Disclosures for: [Ailsa Welch]

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DIET AND BREAST CANCER: NEW APPROACHES ARE NECESSARY

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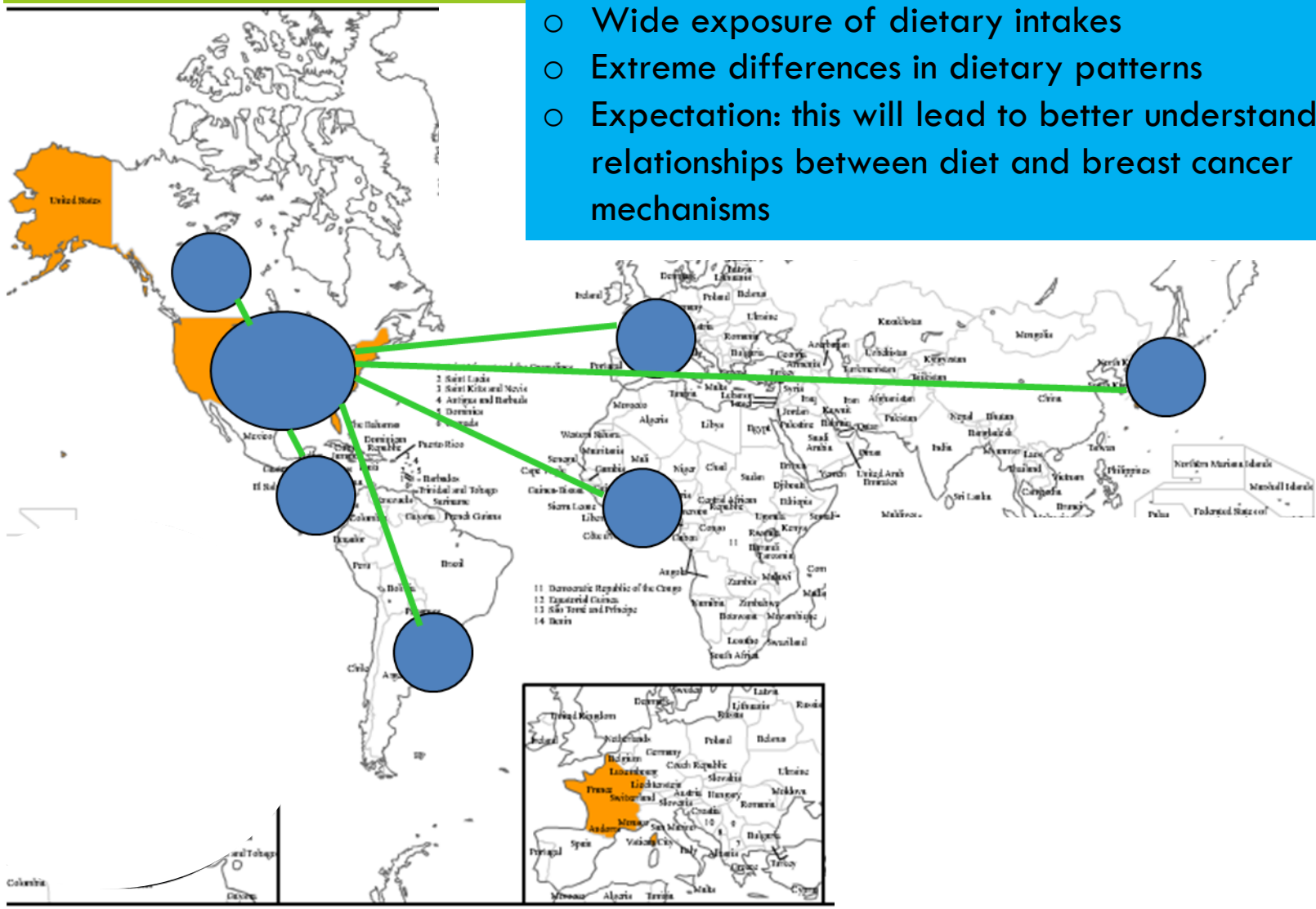
Overview

- Aims and challenges for the IBCN
- Dietary assessment
  - Methodological challenges
  - Measurement error
- Biomarkers of nutritional intake
- Experiences of measuring nutrition in the European Prospective Investigations into Cancer and Nutrition Study (EPIC-Europe, EPIC-UK, EPIC-Norfolk)
- New methods for the IBCN

Diversity of Diet



- Wide exposure of dietary intakes
- Extreme differences in dietary patterns
- Expectation: this will lead to better understanding of relationships between diet and breast cancer mechanisms

Purpose of new approaches for IBCN

- Overall aim: to capture diet more accurately than previously possible, at same time as obtaining breast cancer tissue samples
- Aim to collect
  - Dietary intakes
  - Diet composites
  - Biomarkers/nutrient status measurements (indicators of nutritional exposure)
- Aim to relate dietary composition to epigenetics in breast cancer tissue samples

Challenges

- Diverse populations
- Capturing diet by self report complex
  - Some challenges with measurement error in dietary assessment
- Biomarkers
  - Some challenges with measurement and interpretation
- Some problems to be faced:
  - Literacy
  - Computer availability
  - Trust of researchers

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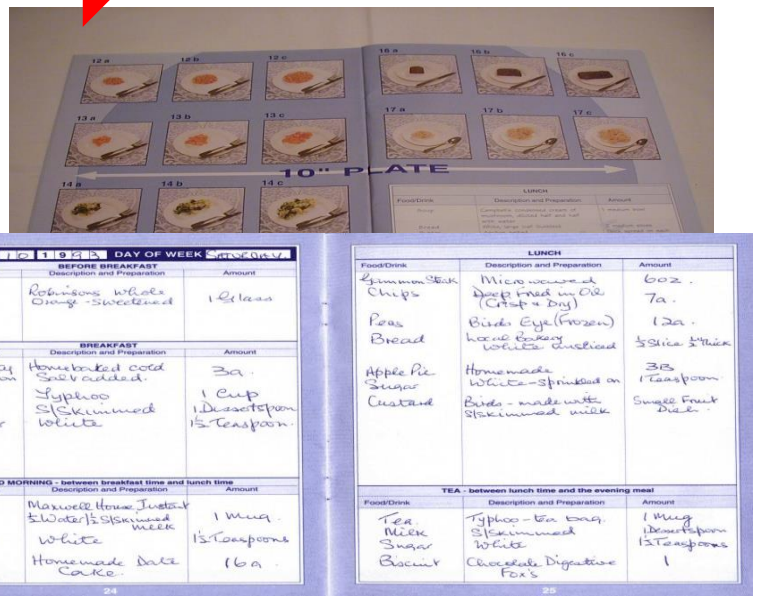
Assessment of dietary intake

- Self-reported or interviewed reports of intake
  - Current or retrospective
- Dietary composites – direct analysis of composition of foods
- Biological markers (biomarkers) of nutritional status

Examples of dietary methods: Open ended versus fixed structure (used in EPIC-Norfolk cohort)

Current → Record/Diary — Frequency/FFQ → Retrospective



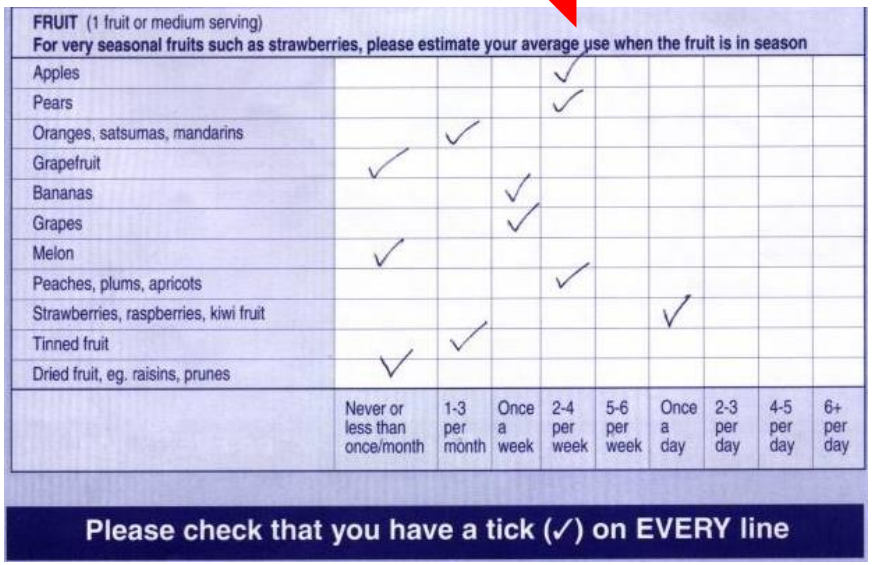
7-day diary

Detailed text information

Requires interpretation

Labour intensive

Welch AA, PHN, 2001



FFQ (Food Frequency Questionnaire)

Epidemiology

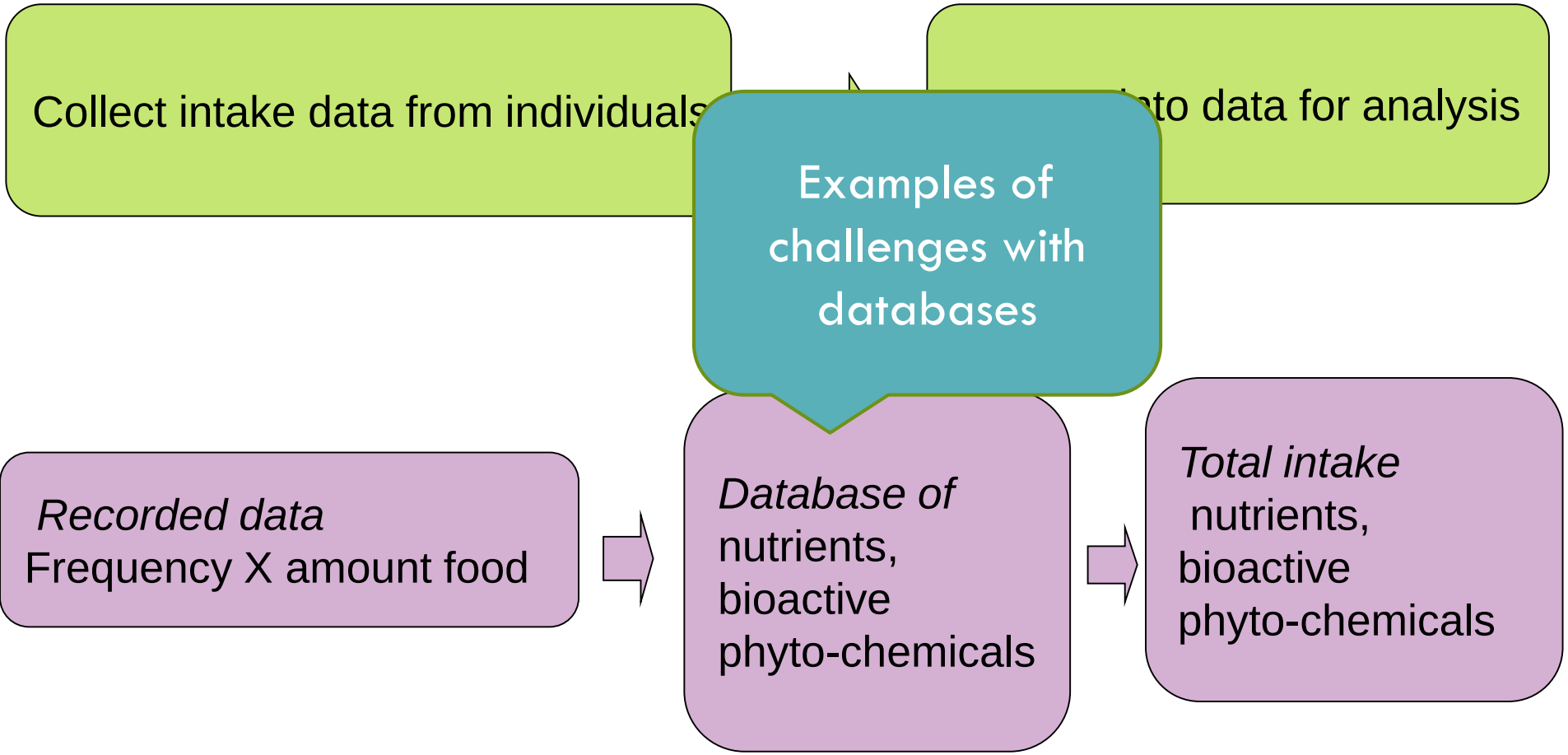
Simpler, limited food list. Fixed structure

> Intakes many nutrients

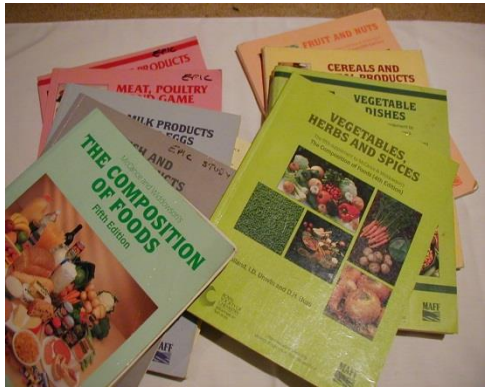
> Measurement error

Welch AA, J Hum Nut Diet, 2005

Methods – principles of obtaining dietary data for analyses in studies



Food nutrient databases: challenges



UK food composition database series (Royal Society of Chemistry 2012)

West African Food Composition Table (FAO 2012)

- Limited food coverage
- Infrequently updated
- Limited coverage nutrients/ bioactives
- Nutrient variability: carotenoids
- Different analytical techniques eg fibre, AOAC, Englyst
- Not all databases are consistently comparable across countries (potential bias)

Measurement error in dietary assessment

- Definition: difference between the measured exposure and the true exposure for diet
- Potential contributory causes for IBCN
  - Questionnaires – omitted foods
  - Length of period of recording
  - Respondent/social desirability bias
  - Interviewer bias
  - Data entry and issues with supporting databases

Example of importance of differences between diet methods

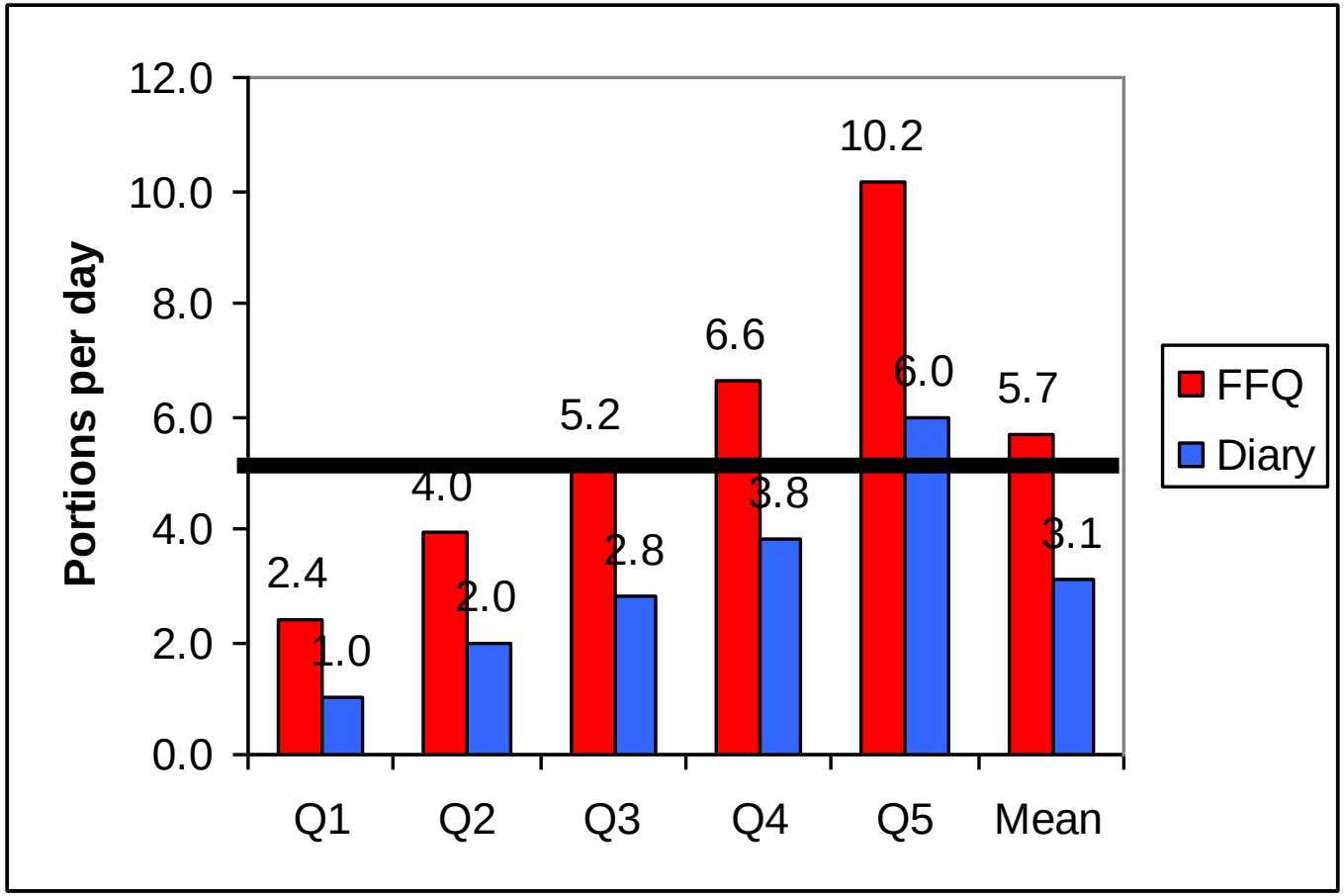
Effects of methodological differences in estimates of consumption on population monitoring (same subjects within same cohort) – fruits and vegetables

FFQ > estimates fruit & vegetables than 'real time/record' methods

Compared with 5-a-day recommendations

challenges for policy

Methods ranked similarly against plasma vitamin C



Bingham S, Luben R, Welch A et al AJE, 2008

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Biomarkers

- Nutritional biomarkers are indicators of nutritional exposure:
  - Nutrients
  - Bioactives
  - More recently: other metabolites

Examples of biomarkers for estimating intake of nutrients/bioactive compounds

Quantitative recovery

Absolute value over period of time (integrates over time), 24-hr urine

- N, Na, K, sucrose, fructose, thiamin
- Energy – Doubly Labelled Water (DLW)
- Fruit & vegetables: hippuric acid (Krupp D, 2012)
- Whole-grain: Total alkylreoscinol, DHBA (3, 5-Dihydroxybenzoic acid), DHPPA (3-(3,5-Dhydroxyphenyl)-Propanoic acid) (Hedrick V, 2012)

Concentration

Relative ranking blood/skin

- *Nutrients*: vitamins C, E, D, B12, folate, fatty acids, carotenoids (recent skin – Mayne S, 2013)
- *Bioactives:* flavonoids, isoflavones

Adipose tissue

- Fatty acids, fat soluble vitamins

Biomarkers of nutritional intake

Utility for direct measurement of diet influenced by:

- Genetics
- Gender
- Homeostatic influences – integrated effects of metabolism
- Physiological effects (plasma vitamin C lower with higher waist:hip ratio)
- Behavioural influences (smoking & plasma vitamin C)
- Non-linear associations (vitamin C plateaus)
- Measurement error in lab
- Limited number available,

though number expanding

(metabolomic approaches)

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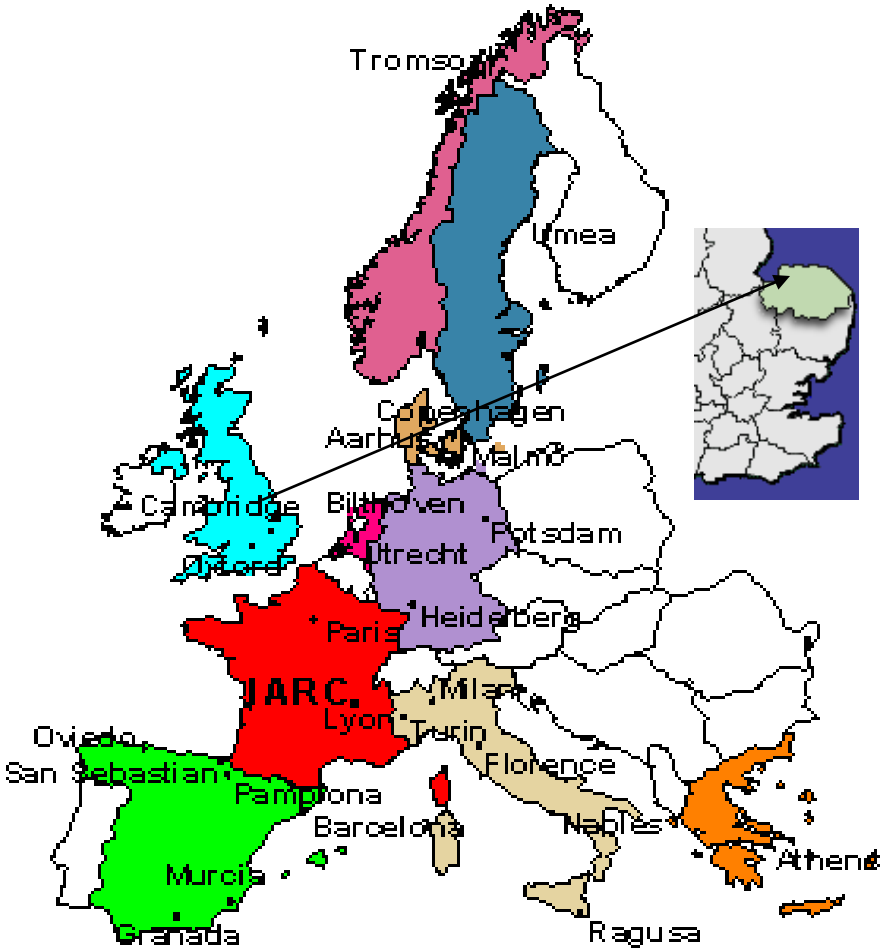
European Prospective Investigation into Cancer and Nutrition



- EPIC-Europe multi-center cohort study of diet and cancer
- 10 countries – started 1993
- 450,000 participants
- EPIC-Norfolk cohort 25,000 people 45-74 Y
- Extended to other chronic diseases eg CVD, diabetes, osteoporosis
- Diverse dietary patterns
- Different dietary assessment methods – literacy challenges
- Different food composition databases

Solutions within EPIC

Databases - standarisation

- Developed European Nutrient Database (ENDB)
- Standard
  Europe, t
  between
- 550-155
- National compilers, food chemists, EPIC nutritionists (Slimani et al, EJCN 2007)

Biomarker validation

- Biomarkers in subsets of the populations for validation of dietary methods. Used urine N, K & blood carotenoids (Bingham SA et al IJE, 2008)

Dietary calibration

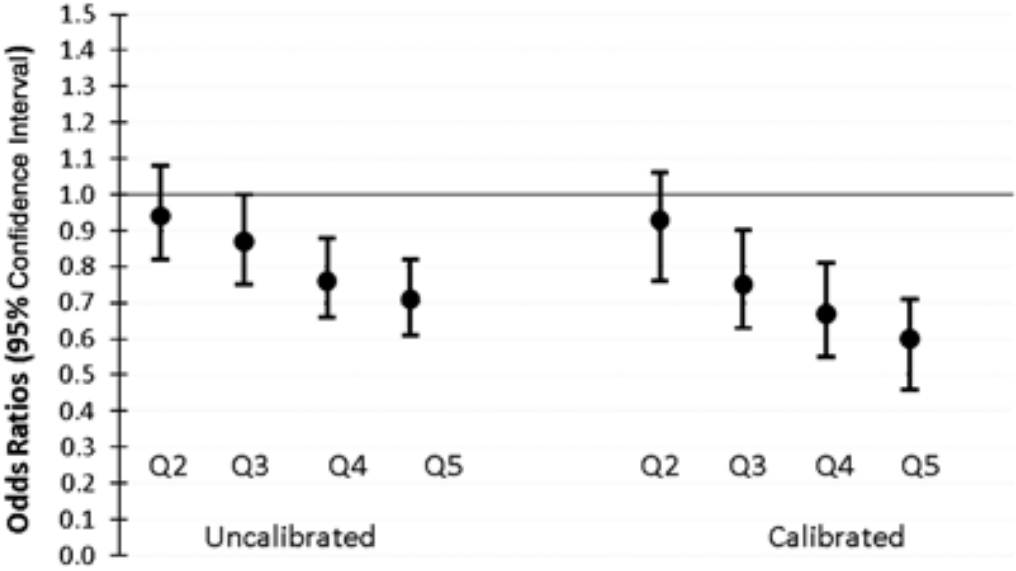
- Development of standardised computer program for 24-hour
  tions
  or food wastage, cooking changes
  - Collection of descriptors for foods
- Interviews in subset of each cohort
- Data used to 'calibrate' main study analyses relating diet to cancer incidence (Bingham SA, Lancet 2003)

Highly labour intensive

Example of solution to measurement error: using calibration of dietary intake with a biomarker in relation to disease outcome

- Protein intake & frailty (Beasley JM, J Am Ger Soc, 2010). Debate on protein recommendations for frailty prevention.
- Calibrated using DLW & N excretion in subsample
- Calibrated values of FFQ used to estimate incident frailty (covariates: BMI, age, race, education, income, smoking & physical activity)
- > association with calibrated % protein intake (per 20% increase in protein versus uncalibrated protein intake)

OR of incident frailty in women 65-79Y



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Proof of principle study

Aim to test feasibility of international sample collections

Phase 1 – diet composites

- Design 1 or 2 dietary patterns that represent common eating patterns in your region. Ideally from nationally representative data. To reflect appropriate energy intake for a woman 18-45 year old

- Phase 2 – 24 H diet record, diet composite, fasting blood & urine
- Collect samples from generally healthy subjects consuming diets representative of the region.
- Record all eaten and drink
- Collect duplicate composite
- Following day – collect fasting blood and urine sample

Summary of participation in the IBCN project: Phase 1

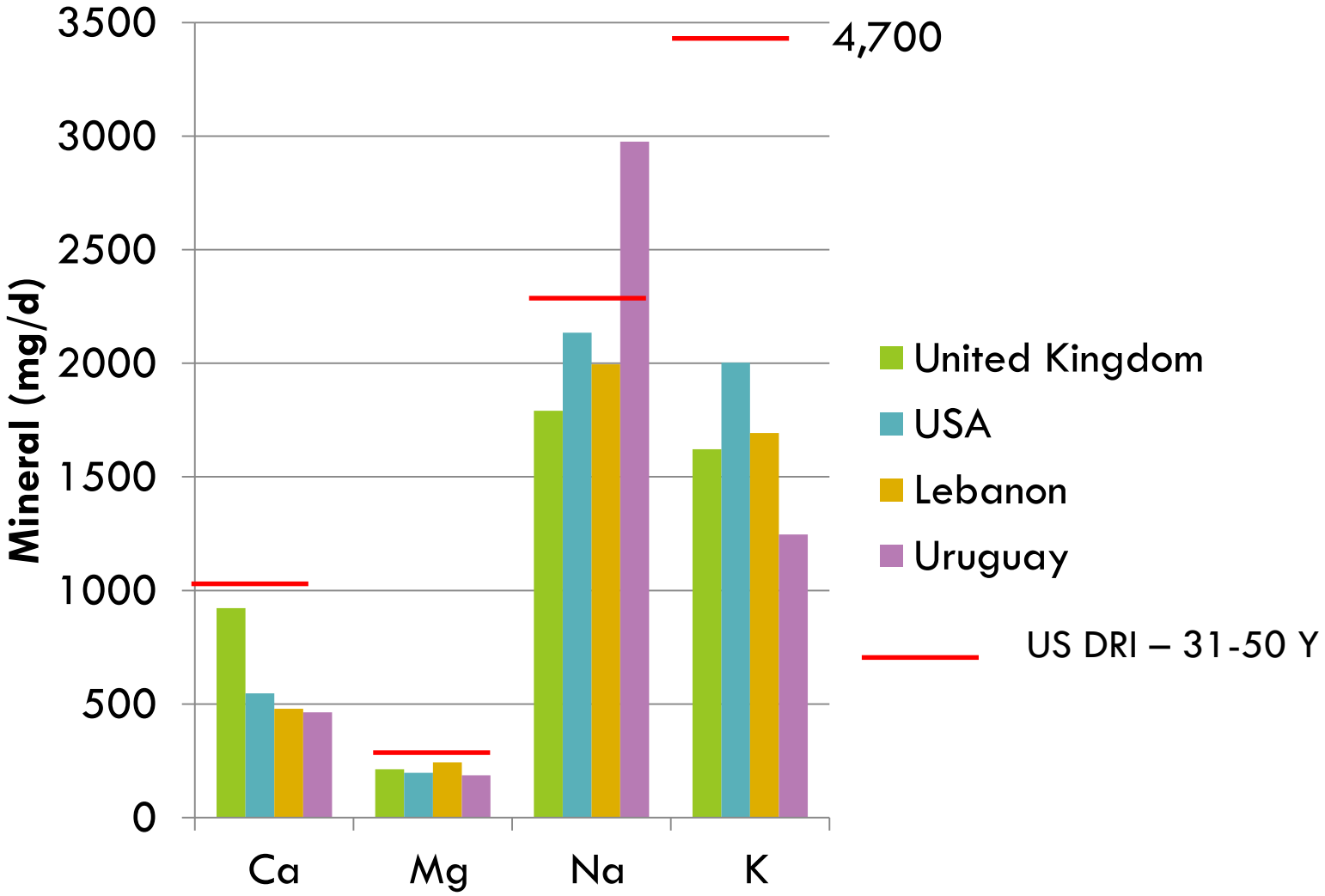
Country	Diet Pattern	Basis for Diet Pattern	Diet Homogenate
Lebanon	X	X	X
France	X	X	
USA	X	X	X
China	X		X
England	X		X
Uruguay	X		X
Ghana			

Results: Dietary diversity, number of food items

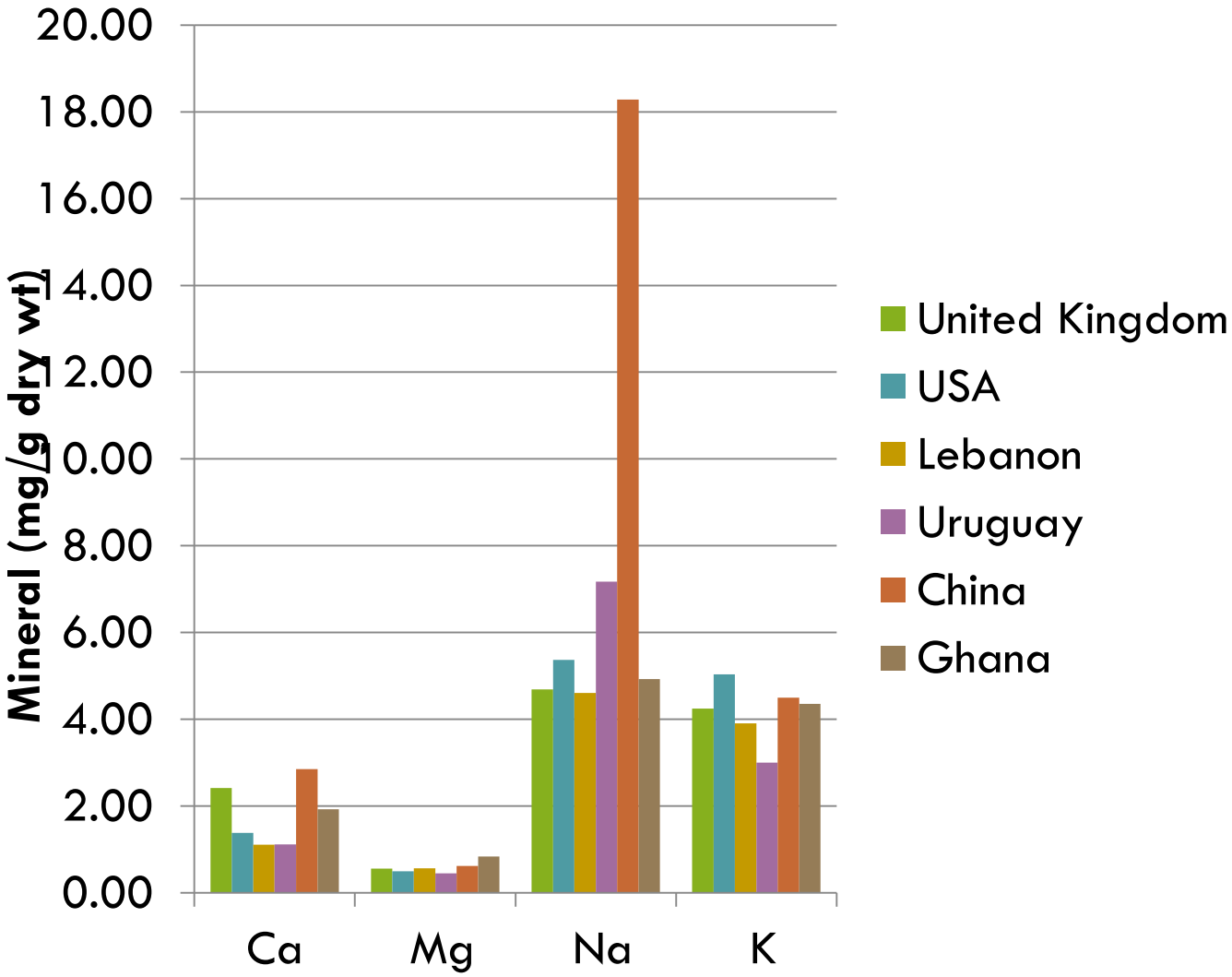
Country	Number of foods	Beverages	Condiments, etc.*
China	6	0	
UK	17	8	1
USA	10	5	4
Lebanon	11	3	2
Uruguay	6	4	2
France	13	4	3

*Includes butter, jam, salt, oil, sugar, salad dressing, cream

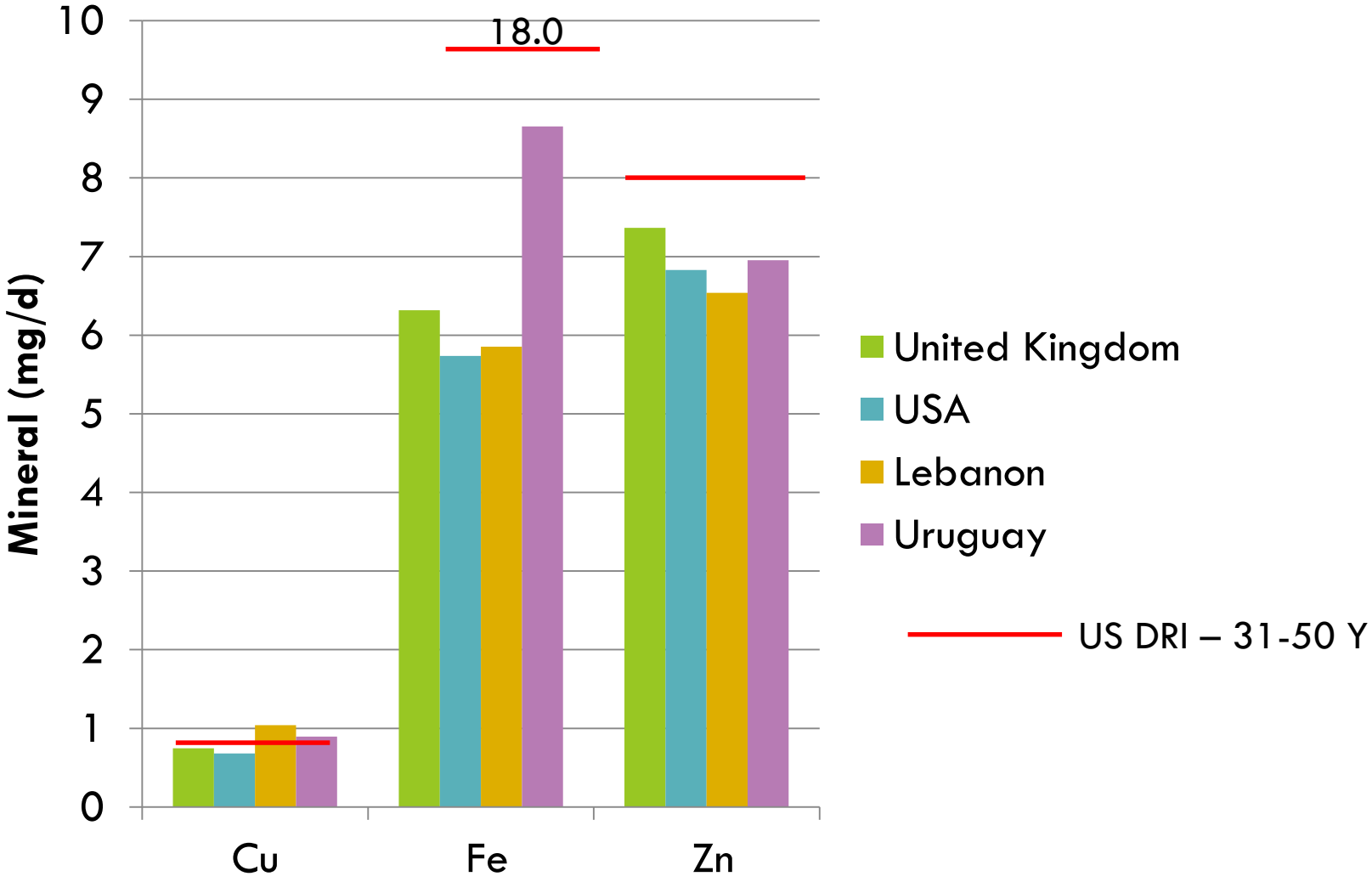
Results: mineral intakes in 4 countries (Ca, Mg, Na, K)



Results: mineral intakes in 6 countries (Ca, Mg, Na, K)



Results: mineral intakes in 4 countries (Cu, Fe, Zn)



Summary of progress on phase 2

Country	Ethics Approval	Number Enrolled	Diet Homogenate Received	Menu & preparation Data	Blood samples Received
Lebanon	**				
France					
USA	X				
China					
England					
Uruguay	**				
Ghana	X	2	X		

** Close to having approval

Learning points & experiences

1. Some countries required special letters from Purdue indicating the contents and reason for shipping the diet homogenates.
2. Shipping generally completed in 4-9 days
3. Requirements for ethics approval vary greatly. Requests from various countries:
   - A proposal for the entire project
   - Record of human subjects training approval (CITI) for Dr. Weaver
   - A literature review on the topic
   - Many countries have not completed the ethics approval as the process is slow and complicated depending on the institutional infrastructure.
   - Memorandum of Agreement with Purdue University required (1 country)
4. US cannot ship supplies for Part 2 until a copy of the ethics approval has been obtained from the country institution.

Further learning points

- There was variation in the type of information received with the diet shipments (weights, menus) so the documents and instructions need to be improved
- Emphasizes the problems working across cultures & disciplines
- Setting up a protocol is not enough when working across countries
  - Solution is potential training

Conclusion

- Extensive progress
- Completion of first stages demonstrate the project is possible

- T H A N K Y O U F O R L I S T E N I N G