sugar, vitamin C, calcium and vitamin D supplements, low fat diets, height	
STRONG EVIDENCE	**Substantial effect on risk unlikely**		

Non-linear dose-response association of BMI and gallbladder cancer
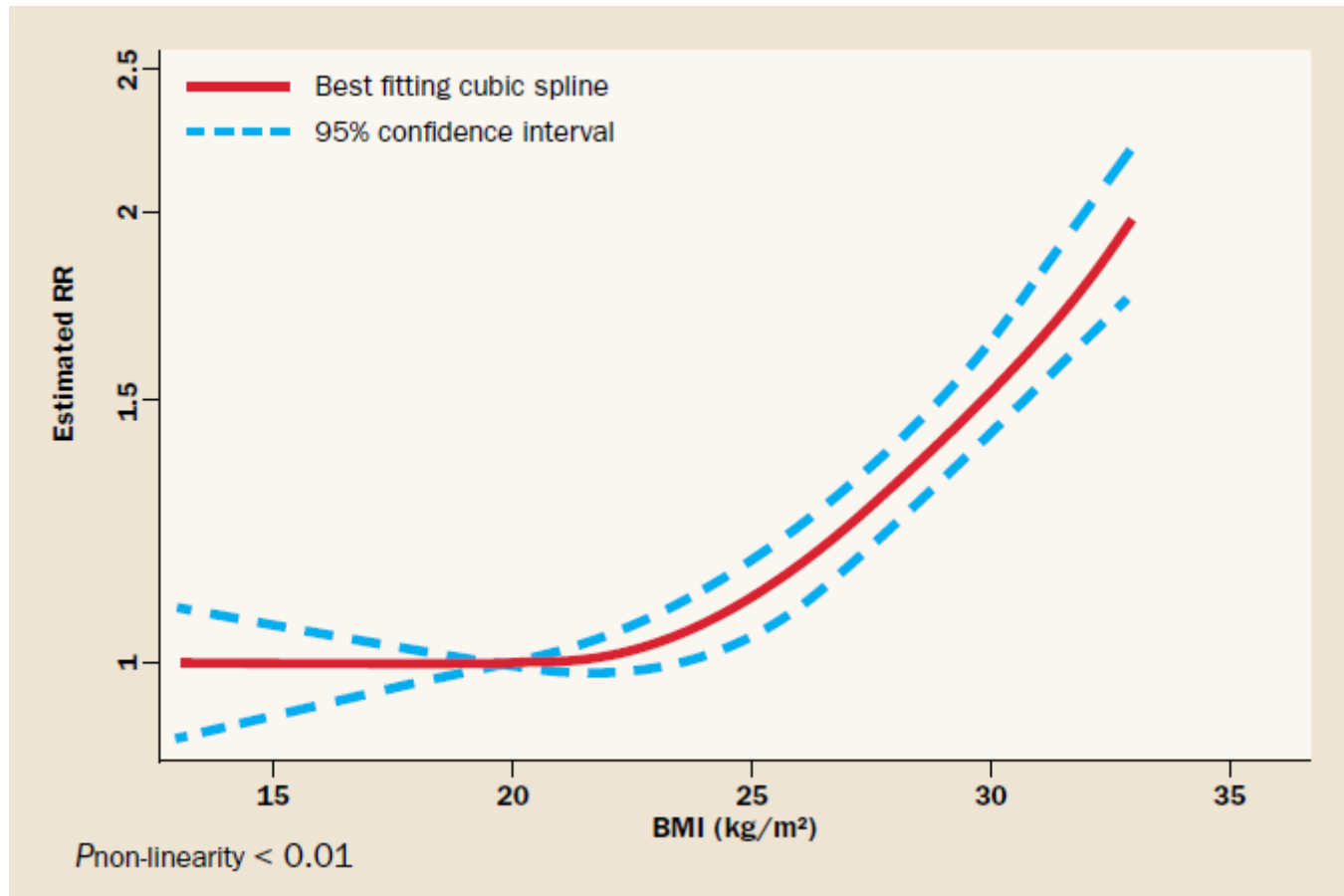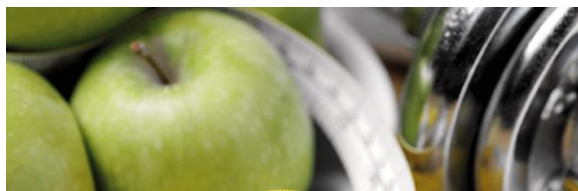
DIET, NUTRITION, PHYSICAL ACTIVITY AND PROSTATE CANCER

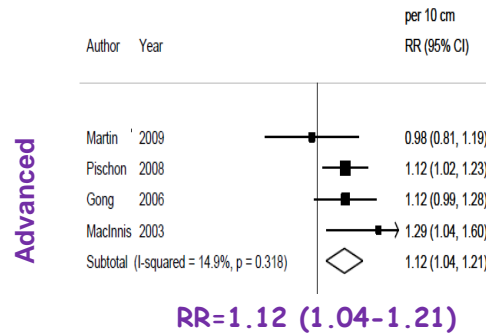|		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	**Convincing**		
	Probable		Body fatness (advanced prostate cancer)[1,2] Adult attained height[3]
LIMITED EVIDENCE	**Limited-suggestive**		Dairy products Diets high in calcium Low plasma alpha-tocopherol concentrations Low plasma selenium concentrations
	Limited-no conclusion	Cereals (grains) and their products, dietary fibre, potatoes, non-starchy vegetables, fruits, pulses (legumes), processed meat, red meat, poultry, fish, eggs, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, plant oils, sugar (sucrose), sugary foods and drinks, coffee, tea, alcoholic drinks, carbohydrate, protein, vitamin A, retinol, alpha carotene, lycopene, folate, thiamin, riboflavin, niacin, vitamin C, vitamin D, vitamin E supplements, gamma-tocopherol, multivitamins, selenium supplements, iron, phosphorus, calcium supplements, zinc, physical activity, energy expenditure, vegetarian diets, Seventh-day Adventist diets, individual dietary patterns, body fatness (non-advanced prostate cancer), birth weight, energy intake	
STRONG EVIDENCE	**Substantial effect on risk unlikely**	Beta-carotene[4,5]	

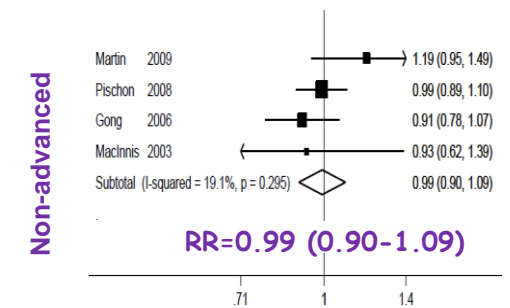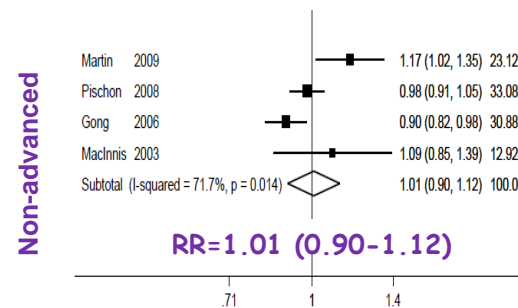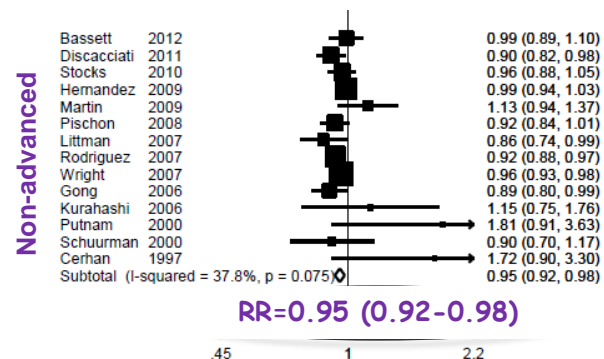# Dose-response meta-analysis of body fatness and prostate cancer
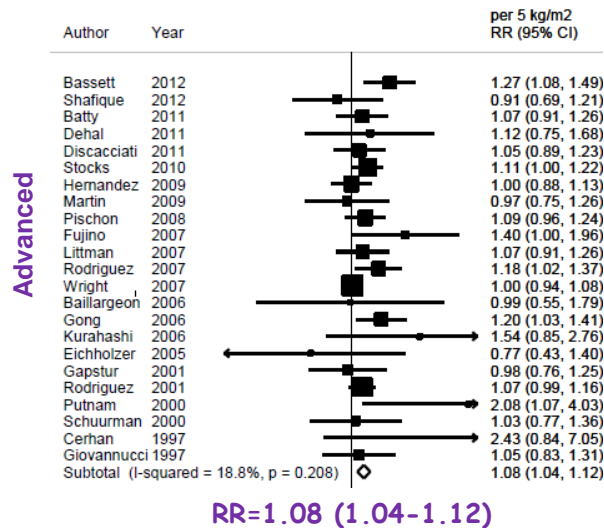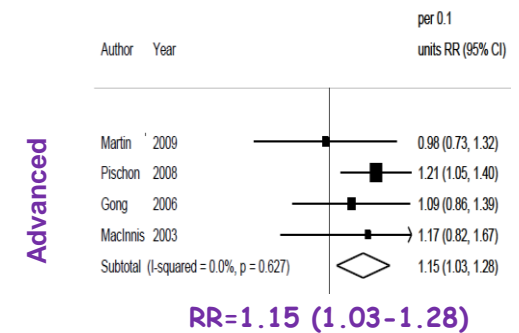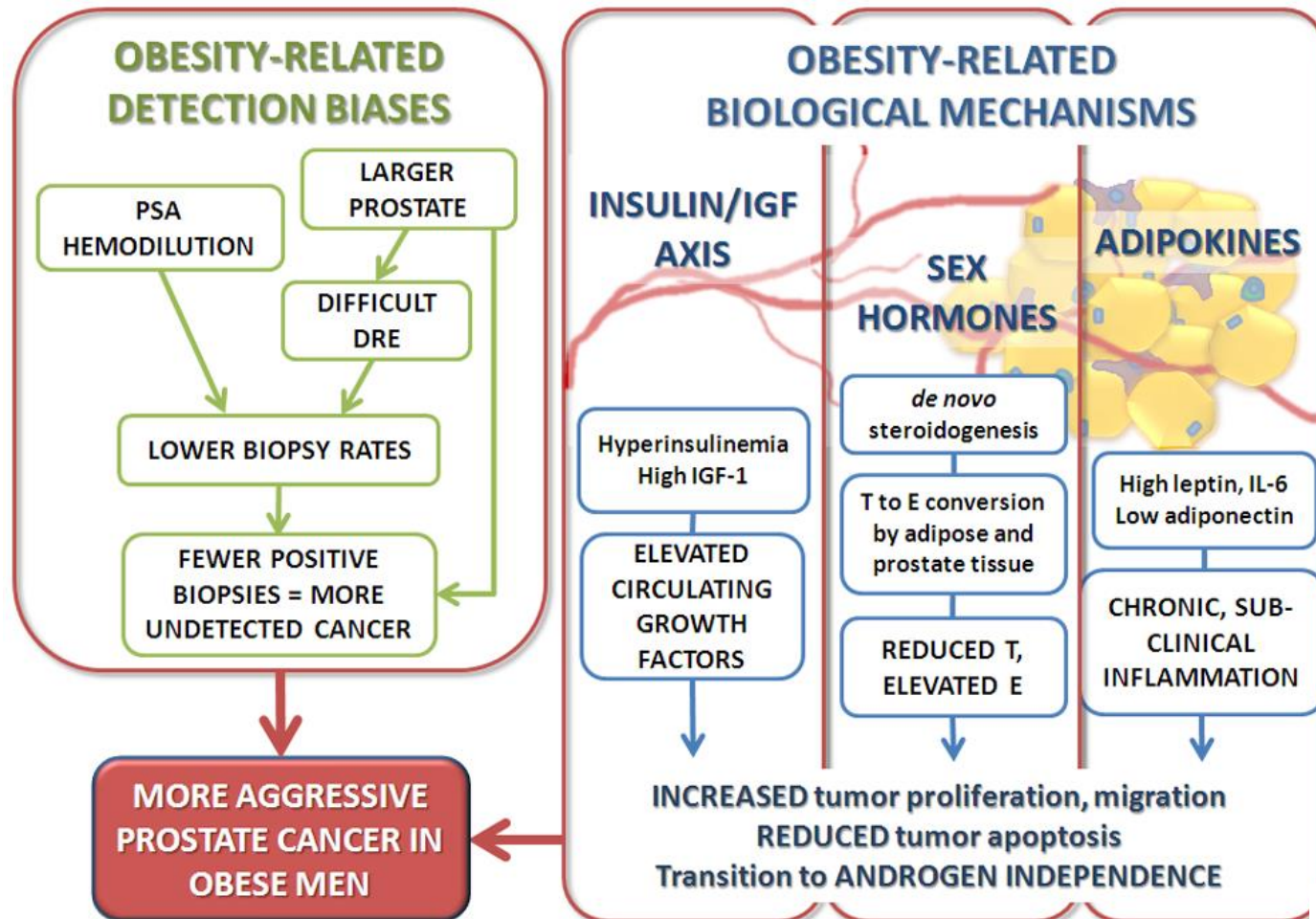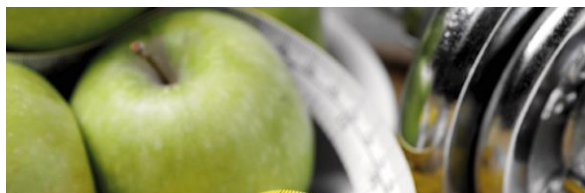
Obesity-related biologic mechanisms and detection biases contributing to the association between obesity and aggressive prostate cancer

DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY TIMEFRAME)

Timing of exposure assessment		BEFORE DIAGNOSIS				LESS THAN 12 MONTHS AFTER DIAGNOSIS				12 MONTHS OR MORE AFTER DIAGNOSIS			
		DECREASES RISK		**INCREASES RISK**		**DECREASES RISK**		**INCREASES RISK**		**DECREASES RISK**		**INCREASES RISK**	
		Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome
STRONG EVIDENCE	**Convincing**												
	Probable												
LIMITED EVIDENCE	**Limited-suggestive**	Physical activity Foods containing fibre	All mortality BC mortality All mortality	Body fatness Total fat Saturated fatty acids	All mortality BC mortality[2] 2nd BC All mortality All mortality			Body fatness	All mortality BC mortality[2] 2nd BC	Physical activity Foods containing fibre Foods containing soy	All mortality All mortality All mortality	Body fatness	All mortality
	Limited-no conclusion[1]	Fruits, vegetables, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, dietary supplements, alcoholic drinks, dietary patterns, underweight, body fatness (premenopause), adult attained height, energy intake				Foods containing fibre, carbohydrate, protein, total fat, saturated fatty acids, alcoholic drinks, physical activity, underweight, body fatness (premenopause), adult attained height, energy intake				Fruits, vegetables, foods containing fibre, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, total fat, saturated fatty acids, alcoholic drinks, dietary patterns, physical activity, body fatness, underweight, height, energy intake			
STRONG EVIDENCE	**Substantial effect on risk unlikely**												

Future directions

Studies of cancer incidence:

- Improve measurements of diet, nutrition, and physical activity

- Perform analyses by cancer molecular subtypes

- Examine potential interactions with genetic predisposition

- Elucidate underlying biologic mechanisms

Studies of cancer survival:

- Address potential confounding by cancer stage, treatment, and comorbidities

- Investigate timing of exposure in relation to cancer diagnosis and treatment

Summary

	Stomach cancer	Liver cancer	Gallbladder cancer	Prostate cancer	Breast cancer survivors
Body fatness	(cardia) 🟥	🟥	🟥	(advanced) 🟥	🟦
Height				🟥	
Alcohol	🟥	🟥			
Salting	🟥				
Processed meat	(non-cardia) 🟥				
Coffee		🟩			
Aflatoxins		🟥			
Beta-carotene				🟨	
Total fat					🟦
Saturated fat					🟦
Foods containing soy					🟦
Fiber					🟦
Physical activity					🟦

Increased risk	Decreased risk	Substantial effect on risk unlikely	Limited-suggestive evidence
🟥	🟩	🟨	🟦

Thank you for your attention!