Biomarkers: examples from cancer epidemiology

In memory of Sheila Bingham

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Sheila Bingham (Rodwell) 1947-2009

Outstanding contributions to nutrition include:

- nutritional biomarkers
- health effects of dietary fibre
- effects of meat on endogenous nitrosation
- application of detailed nutritional methods to large-scale epidemiology

Established the MRC Centre for Nutrition and Cancer in Cambridge in 2005

Long standing contributions to:

- Committee on Medical Aspects of Food Policy
- Scientific Advisory Committee on Nutrition

Honours:

- Fellow of the Academy of Medical Sciences
- Professorships in Cambridge and Coleraine
- Appointed OBE in June 2009

- Biomarkers for validation
  - Example of choice of food diaries in British arm of EPIC
- Biomarkers for large-scale epidemiology – examples from EPIC
  - Long-term reliability
  - Confounding
  - Reverse causation
- Biomonitoring
  - Standardized methods
  - Stable assay: chemical standards for accuracy, negligible assay drift
- Conclusions

Biomarkers during validation of dietary questionnaires in the British EPIC centres

Reference measure	Dietary measure	Timing	Spearman correlations	
			7-day diary	FFQ
Urinary nitrogen from up to 8 x 24-h collections, g/24 h	Dietary nitrogen, g/d	During 1 year	0.67*	0.49*
Urinary potassium from up to 8 x 24-h collections, g/24 h	Dietary potassium, g/d	During 1 year	0.64*	0.41*
Energy from 16 x 1-d weighed records, MJ/d	Dietary energy, MJ/d	During 1 year	0.59	0.52
Dietary fat from 16 x 1-d weighed records, % energy	Dietary fat % energy	During 1 year	0.77	0.64
Serum cholesteryl ester saturated fatty acids, %	Saturated fatty acids, % of fat	One blood sample	0.16	0.26
Serum cholesteryl ester linoleic acid, %	Linoleic acid, % of fat	One blood sample	0.62	0.53

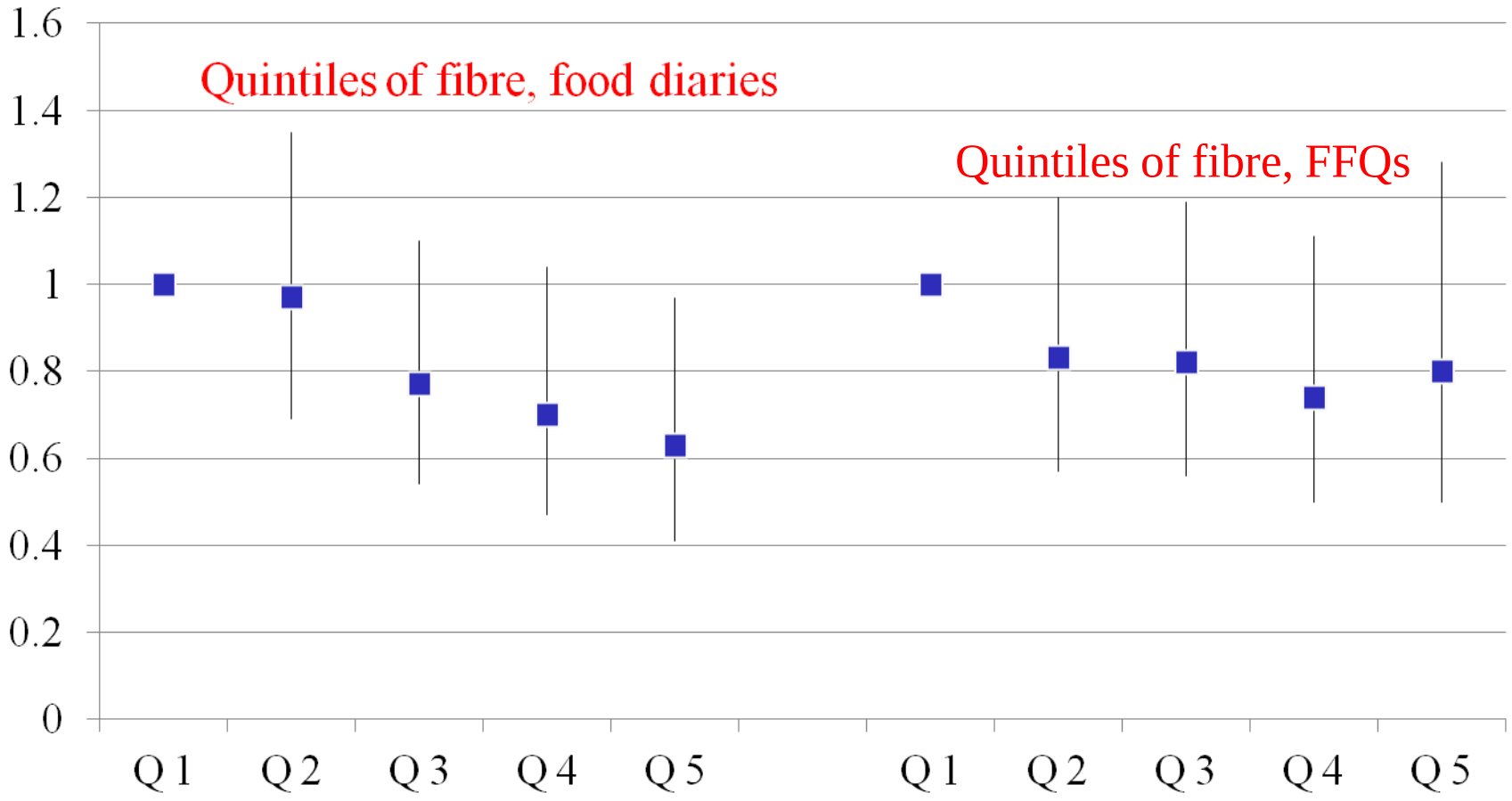
* Energy-adjusted. Data from 156 women in Bingham et al 1997 and 403 women in Brunner et al 2001

Application of detailed nutritional methods to large-scale epidemiology

- Bingham et al Lancet 2003: “Are imprecise methods obscuring a relation between fat and breast cancer?”

- MRC Centre for Nutrition and Cancer: UK Dietary Cohort Consortium of 8 prospective studies with 4-7 day food diaries, total cohort about 100,000 participants
  - EPIC-Norfolk
  - EPIC-Oxford
  - UK Women’s Cohort Study
  - Whitehall II
  - MRC NSHD
  - ProtecT
  - Oxford Vegetarian Study
  - Guernsey Study

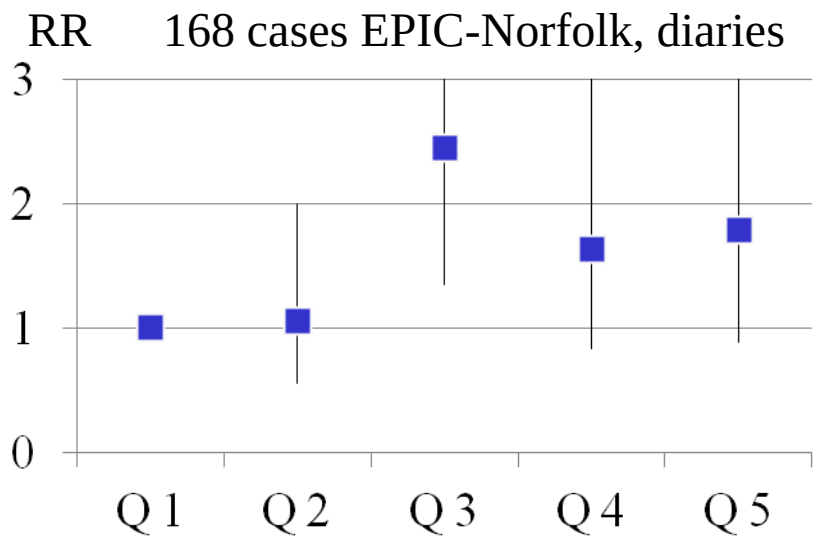
Dietary fibre and colorectal cancer: UK Dietary Cohort Consortium

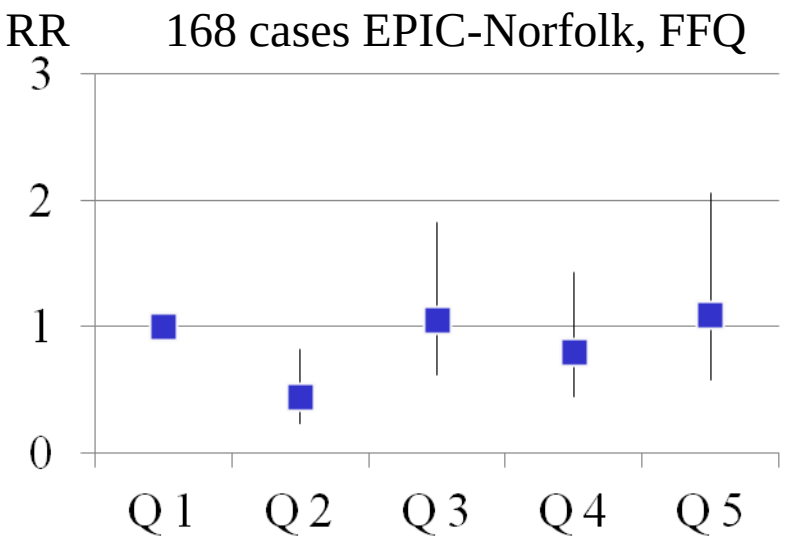


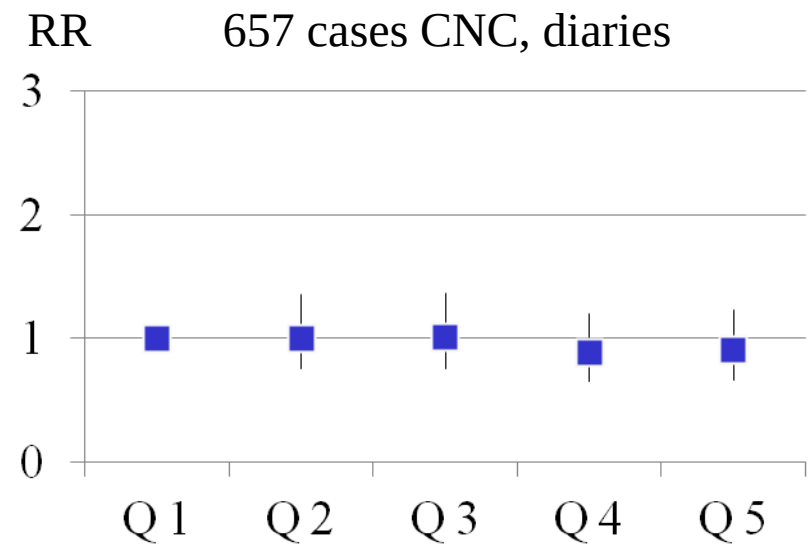
579 cases/1996 controls in 7 cohorts. Dahm et al JNCI 2010

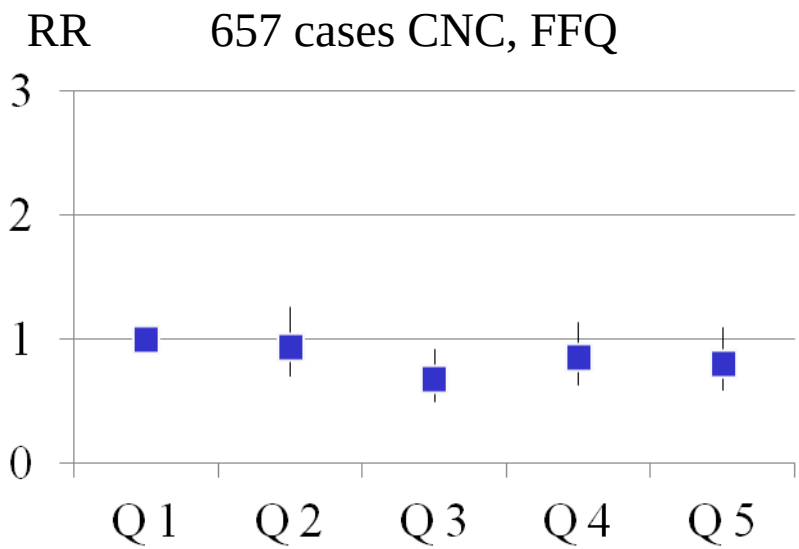
Dietary fat and breast cancer

Dietary total fat as % energy and breast cancer: EPIC-Norfolk 2003 and CNC 2011









Bingham et al Lancet 2003; Key et al AJCN 2011

Trials of low fat diet and breast cancer risk

Trial	Number of cases	RR (95% CI)
Women's Health Initiative (Prentice et al JAMA 2006)	1727	0.91 (0.83-1.01)
Canadian trial (Martin et al Cancer Res 2011)	220	1.19 (0.91-1.55)
Pooled	1947	0.94 (0.86-1.03)

Food diaries in large-scale epidemiology

- Biomarkers show food diaries are more precise than FFQs for some nutrients, at least over a short period
- But extended analyses in Britain have not confirmed that fat estimated by food diaries is positively associated with breast cancer
- Diaries have limitations
  - Slow and very expensive to code
  - Generally nested case-control design – versus full cohort analysis with FFQs
  - Diary coding is subject to errors, rather like laboratory assays. Therefore case-control sets should be batched, and coding variations should be measured, as is done for laboratory assays
- The future for large-scale epidemiology is electronic methods

Biomarkers for large-scale epidemiology

- Long-term reliability
- Confounding
- Reverse causation

Reproducibility of some biomarkers over 1-3 years, Nurses' Health Studies

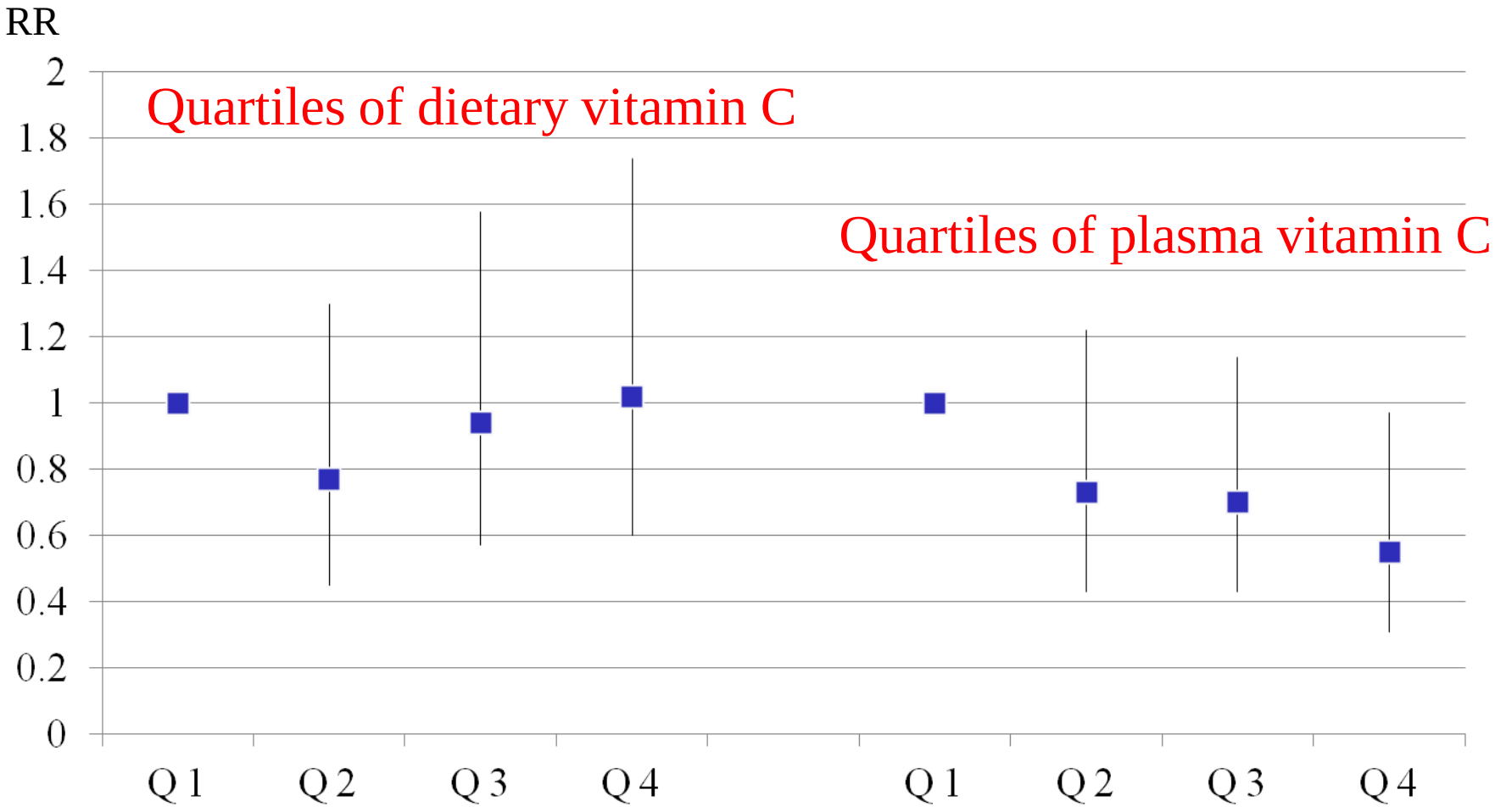
Biomarker	ICC
Plasma beta-carotene	0.73
Plasma alpha-tocopherol	0.83
Red blood cell n-3 PUFAs	0.68
Red blood cell n-6 PUFAs	0.39
Plasma 25-OH vitamin D	0.72
Plasma genistein	0.02
Blood pressure	0.62
Serum cholesterol	0.65

Authors: ICC of 0.4 and above is sufficient to use single measure.

Kotsopoulos et al CEBP 2012

Vitamin C and stomach cancer

Plasma and dietary vitamin C and risk of stomach cancer in EPIC



215 cases and 416 controls. Jenab et al Carcinogenesis 2006

Vitamin C, smoking and stomach cancer in EPIC

Smoking status	Plasma vitamin C µmol/l	RR for plasma vitamin C increase of 19.4 µmol/l	Extended follow-up, RR for dietary citrus fruit increase of 50 g/d
Never	43.5	1.13 (0.86-1.47)	1.00 (0.90-1.11)
Former	40.6	0.91 (0.67-1.24)	1.01 (0.90-1.14)
Current	38.9	0.67 (0.43-1.06)	0.86 (0.74-1.01)
P for difference	NS	-	0.07

Jenab et al Carcinogenesis 2006; Gonzalez et al Int J Cancer 2012

Vitamin C and stomach cancer: comments

- Stomach cancer risk appears to be more related to plasma vitamin C than to dietary vitamin C, or dietary citrus fruit

- But we can't yet exclude:
  - **residual confounding -** e.g. by smoking
  - **reverse causality** – growing tumour present before diagnosis may affect absorption and metabolism

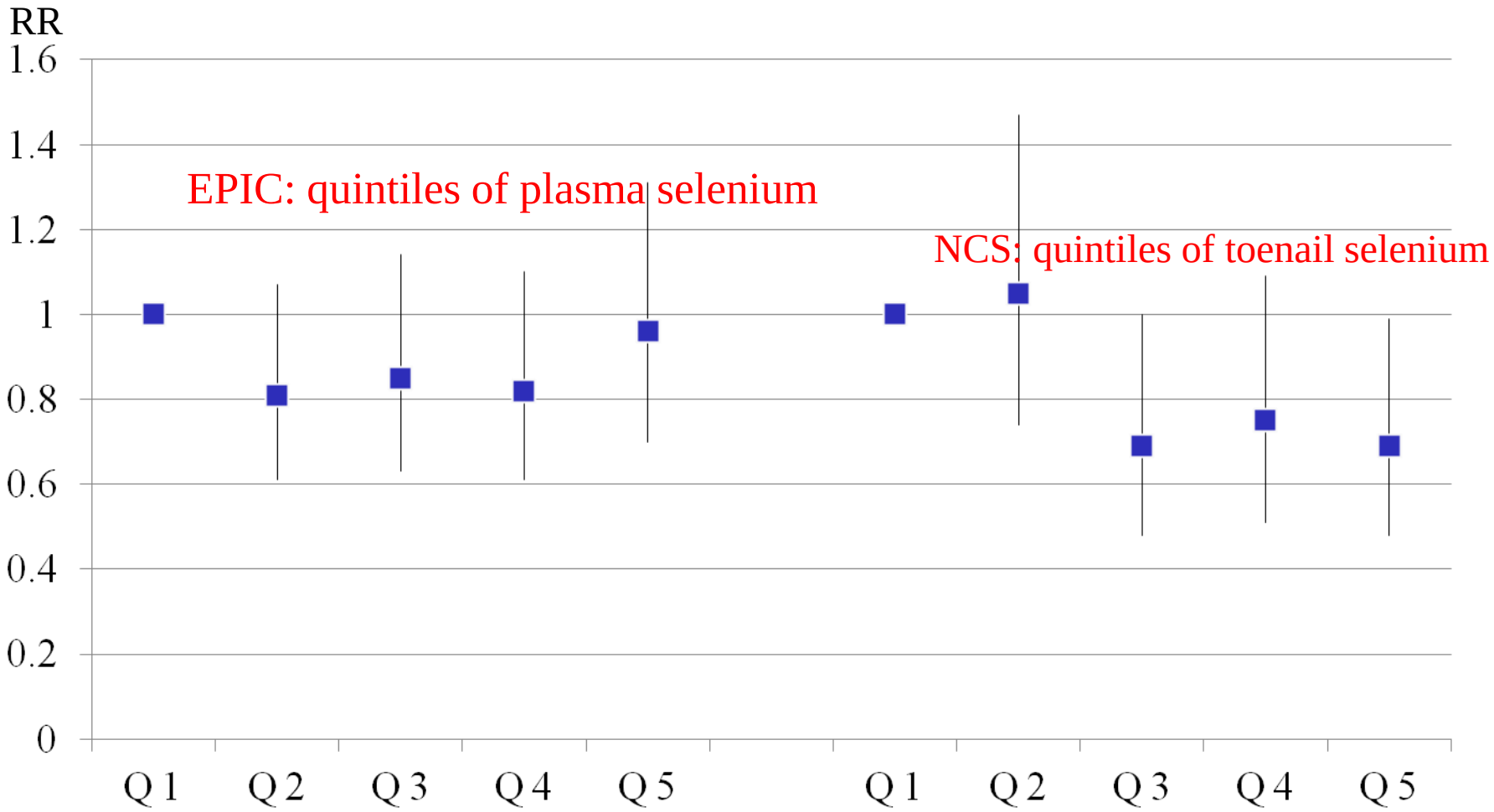
- More data needed, with longer follow-up

Selenium and prostate cancer

- Generally agreed that dietary measures are not useful, therefore biomarkers are needed

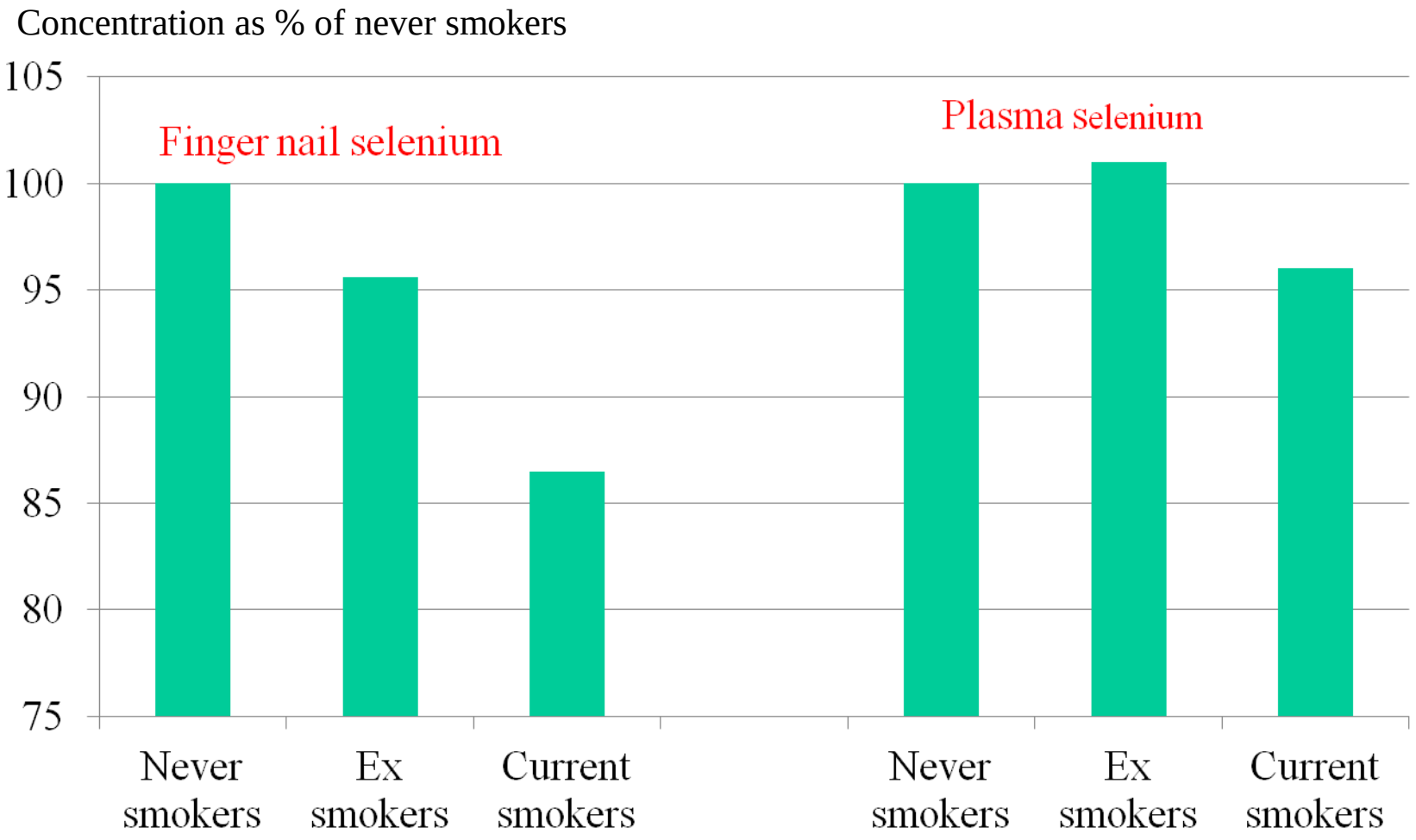
- Reproducibility seems good:
  - e.g. Taylor 1987, serum over 1 y, ICC = 0.76

Plasma and toenail selenium and risk of prostate cancer in EPIC and Netherlands Cohort Study



EPIC 959 cases/1059 controls, Allen AJCN 2008.
NCS 540 cases/1211 subcohort, van den Brandt CEBP 2003

Smoking and selenium



Finger nail study in England, plasma study EPIC Europe. Allen et al 2004; 2008

Selenium and prostate cancer: comments

- Different biomarkers - such as plasma and toenails - may give different results and may be differentially affected by confounding factors

- A large randomized trial has shown no benefit of supplementation - in a high selenium area (SELECT in the USA)

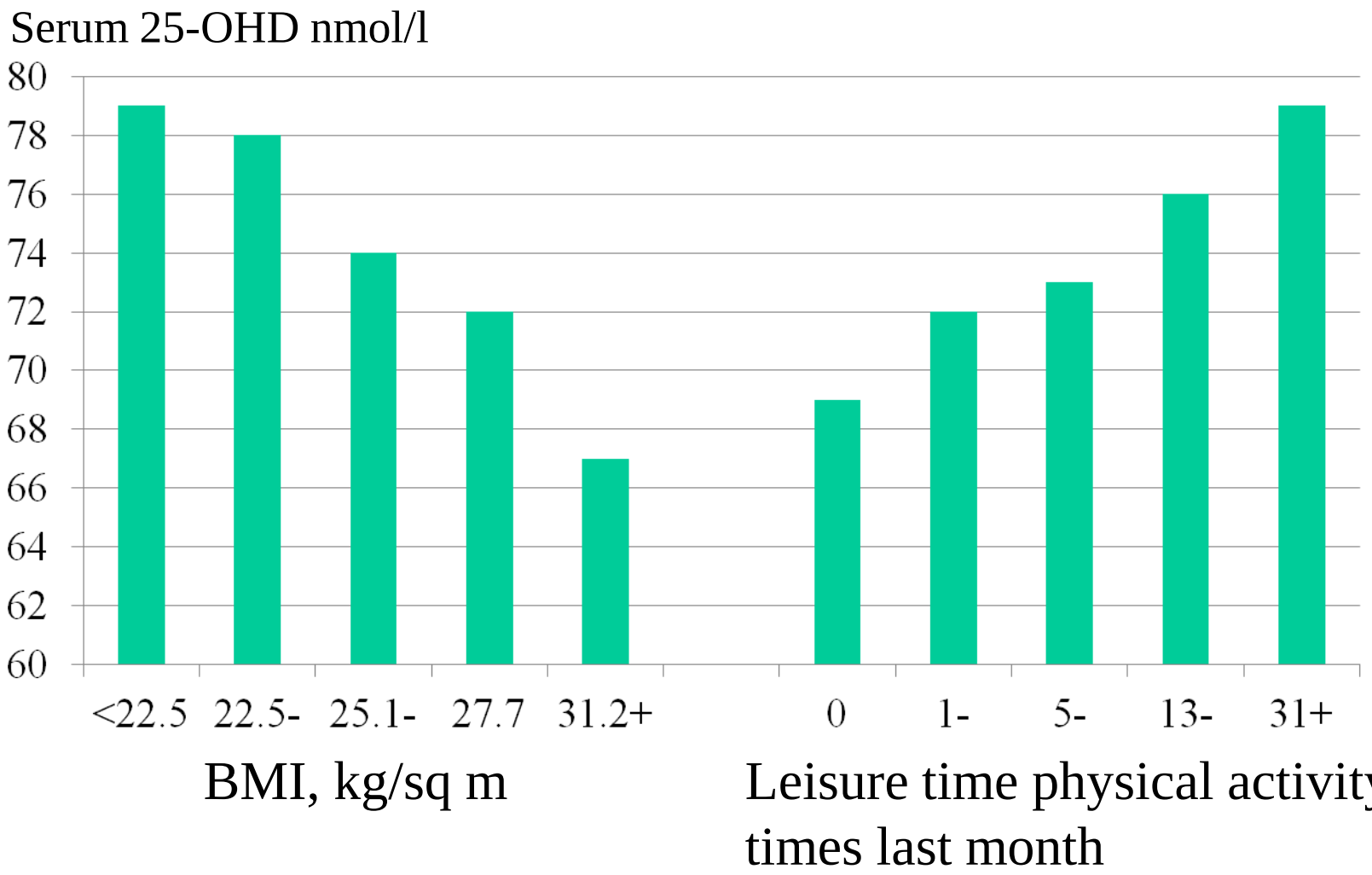
Vitamin D and cancer

- Generally agreed that dietary measures are not useful, therefore biomarkers are needed

- Reproducibility seems fair to good:
  - Al-Delaimy et al Biomarkers 1987, EPIC-Netherlands, serum over 2-5 y, ICC = 0.65
  - Meng et al CEBP 2012, WHI, plasma over 5 y, ICC = 0.59 (0.54-0.64)

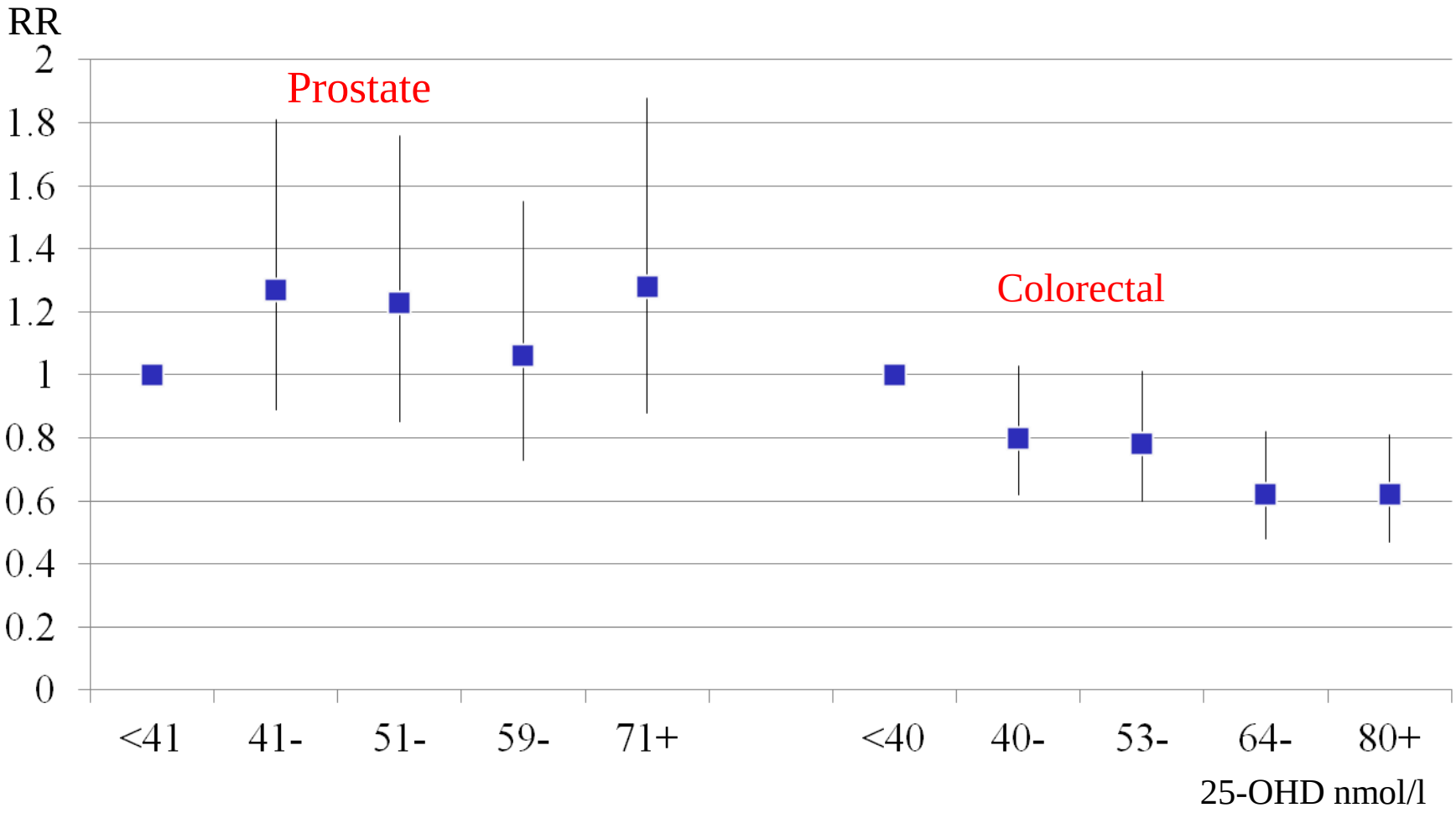
- Confounding may be a big problem?

Serum 25-OHD, BMI and physical activity



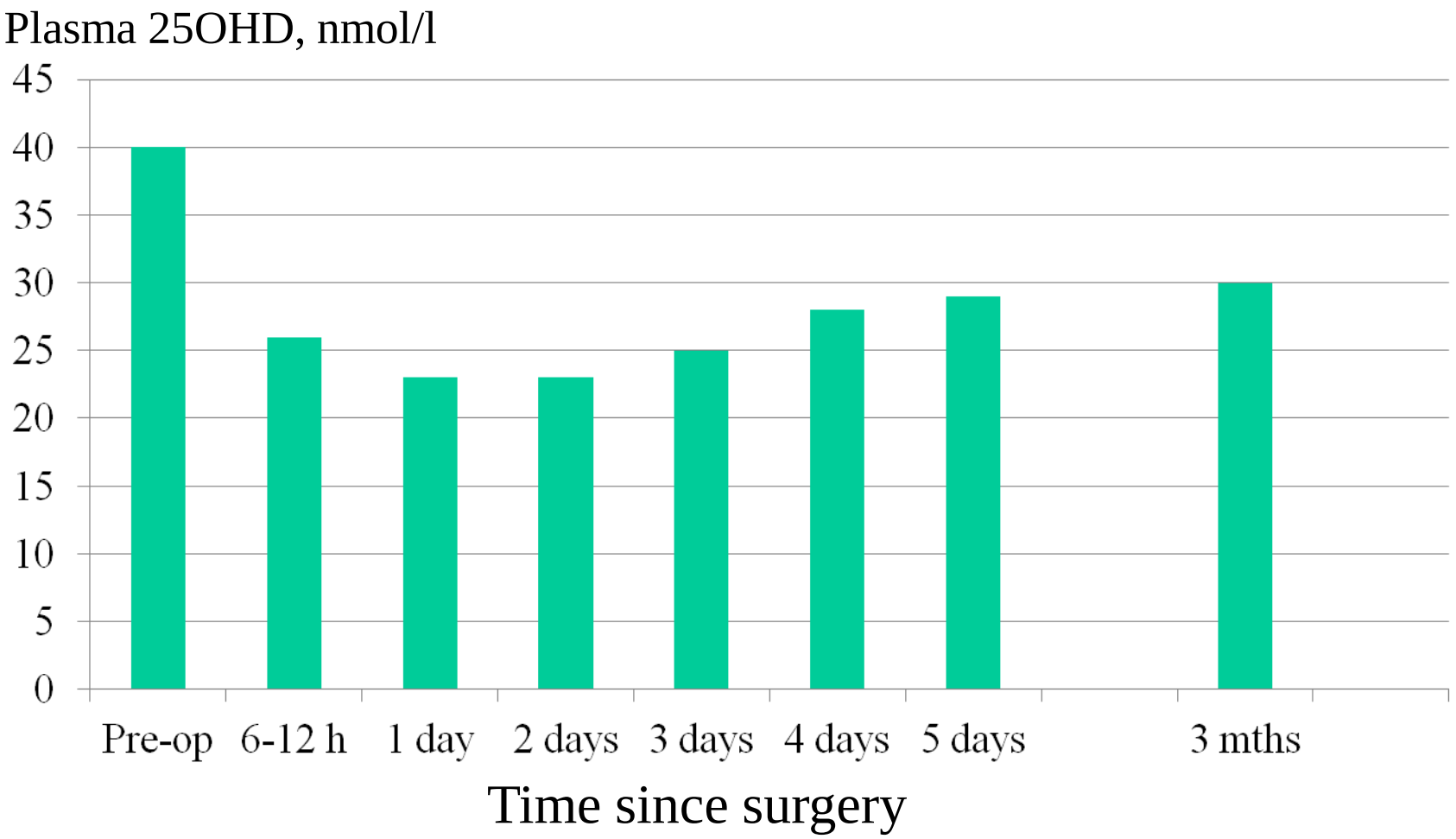
15,148 participants in NHANES III. Scragg et al Am J Epidemiol 2008

Vitamin D, prostate and colorectal cancer in EPIC



Prostate 652 cases/752 controls, Travis AJE 2009.
Colorectal 1248 cases/1248 controls. Mean follow-up 3.8 y. Jenab BMJ 2010.

Reverse causality? – example of plasma 25-OH vitamin D after elective knee surgery



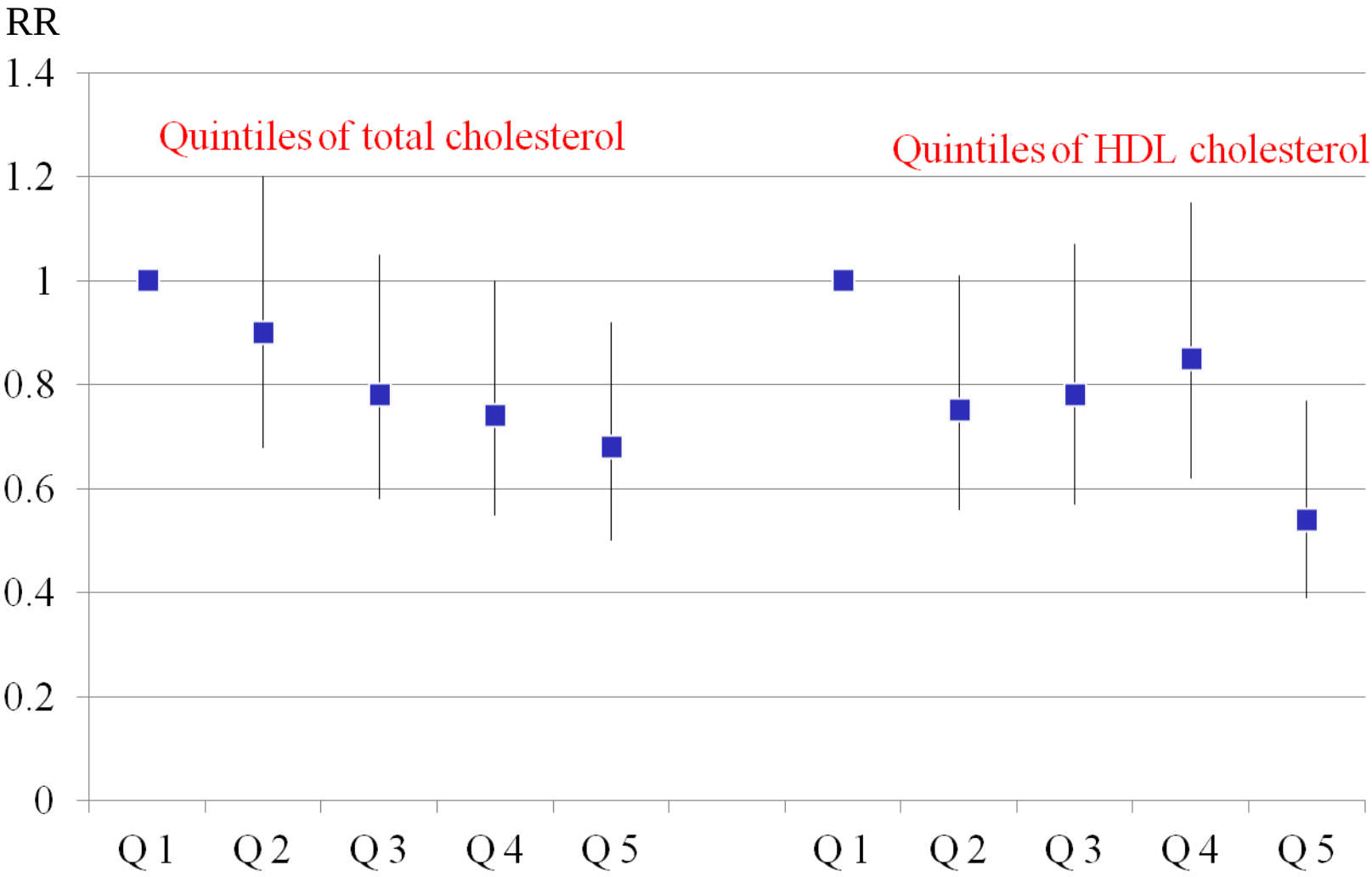
33 patients, knee arthroplasty. Reid et al AJCN 2011

Reverse causality: example of cholesterol and colon cancer

- Rose 1974
  - Prospective study, 90 deaths from colon cancer
  - Cases had lower than expected blood cholesterol

- Kritchevsky 1991
  - Cholesterol measured every 2 months in prospective study, 103 incident cancer cases
  - Cholesterol started to decrease 2 years before cancer diagnosis

Serum lipids and colorectal cancer in EPIC



1238 cases/1238 controls. Mean follow-up 3.8 y. Van Duijnhoven et al Gut 2011

Cholesterol and cancer, Mendelian randomization study

Analysis	Change in LDL cholesterol	RR	*P* for difference in RRs
Measured cholesterol	50% increase	0.91 (0.83-0.99)	0.03
Genetic predictors of cholesterol	50% increase	1.04 (0.95-1.15)	

Copenhagen City Heart Study and Copenhagen General Population Study.
Benn et al, JNCI 2011

Requirements for future studies

Long-term reliability

- Available data are sparse - and non-existent for some biomarkers
- Need data over 10 years - or more
- Repeat samples in whole cohort would help

Confounding

- A big problem: more emphasis needed on factors which affect biomarkers, e.g. smoking, to quantify and understand mechanisms

Reverse causation

- Needs much more investigation
- Large studies with long follow-up
- Repeat samples would help