UNIVERSITÉ DE GENÈVE

GENEVA SCHOOL OF ECONOMICS AND MANAGEMENT

A Bayesian hierarchical model to integrate dietary exposure and biomarker measurements for the risk of cancer

Marta Pittavino, PhD

Senior Research Associate, Research Center for Statistics
UNIGE, Geneva - Switzerland

Summary

- Outline on measurement error
  - Combine biomarkers with self-reports
- A Bayesian hierarchical model with three components
  - An application from the EPIC study
- Concluding remarks

Outline on measurement error

- Difference between the actual true value and the measured value

Outline on measurement error

- Difference between the actual true value and the measured value
- Self-reported assessments (questionnaire: **Q** and 24-HDR: **R**) of dietary exposure prone to random and systematic measurement errors

Outline on measurement error

- Difference between the actual true value and the measured value
- Self-reported assessments (questionnaire: **Q** and 24-HDR: **R**) of dietary exposure prone to random and systematic measurement errors
- Estimates of the association between dietary factors and risk of disease can be biased

Outline on measurement error

- Difference between the actual true value and the measured value
- Self-reported assessments (questionnaire: **Q** and 24-HDR: **R**) of dietary exposure prone to random and systematic measurement errors
- Estimates of the association between dietary factors and risk of disease can be biased

- It has been suggested to complement self-reports with objective measurements, as **dietary biomarkers (M)**

Why combine self-reports and biomarkers?

- Objective biomarkers have long integrated self-reported dietary (or physical activity) measurements

- Several validation studies with *recovery* (OPEN, NHS, WHI, EPIC) and *concentration* biomarker measurements (Ferrari *et al.*, AJE, 2007)

- Biomarkers also integrated in diet-disease association studies (Freedman *et al.*, EPI, 2011; Tasevska *et al.*, AJE, 2018; Prentice *et al.*, AJE, 2017)

Motivating scenario

- Plasma levels of Vit-B6 were inversely associated with kidney cancer risk in EPIC (Johansson, JNCI, 2014)
  - Serum levels of Vit-B6, unlike Q measurements, were inversely related to lung cancer (Johansson, JAMA, 2010)
  - Dietary folate inversely related to breast cancer (de Battle, JNCI, 2014), unlike plasma levels (Matejcic, IJC, 2017)

Application

- Data from two EPIC nested case-control studies on kidney (n=1,108) and lung (n=1,764) cancers

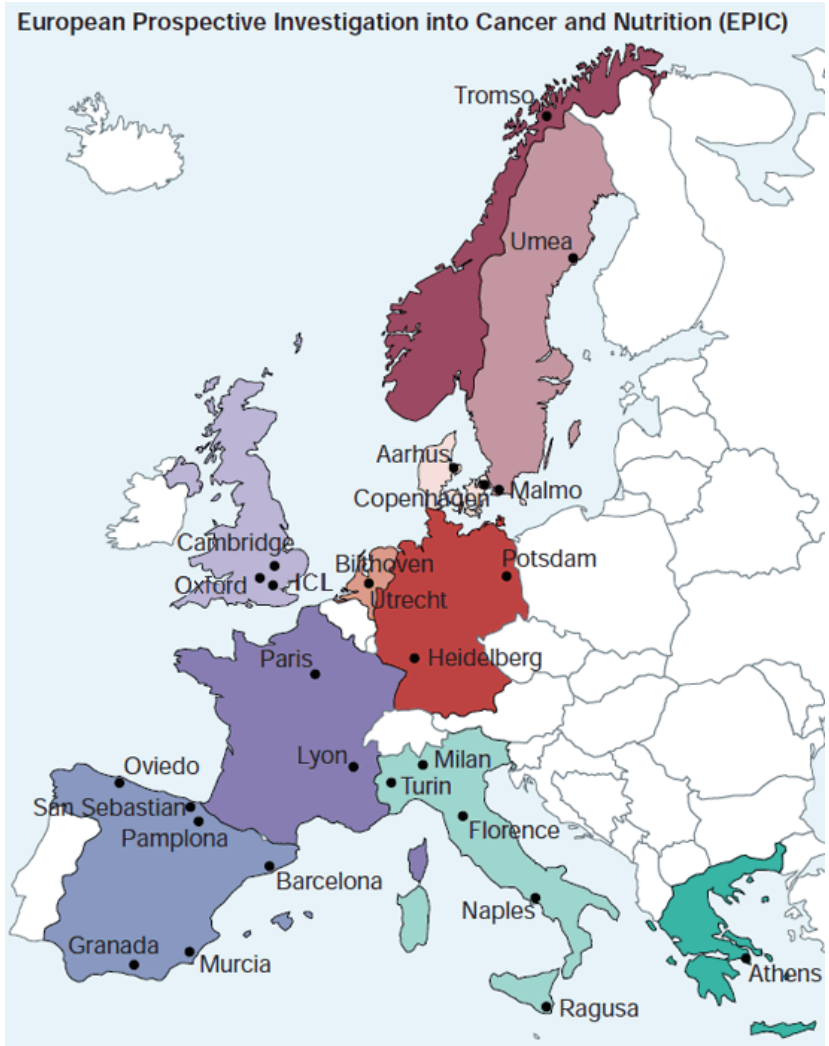
- Q, R and M measurements on vit-B6 and folate

  R measurements, available on $\sim$10% of the sample, were imputed

  Data were log-transformed to approximate normality

The EPIC Study

- Prospective cohort with 500,000 participants from 23 centres
  - Dietary and lifestyle exposures assessed at baseline
  - Biological samples collected at baseline from 80% disease-free participants



International Agency for Research on Cancer

World Health Organization

The setting

- Develop a Bayesian latent factor hierarchical model to:

- Integrate self-reported (Q) and (R) with *concentration* biomarker (M) measurements

- Evaluate the measurement error structure

- Estimate the unknown association between unknown true dietary intakes (X) and risk of disease (Y)

How did we get here?

- Long time ago, Ray Caroll and Pietro Ferrari discussed the idea of a Bayesian model for measurement errors
- DQs and 24-HDRs of energy and fat intakes were related to the risk of breast cancer in EPIC

Pietro Ferrari and Martyn Plummer submitted an applicationto WCRF in 2013.

First results were produced last year

STATISTICS IN MEDICINE
Statist. Med. 2008; **27**:6037–6054
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3444

A Bayesian multilevel model for estimating the diet/disease relationship in a multicenter study with exposures measured with error: The EPIC study

Pietro Ferrari[1,*,†], Raymond J. Carroll[2], Paul Gustafson[3] and Elio Riboli[4]

[1]*International Agency for Research on Cancer, Lyon, France*
[2]*Texas A&M University, College Station, U.S.A.*
[3]*Department of Statistics, University of British Columbia, Vancouver, Canada*
[4]*St Mary's Campus, Imperial College, London, U.K.*

How did we get here?

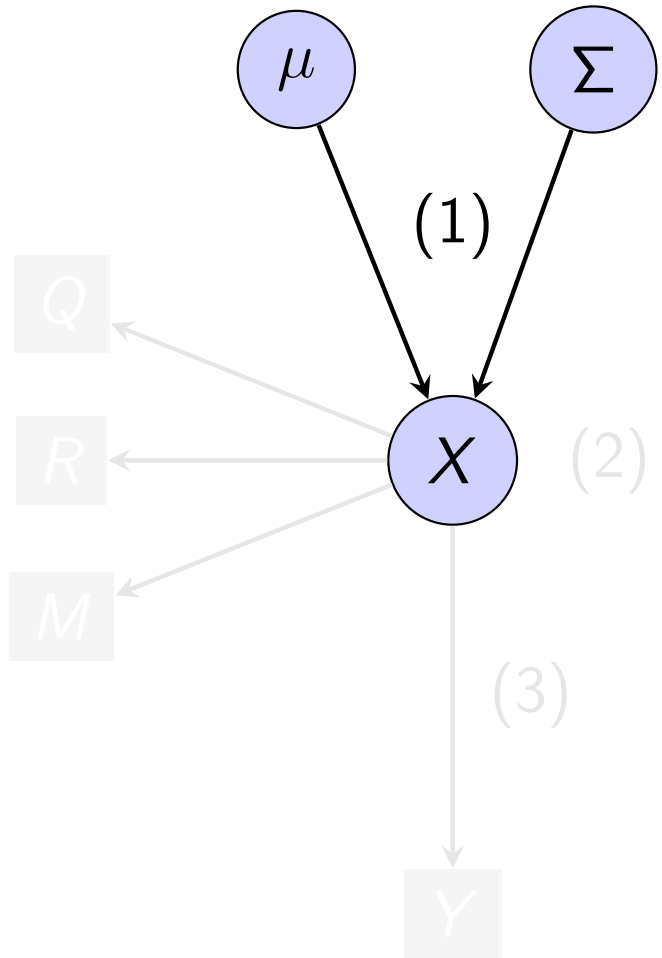
- Long time ago, Ray Caroll and Pietro Ferrari discussed the idea of a Bayesian model for measurement errors
  - Combine DQs and 24-HDRs of energy and fat intakes, and relate them to risk of breast cancer in EPIC
- Pietro Ferrari and Martyn Plummer submitted an applicationto WCRF in 2013
  - First results were produced in 2017

The Bayesian hierarchical model

1) Exposure model: $p(X|\mu, \Sigma)$

2) Measurement model: $p(Q, R, M|X)$

3) Disease model: $p(Y|X)$

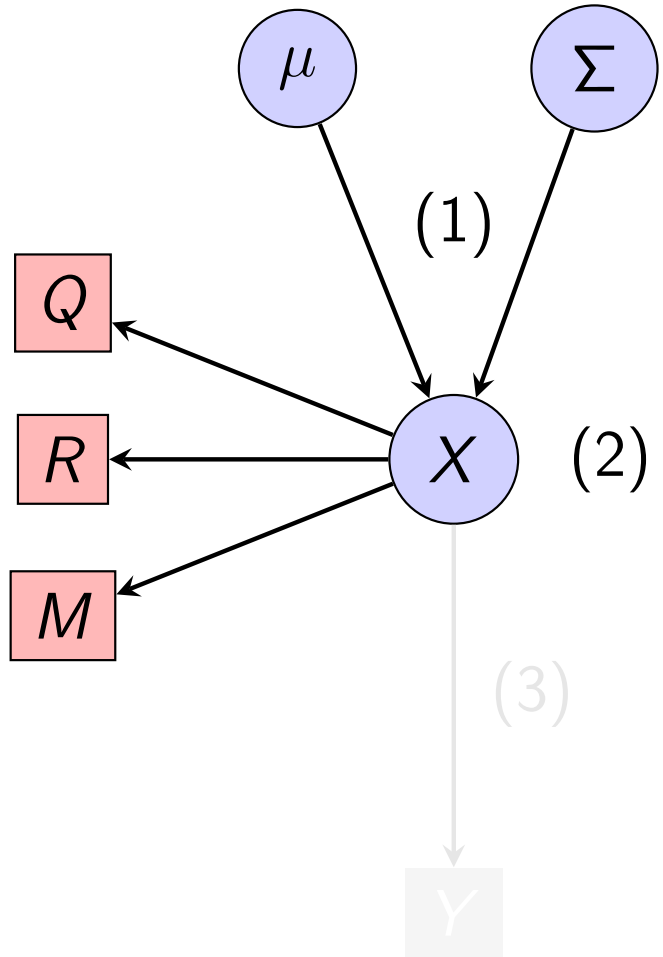


The Bayesian hierarchical model

1) Exposure model: $p(X|\mu, \Sigma)$

2) Measurement model:
$p(Q, R, M|X)$

3) Disease model: $p(Y|X)$

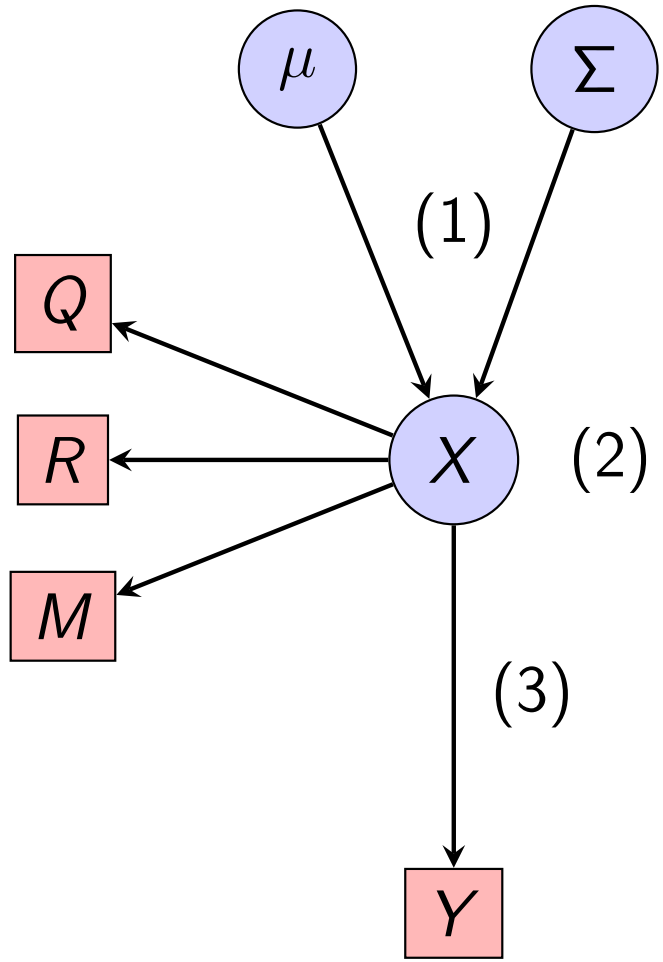


The Bayesian hierarchical model

1) Exposure model:
   $p(X|\mu, \Sigma)$

2) Measurement model:
   $p(Q, R, M|X)$

3) Disease model: $p(Y|X)$



1. The exposure model

- X_{ik}: vector of unknown true (latent factor) dietary intake of vit-B6 and folate ($k = 1, 2$), with $i = 1, \ldots, n$:

$$X_{ik} \sim MVN(\mu_k, \Sigma_X) = MVN(0, \Sigma_X)$$

$$\Sigma_X^{-1} \sim Wishart(\boldsymbol{D_x}, \boldsymbol{r_x})$$

1. The exposure model

- X_{ik}: vector of unknown true (latent factor) dietary intake of vit-B6 and folate ($k = 1, 2$), with $i = 1, \ldots, n$:

$$X_{ik} \sim MVN(\mu_k, \Sigma_X) = MVN(0, \Sigma_X)$$

$$\Sigma_X^{-1} \sim Wishart(\boldsymbol{D_x}, \boldsymbol{r_x})$$

- -

- D_x: scale matrix, $(k \times k)$
- r_x: rank of the Wishart distribution

2. The measurement model

- for $i = 1, \ldots, n$ and $k = 1, 2$:

$$
\begin{aligned}
Q_{ik} &= \alpha_{Q_k} + \beta_{Q_k} \cdot X_{ik} + \epsilon_{Q_k} \\
R_{ik} &= X_{ik} + \epsilon_{R_k} \\
M_{ik} &= \alpha_{M_k} + \beta_{M_k} \cdot X_{ik} + \epsilon_{M_k}
\end{aligned}
$$

2. The measurement model

- for $i = 1, \ldots, n$ and $k = 1, 2$:

$$\begin{aligned} Q_{ik} &= \alpha_{Q_k} + \beta_{Q_k} \cdot X_{ik} + \epsilon_{Q_k} \\ R_{ik} &= X_{ik} + \epsilon_{R_k} \\ M_{ik} &= \alpha_{M_k} + \beta_{M_k} \cdot X_{ik} + \epsilon_{M_k} \end{aligned}$$

  - Assumptions:

$$cov(\epsilon_{Q_k}, \epsilon_{R_k}) \neq 0, cov(\epsilon_{Q_1}, \epsilon_{Q_2}) \neq 0, cov(\epsilon_{R_1}, \epsilon_{R_2}) \neq 0,$$

2. The measurement model

- for $i = 1, \ldots, n$ and $k = 1, 2$:

$$\begin{aligned} Q_{ik} &= \alpha_{Q_k} + \beta_{Q_k} \cdot X_{ik} + \epsilon_{Q_k} \\ R_{ik} &= X_{ik} + \epsilon_{R_k} \\ M_{ik} &= \alpha_{M_k} + \beta_{M_k} \cdot X_{ik} + \epsilon_{M_k} \end{aligned}$$

  - Assumptions:

$$cov(\epsilon_{Q_k}, \epsilon_{R_k}) \neq 0, cov(\epsilon_{Q_1}, \epsilon_{Q_2}) \neq 0, cov(\epsilon_{R_1}, \epsilon_{R_2}) \neq 0,$$

$$cov(\epsilon_{Q_k}, \epsilon_{M_k}) = 0, cov(\epsilon_{R_k}, \epsilon_{M_k}) = 0, cov(\epsilon_{M_1}, \epsilon_{M_2}) = 0$$

2. The measurement model (ii)

- for $i = 1, \ldots, n$ and $k = 1, 2$:

$$
\begin{aligned}
Q_{ik} &= \alpha_{Q_k} + \beta_{Q_k} \cdot X_{ik} + \epsilon_{Q_k} \\
R_{ik} &= X_{ik} + \epsilon_{R_k} \\
M_{ik} &= \alpha_{M_k} + \beta_{M_k} \cdot X_{ik} + \epsilon_{M_k}
\end{aligned}
$$

2. The measurement model (ii)

- for $i = 1, \ldots, n$ and $k = 1, 2$:

$$\begin{aligned} Q_{ik} &= \alpha_{Q_k} + \beta_{Q_k} \cdot X_{ik} + \epsilon_{Q_k} \\ R_{ik} &= X_{ik} + \epsilon_{R_k} \\ M_{ik} &= \alpha_{M_k} + \beta_{M_k} \cdot X_{ik} + \epsilon_{M_k} \end{aligned}$$

  - Prior distributions:

$$\begin{aligned} \alpha_{Q_k} &\sim N(0, \boldsymbol{\sigma^2_{\alpha_{Q_k}}}), & \beta_{Q_k} &\sim N(0, \boldsymbol{\sigma^2_{\beta_{Q_k}}}) \\ \epsilon_{QR} &\sim MVN(0, \Sigma_{\epsilon_{QR}}), & \Sigma^{-1}_{\epsilon_{QR}} &\sim Wishart(\boldsymbol{D_{\epsilon_{QR}}}, \boldsymbol{r_{\epsilon_{QR}}}) \end{aligned}$$

2. The measurement model (ii)

- for $i = 1, \ldots, n$ and $k = 1, 2$:

$$\begin{aligned} Q_{ik} &= \alpha_{Q_k} + \beta_{Q_k} \cdot X_{ik} + \epsilon_{Q_k} \\ R_{ik} &= X_{ik} + \epsilon_{R_k} \\ M_{ik} &= \alpha_{M_k} + \beta_{M_k} \cdot X_{ik} + \epsilon_{M_k} \end{aligned}$$

  - Prior distributions:

$$\begin{array}{llll} \alpha_{Q_k} & \sim N(0, \boldsymbol{\sigma^2_{\alpha_{Q_k}}}), & \beta_{Q_k} & \sim N(0, \boldsymbol{\sigma^2_{\beta_{Q_k}}}) \\ \epsilon_{QR} & \sim MVN(0, \Sigma_{\epsilon_{QR}}), & \Sigma^{-1}_{\epsilon_{QR}} & \sim Wishart(\boldsymbol{D_{\epsilon_{QR}}}, \boldsymbol{r_{\epsilon_{QR}}}) \\ \alpha_{M_k} & \sim N(0, \boldsymbol{\sigma^2_{\alpha_{M_k}}}), & \beta_{M_k} & \sim N(0, \boldsymbol{\sigma^2_{\beta_{M_k}}}) \\ \epsilon_{M} & \sim MVN(0, \Sigma_{\epsilon_M}), & \Sigma^{-1}_{\epsilon_M} & \sim Wishart(\boldsymbol{D_{\epsilon_M}}, \boldsymbol{r_{\epsilon_M}}) \end{array}$$

3. The disease model

- $Y_i \in (0, 1)$: disease indicator for the i^{th} study subject

  $Y_i \sim Bin(1, \pi_i)$, with π_i the probability of developing the disease

  - A conditional logistic model is assumed as:

$$P(Y_i|X_k, Z_p) = H(\gamma_1 \cdot X_{i1} + \gamma_2 \cdot X_{i2} + Z_{ip}^T \gamma_3)$$

3. The disease model

- $Y_i \in (0, 1)$: disease indicator for the i^{th} study subject

  $Y_i \sim Bin(1, \pi_i)$, with π_i the probability of developing the disease

  - A conditional logistic model is assumed as:

$$P(Y_i|X_k, Z_p) = H(\gamma_1 \cdot X_{i1} + \gamma_2 \cdot X_{i2} + Z_{ip}^T \gamma_3)$$

$$\Gamma = (\gamma_1, \gamma_2, \gamma_3) \sim N(0, \sigma^2_{\Gamma_{(k+p)}})$$

Analytical steps

- R measurements, available on $\sim$10% of the sample, were imputed as $E(R|Q)$
  - Data were log-transformed to approximate normality
  - Residuals were computed by country, study, smoking, batch, age and sex (M), country, age and sex (Q), age and sex (R)
  - Disease models were run separately by study
  - Only results for kidney cancer disease model are shown
- Analyses were run in R with JAGS (Martyn Plummer)

3. Results: disease model

Table 3. Relative risk estimates ($\hat{RR}_k = e^{\hat{\gamma}_k}$).

	Vit-B6		Folate	
	$\hat{RR}_1$	(95% CI[1])	$\hat{RR}_2$	(95% CI[1])
Q	1.00	(0.88, 1.14)	0.96	(0.84, 1.10)
R	-	-	-	-
M	0.79	(0.69, 0.89)	0.95	(0.84, 1.07)

3. Results: disease model

Table 3. Relative risk estimates ($\hat{RR}_k = e^{\hat{\gamma}_k}$).

	Vit-B6		Folate	
	$\hat{RR}_1$	(95% CI[1])	$\hat{RR}_2$	(95% CI[1])
Q	1.00	(0.88, 1.14)	0.96	(0.84, 1.10)
R	-	-	-	-
M	0.79	(0.69, 0.89)	0.95	(0.84, 1.07)
X	0.71	(0.58, 0.88)	0.85	(0.72, 1.02)

[1]Credible Intervals

Concluding remarks

- Challenging to tackle the complexity of dietary and biomarker measurements

- After measurement error correction Vit-B6 and folate intakes were inversely associated with the risk of kidney cancer

- Aspects still to tune up

- Great potential to use data from studies with available *concentration* biomarker data

Concluding remarks (ii)

- Are Bayesian modelling worth the trouble in nutritional epidemiology?
  - They are flexible and can be very informative
- Need of informative data, possibly replicates of R (and M) measurements
  - Need of more biomarker measurements of dietary exposure

Acknowledgments

- Pietro Ferrari, Hannah Lennon, Martyn Plummer

- WCRF/AICR for funding the project

- Mattias Johansson, Veronique Chajes

- Ray Carroll, Paul Gustafson, Victor Kipnis, Heather Bowles

- EPIC collaborators