Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

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This series is dedicated to the memory of Dr. Arthur Schatzkin

In recognition of his internationally renowned contributions to the field of nutrition epidemiology and his commitment to understanding measurement error associated with dietary assessment.

Objectives

Learning objectives

- Understanding the motivation for combining dietary self-reports and biomarkers
- Understanding different methods of combining self-reports and biomarkers, their aims and the knowledge required for implementing each method
- Understanding the potential gains of such combination and the limitations to the methods

Introduction

Main results on impact of measurement error

- When a dietary exposure measured with error is included in a disease outcome regression model:
  a) Risk estimates are factored down (attenuated)
  b) Study power is decreased (see lectures 6-7)
- These problems are caused by a loss of information about usual dietary intake caused by the measurement error
- In the previous lecture and in this lecture we deal with this loss of information
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

**In Lecture 10 we described how combining self-report instruments could increase information about usual intake and thereby help with relative risk estimation and power.**

**In this lecture we focus on combining dietary self-reports with biomarkers, to increase information about intake.**

### Introduction

**Supplying further information about intake**

- In Lecture 10 we described how combining self-report instruments could increase information about usual intake and thereby help with relative risk estimation and power.
- In this lecture we focus on combining dietary self-reports with biomarkers, to increase information about intake.

### Background

- Suppose we have a nutritional cohort study in which we want to relate usual intake, T, of a specific nutrient to a health outcome, Y.
- We will consider the case where Y indicates whether an individual develops a specific disease (Y=1) or not (Y=0).
- We cannot measure T exactly and in its place we obtain a self-report from a food frequency questionnaire, Q.

### Disease model - logistic regression

**Disease model:**

\[
\log \{ \text{Odds}(Y = 1) \} = \alpha_0 + \alpha_T T + \alpha_{Z_1} Z_1 + \ldots + \alpha_{Z_p} Z_p
\]

- Y = health outcome variable (0 or 1)
- T = dietary exposure (true usual intake)
- \(Z_1, \ldots, Z_p\) = other exposures, confounders, effect modifiers or intermediate variables
- \(\alpha\)'s = log odds ratios for the explanatory variables

### Attenuation

**Disease model:**

\[
\log \{ \text{Odds}(Y = 1) \} = \alpha_0 + \alpha_T T + \alpha_{Z_1} Z_1 + \ldots + \alpha_{Z_p} Z_p
\]

- Instead of T, we obtain a report Q.
- If we use Q instead of T in the regression, then our estimate of \(\alpha_1\) will be attenuated.

### Regression calibration to adjust the estimate

**Regression calibration:**

\[
\log \{ \text{Odds}(Y = 1) \} = \alpha_0 + \alpha_T T + \alpha_{Z_1} Z_1 + \ldots + \alpha_{Z_p} Z_p
\]

- Instead of using Q in the regression, use \(E(T|Q,Z)\).
- \(E(T|Q,Z)\) is the value of true intake that is predicted when the report is Q and the other explanatory variables are \(Z_1, \ldots, Z_p\).

### Usual regression calibration does not increase power

- Regression calibration removes bias from the estimate, but usually makes little or no change to the result of the test of the null hypothesis that the log odds ratio is zero.
- Occasionally a result that was significant using the unadjusted method will become non-significant - see Lecture 7.

- This is because usual regression calibration uses the same information, Q, about dietary intake as does the unadjusted method.
- In this lecture, we will consider using together with Q, a biomarker value, M.
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

Methods of combining self-report and biomarker

- Two main approaches to combining self-reports and biomarkers:
  - **Direct** methods, that can sometimes recover lost power but do not yield unbiased estimates of relative risk
  - A more complex **modeling-based** method, that recovers lost power and gives unbiased relative risk estimates, but that requires more information about the biomarker’s relation to true usual intake

Introduction

Biomarkers

**Dietary biomarkers:** Biological measurements related to dietary intake

- **Recovery biomarkers**
  - Ideal measures of intake that have no (or minimal) bias
  - Only a few are known

- **Concentration biomarkers**
  - Other biomarkers that are correlated with dietary intake; these comprise the vast majority of biomarkers

**Biomarkers (1)**

**Biomarkers (2)**

- **Recovery biomarkers**
  i. Based on recovery of specific biological products directly related to intake, and not subject to substantial inter-individual differences in metabolism
  ii. Measure short-term intake
  iii. Only a few are known:
    - Doubly-labeled water for energy intake*
    - Urinary nitrogen for protein intake
    - Urinary potassium for potassium intake
  iv. Measure intake directly with minimal bias. The error is independent of true intake

* Under assumption that person is in energy balance

**Concentration biomarkers**

**Biomarkers (3)**

- **Concentration biomarkers**
  i. Concentrations in blood, urine or tissues of specific chemicals or compounds
  ii. Related to dietary intake but not in a straightforward manner
  iii. Could depend on factors that affect metabolism (e.g., gender, smoking, other dietary intakes)
  iv. Very many are known:
    - e.g., Serum lipids, carotenoids, vitamins, metals

**Biomarkers (4)**

Use of biomarkers

- **Recovery biomarkers:**
  i. As the reference instrument in validation studies (see Lectures 6 and 7)
  ii. Combined with self-reports, using the same methodology as described in lecture 10

- **Concentration biomarkers:**
  i. Combined with self-reports using methods we will describe in this lecture
Suppose that we conduct to investigate the association between a dietary intake \( T \) and a health outcome \( Y \).

We measure the dietary intake using a self-report instrument, e.g., an FFQ, value denoted by \( Q \). We also measure a dietary biomarker for the intake, with value \( M \).

In the usual unadjusted method, we regress:

\[
\text{Outcome } Y \text{ on (i) FFQ reported intake } Q, \text{ and (ii) confounders } Z
\]

leading to loss of power, because of measurement error in the FFQ-report \( Q \).

Instead, we can incorporate the dietary biomarker value \( M \) into the analysis, as follows:

In the principal component (PC) method, we regress:

\[
\text{Outcome } Y \text{ on:}
\begin{align*}
\text{(i) first principal component of } (Q,M), \text{ and} \\
\text{(ii) confounders } Z
\end{align*}
\]

In Howe's method we regress:

\[
\text{Outcome } Y \text{ on:}
\begin{align*}
\text{(i) sum of the ranks of } Q \text{ and } M, \text{ and} \\
\text{(ii) confounders } Z
\end{align*}
\]

Note that these two methods (PC and Howe's):

1. Do not adjust for the attenuation in the estimated relative risk
2. Will in some circumstances recover some of the lost power caused by measurement error
3. Do not require knowledge of the quantitative relationship between marker level and true dietary intake
4. Do require that the marker (as well as the FFQ) is measured in all participants*

* A small amount of missing data may be accommodated

Details – PC method:
1. The first principal component is given by:
   \[
   \text{PC} = \frac{Q}{\text{sd}(Q)} + \frac{M}{\text{sd}(M)}
   \]
   if \( Q \) and \( M \) are positively correlated
2. The first principal component is given by:
   \[
   \text{PC} = \frac{Q}{\text{sd}(Q)} - \frac{M}{\text{sd}(M)}
   \]
   if \( Q \) and \( M \) are negatively correlated
3. Regress \( Y \) on PC and confounders, \( Z \)
4. Test the statistical significance of the coefficient of PC

Details – Howe's method:
1. The method is a non-parametric procedure
2. Rank the \( Q \)'s according to their values from lowest to highest
3. Rank the \( M \)'s according to their values from lowest to highest
4. For each individual calculate \( H = Q \text{-rank} + M \text{-rank} \) (or, if \( Q \) and \( M \) are negatively correlated, \( H = Q \text{-rank} - M \text{-rank} \))
5. Regress \( Y \) on \( H \) and confounders, \( Z \)
6. Test the statistical significance of the coefficient of \( H \)
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

**Example:** Carotenoids in Eye Disease Study (CAREDS)

1. Ancillary study of the Women’s Health Initiative Observational Study
2. 1802 women were recruited to CAREDS during 2001-4
3. Disease of interest, Y: nuclear eye cataract; defined according to current eye examination or reported previous treatment for cataract

**Direct methods**

**Example – Carotenoids in Eye Disease Study (CAREDS):**

Logistic regression analyses relating nuclear cataract to dietary lutein/zeaxanthin

<table>
<thead>
<tr>
<th>Method</th>
<th>Estimated Odds Ratio</th>
<th>95% CI</th>
<th>Z-value</th>
<th>Sample size ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.75</td>
<td>(0.57,0.99)</td>
<td>-2.04</td>
<td>-</td>
</tr>
<tr>
<td>PC</td>
<td>0.65</td>
<td>(0.49,0.86)</td>
<td>-3.05</td>
<td>0.45</td>
</tr>
<tr>
<td>Howe</td>
<td>0.65</td>
<td>(0.49,0.85)</td>
<td>-3.11</td>
<td>0.43</td>
</tr>
</tbody>
</table>

\(^1\) Comparing the 90th percentile to the 10th percentile
\(^*\) Compared to the unadjusted method:
Sample size required is proportional to \(1/z^2\)
So sample size ratio is the inverse ratio of the \(z^2\) values

**Disadvantages of the direct methods:**

1. They do not always increase statistical power, and sometimes decrease it* 
2. The estimated odds ratios are attenuated 
3. The combined measure (PC or Howe) does not have any recognized units

* For example, when the marker is poorly correlated with intake, or has a weaker relationship with disease than the self-reported intake

**Modeling the intake-marker-disease relationship (1a)**

To make progress in addressing these deficiencies, we have to consider models of diet, their markers and health outcomes, including aspects of causality
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

Causal pathways: dietary intake, biomarkers, and disease

- True dietary intake: \( T \)
- True biomarker level: \( M_T \)
- Health outcome: \( Y \)
- Measured Marker: \( M \)
- Confounders: \( Z \)
- Reported Intake: \( Q \)

Main assumptions:
- Dietary intake \( T \) causally affects the biomarker level \( M_T \)
- The biomarker level \( M_T \) may (at least partially) mediate the effect of dietary intake \( T \) on disease \( Y \)
- The main confounders \( Z \) are known and are measured exactly

Statistical Models that describe the causal pathways:

1. Health outcome model:
   \[
   \logit(P(Y = 1)) = \alpha_0 + \alpha_1 T + \alpha_2 M_T + \alpha_3 Z
   \]
2. Marker-Intake model:
   \[
   M_T = \gamma_0 + \gamma_1 T + \gamma_2 Z + \varepsilon_M
   \]
3. Reported intake model:
   \[
   Q = \beta_0 + \beta_1 T + \varepsilon_Q
   \]
4. Measured marker model:
   \[
   M = M_T + \varepsilon_M
   \]
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

4. Measured marker model

True dietary intake: T
True biomarker level: M
Health outcome: Y
Confounders: Z
Reported Intake: Q

Measured Marker: M

Confounders: Z

Modeling the intake-marker-disease relationship

What is the target?

What is the target? (1)

Model without measurement error

Direct (non-mediated) effect of diet on disease = $\alpha_1$
Indirect (mediated) effect of diet on disease = $\gamma_1\alpha_2$
Total effect of diet on disease = $\alpha_1 + \gamma_1\alpha_2$

What is the target? (2)

- Total effect of diet on disease = $\alpha_1 + \gamma_1\alpha_2$
- We will denote this quantity by $\alpha_1^*$
- Our object is:
  - to estimate $\alpha_1^*$
  - and to test whether $\alpha_1^* = 0$

What is the target? (3)

Note that when there is no measurement error we can estimate $\alpha_1^*$ by dropping $M_T$ from the model

$\logit(P(Y = 1)) = \alpha_1^* + \alpha_2^* T + \alpha_2^* Z$

Introduction

Biomarkers

Direct methods

Modeling

What is the target?

Estimation

Hypothesis testing

Discussion

Summary

WHAT IS THE TARGET?

WHAT IS THE TARGET?

WHAT IS THE TARGET?

ESTIMATION
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

**Methods:**

1. **Unadjusted:**
   Regress health outcome on Q and Z and take the coefficient of Q

2. **Regression Calibration**
   Regress health outcome on \( E(T|Q,Z) \) and Z and take the coefficient of \( E(T|Q,Z) \)

3. **“Enhanced” Regression Calibration:**
   Regress health outcome on \( E(T|Q,M,Z) \) and Z and take the coefficient of \( E(T|Q,M,Z) \)

4. **New method:**
   Regress health outcome on \( E(T|Q,M,Z) \), \( E(M_T|Q,M,Z) \) and Z and calculate \( \alpha_1 + \gamma_1 \alpha_2 \)

**Estimation:**

**Estimating the total dietary effect (1)**

**Methods:**

1. **Unadjusted:**
   Directly implemented: logistic regression of \( Y \sim Q, Z \)

2. **Regression Calibration:**
   First determine \( E(T|Q,Z) \); then \( Y \sim E(T|Q,Z), Z \)

3. **“Enhanced” Regression Calibration:**
   First determine \( E(T|Q,M,Z) \); then \( Y \sim E(T|Q,M,Z), Z \)

4. **New method:**
   First determine \( E(T|Q,M,Z) \), \( E(M_T|Q,M,Z) \); then \( Y \sim E(T|Q,M,Z), E(M_T|Q,M,Z), Z \); then calculate \( \alpha_1 + \gamma_1 \alpha_2 \)

**Estimation:**

**Estimating the total dietary effect (2)**

The first three methods take the following model and substitute different quantities for \( T: Q \) or \( E(T|Q,Z) \) or \( E(T|Q,M,Z) \)

\[
\logit(P(Y = 1)) = \alpha_{1y} + \alpha_1 T + \alpha_2 M + \alpha_3 Z
\]

**Estimation:**

**Estimating the total dietary effect (3)**

The new method takes the full model and substitutes \( E(T|Q,M,Z) \) for \( T \) and \( E(M_T|Q,M,Z) \) for \( M_T \)

The parameters \( \alpha_1 \) and \( \alpha_2 \) are estimated and then \( \alpha_1 + \gamma_1 \alpha_2 \)

\[
\logit(P(Y = 1)) = \alpha_{1y} + \alpha_1 T + \alpha_2 M + \alpha_3 Z
\]

**Estimation:**

**Estimating the total dietary effect (4)**

Which of these methods estimates \( \alpha_{1y} \) without bias?

- **Unadjusted**
  - Unbiased only if Q has no measurement error

- **Regression Calibration**
  - Unbiased

- **“Enhanced” Regression Calibration**
  - Unbiased only if marker does not mediate the effect of diet (\( \alpha_2 = 0 \))

- **New method**
  - Unbiased

**Implementing the estimation (1)**

- Data available: Q, M, Z
- Example – (CAREDS):
  - Y: eye cataract (yes/no)
  - Q: log FFQ-reported lutein plus zeaxanthin
  - M: log serum level of lutein plus zeaxanthin
  - Z: age(y) smoking (0=never, 1=past, 2=current)

**Implementing the estimation (2)**

- Methods:
  1. **Unadjusted**
     Directly implemented: logistic regression of \( Y \sim Q, Z \)
  2. **Regression Calibration**
     First determine \( E(T|Q,Z) \); then \( Y \sim E(T|Q,Z), Z \)
  3. **“Enhanced” Regression Calibration**
     First determine \( E(T|Q,M,Z) \); then \( Y \sim E(T|Q,M,Z), Z \)
  4. **New method**
     First determine \( E(T|Q,M,Z) \), \( E(M_T|Q,M,Z) \); then \( Y \sim E(T|Q,M,Z), E(M_T|Q,M,Z), Z \); then calculate \( \alpha_1 + \gamma_1 \alpha_2 \)
Implementing the estimation (3)

Determining the calibration equations:

- Usually one needs feeding studies to relate biomarker to dietary intake, and population studies of the biomarkers and the dietary instruments to obtain population means and SDs.

CAREDS:

- Feeding studies:
  - Van het Hoff et al., Am J Clin Nutr 1999, 70:261
  - Brevik et al., Eur J Clin Nutr 2004, 58:1166

- Population studies:
  - Delcourt et al., Invest Ophthalmol Vis Sci 2006, 47:2329
  - Dixon et al., J Nutr 2006, 136:3054
  - Mares et al., Am J Clin Nutr 2006, 84:1107

Implementing the estimation (4)

Determining the calibration equations (cont’d)

- Using data from these studies, we built three models (all measurements were transformed to the log scale)
  - Marker-intake model:
    \[ M_t = 5.29 + 0.60T + \varepsilon, \text{ var}(\varepsilon) = 0.10 \]
  - Reported intake model:
    \[ Q = 0.35 + 0.71T + \varepsilon_Q, \text{ var}(\varepsilon_Q) = 0.36 \]
  - Measured marker model:
    \[ M = M_t + \varepsilon, \text{ var}(\varepsilon) = 0.05 \]

- Note that in these models it is assumed that the confounders Z have no bearing on measurement error.

Implementing the estimation (5)

Determining the calibration equations (cont’d)

- The final step is to turn these measurement error models into calibration equations.

**Regression Calibration**

\[ E(T | Q, Z) = 0.355 Q + 0.00560 \text{ age} - 0.101 \text{ smoking} \]

**Enhanced Regression Calibration**

\[ E(T | Q, M, Z) = 0.242 Q + 0.515 M + 0.00692 \text{ age} - 0.0954 \text{ smoking} \]

**New Method**

\[ E(T | Q, M, Z) = 0.242 Q + 0.515 M + 0.00692 \text{ age} - 0.0954 \text{ smoking} \]

\[ E(M_0 | Q, M, Z) = 0.051Q + 0.769M + 0.00595 \text{ age} - 0.0023 \text{ smoking} \]

Implementing the estimation (6)

**Results**

- Logistic Regression Analyses Relating Nuclear Cataracts to Dietary Lutein and Zeaxanthin in the CAREDS study

<table>
<thead>
<tr>
<th>Method</th>
<th>Log Odds Ratio</th>
<th>Standard Error</th>
<th>z-value</th>
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<tbody>
<tr>
<td>Unadjusted</td>
<td>-0.16</td>
<td>0.08</td>
<td>-2.07</td>
</tr>
<tr>
<td>Regression Calibration</td>
<td>-0.46</td>
<td>0.22</td>
<td>-2.07</td>
</tr>
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<td>Enhanced Regression Calibration</td>
<td>-0.51</td>
<td>0.16</td>
<td>-3.15</td>
</tr>
<tr>
<td>New Method</td>
<td>-0.44</td>
<td>0.22</td>
<td>-2.00</td>
</tr>
</tbody>
</table>

Implementing the estimation (7)

**Conclusion**

- For this study either regression calibration or the new method could be used, since theoretically both are unbiased.

- Therefore, the point estimate for the log odds ratio could be taken as **-0.45** (midway between the two estimates). This translates into an odds ratio of **0.73** corresponding to a doubling of lutein/zeaxanthin intake.

\[ \text{z} = 0.73 = \exp(-0.45 \times \ln(2)) \]
Besides estimating the odds ratio, we also want to test whether $\alpha = 0$. The four methods of estimation each lead to a test of this null hypothesis:
- Compare $z = \text{estimate}/\text{SE}$ with the standard normal distribution.

### Hypothesis Testing: Testing the null hypothesis of a zero total dietary effect (1)

- Which of these methods is valid?
  - i.e., yields a test that has the correct probability of rejecting the null hypothesis when it’s true
- Answer:
  - All four methods yield valid tests!
- Why?
  - Because each estimation method is unbiased when the total dietary effect $\alpha$ is zero, even though the unadjusted and enhanced RC methods are otherwise biased.

### Hypothesis Testing: Testing the null hypothesis of a zero total dietary effect (2)

**Example:** Logistic Regression Analyses Relating Nuclear Cataracts to Dietary Lutein and Zeaxanthin in the CAREDS study

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<td>0.038</td>
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<tr>
<td>Enhanced Regression Calibration</td>
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### Hypothesis Testing: Testing the null hypothesis of a zero total dietary effect (3)

- Since all of these methods of testing the null hypothesis are valid, which is the most powerful?
- Answer:
  - The enhanced RC method

### Hypothesis Testing: Testing the null hypothesis of a zero total dietary effect (4)

- Required sample size is reduced by $>50%$.

### Hypothesis Testing: Testing the null hypothesis of a zero total dietary effect (5)

Logistic Regression Analyses Relating Nuclear Cataracts to Dietary Lutein and Zeaxanthin in the CAREDS study:
- The method leading to the largest $z$-value and smallest $P$ is Enhanced Regression Calibration.

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### Hypothesis Testing: Testing the null hypothesis of a zero total dietary effect (6)

**Sample size savings:**
- Estimated sample size required is proportional to $1/z^2$
- Estimated sample size ratio for Enhanced RC versus RC = $(2.07/3.15)^2 = 0.43$
- Required sample size is reduced by $>50%$.

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**Hypothesis testing**

**Testing the null hypothesis of a zero total dietary effect (7)**

- Recommended overall strategy:
  - Estimate the odds ratio using an unbiased method—either the new method or, for cases like CAREDS, the RC method
  - Test the odds ratio using Enhanced RC that incorporates marker information and thus increases power

**Discussion**

**An example where the RC method gives biased estimates**

- Prentice et al: Am J Epidemiol. 2009;169:977, consider using body mass index (BMI) to help predict energy intake
- The “biomarker” BMI is related to error in the FFQ energy report. Obese persons under-report more

**Discussion**

**Sometimes the biomarker may be a confounder as well as a mediator!**

- The “biomarker” BMI could affect energy intake or could mediate its effect. In such circumstances, it is unclear what to do

**Discussion**

**Costs of including a biomarker**

- The methods described (except unadjusted and RC) all require that biomarker values can be obtained for any individual in the study
- This requires storing biological samples on all individuals. The cost of taking the sample and storing it needs to be reckoned against the increased power that could accrue from their use
- Cost of the assay is less crucial, since nested case-control designs can be used to analyze the data
- Many prospective studies now incorporate biobanks allowing the use of the methods described

**Discussion**

**Can we measure all the important confounders?**

- The methods described all require that all important confounders of both dietary intake and the biomarker are identified and measured
- Unfortunately, however hard we try, we can never be sure that we have identified and measured all of these confounders
- Introducing the marker into the analysis introduces a new set of potential confounders
- For this reason, extra care in the interpretation of results is required
Combining self-report dietary intake data and biomarker data to reduce the effects of measurement error

As shown in the CAREDS example, it is not a simple matter to set up the calibration equations needed to implement Enhanced RC or the new method.

Sometimes, as in that example, previous feeding studies and population studies may be available. Otherwise, special feeding or calibration studies will be required.

In addition the number of biomarkers known to provide good prediction of true usual intake are limited.

Prentice et al are currently conducting a large feeding study to identify new biomarkers and develop calibration equations for several foods and nutrients, as part of the WHI.

Discussion
Do we have the necessary information to execute enhanced RC or the new method?

1. Usual Regression Calibration does not usually increase the power to detect diet-health outcome relationships.
2. Using biomarkers can sometimes increase power.
3. Simple methods such as Howe’s method or principal components can be used, and are sometimes successful, but (a) do not guarantee increase in power, and (b) can sometimes even reduce power!
4. More complex methods such as Enhanced Regression Calibration can yield important gains in power, but require considerable extra information regarding the relationship between the biomarker and dietary intake.
5. The methods require availability of biological specimens for the individuals in the study, and may be feasible in prospective studies that have incorporated biobanks.

Summary

 QUESTIONS & ANSWERS

Moderator: Kevin Dodd

Please submit questions using the Chat function

Next Session

Assessing diet-health relationships using a short-term unbiased dietary instrument: focus on risk models with multiple dietary components

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