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Metabolomics: a tool to aid dietary assessment in nutrition

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Applications of metabolomics to nutrition is a rapidly growing field with applications ranging from assessment of diet related diseases to understanding molecular mechanisms behind the health benefits of certain diets. The field of dietary biomarkers and in particular food intake biomarkers has expanded rapidly in recent years. Food intake biomarkers are biomarkers that reflect food intake and have the potential to aid dietary assessment. This review focuses on food intake biomarkers and the use of biomarkers for assessment of dietary patterns. In the case of food intake biomarkers two recent examples demonstrating that such biomarkers can actually be used for food intake assessment are highlighted. What makes these examples stand out is the fact that food intake was quantified using urinary biomarkers. For the dietary pattern section, there are two studies of note which developed models that were capable of classifying individuals into dietary patterns. Overall, these studies have made significant progress in the field and the future is promising for food intake biomarkers.

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Introduction

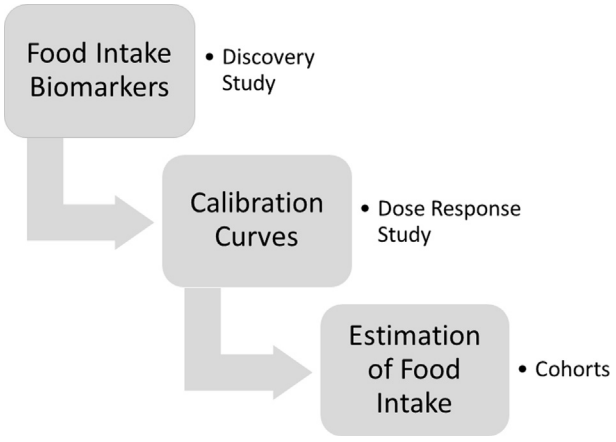
In recent years there has been a notable increase in papers dealing with dietary biomarkers or food intake biomarkers. The explosion of this field reflects the potential of metabolomics in nutrition research but also brings with it a word of caution. Ultimately, for those working in the field of nutrition these biomarkers of food intake should have a clear relationship with food intake and should enable researchers to determine intake in an objective manner. The reason for this need of objective dietary biomarkers is that the current methods for dietary assessment rely on self-reported intake and have a number of well-documented errors associated with them [1,2]. In recent years there have been a number of review articles covering the topic of dietary biomarkers [3–6]. In an attempt to avoid duplication of other work and to critically appraise the field the present review will focus on two emerging aspects: first, food intake biomarkers in the context of determining intake and second, use of biomarkers for dietary pattern analysis (Figures 1 and 2). The present review will not cover the technical aspects of measuring biomarkers using metabolomics: for these aspects the reader is referred to a number of informative reviews in the field [7•,8]. Briefly, metabolomics can be defined as the measurement of small molecules present in samples such as urine and blood. The goal is to identify metabolites that have altered concentrations under different conditions and to relate these changes back to the biological question. In the case of food intake biomarkers the goal is to identify biomarkers that are reflective of food intake. The techniques commonly used for metabolomics include NMR and mass spectrometry-based techniques such as LC–MS and GC–MS. While the different approaches have their own advantages and disadvantages there is a growing trend to now apply multiple techniques/platforms to obtain a better coverage of metabolites.

Food intake biomarkers

In recent years there has been a number of articles demonstrating positive correlations between intakes of certain foods and biomarker levels [9–12]. While these are potentially interesting articles supporting the role of metabolomics in the field they do fall short for translation into use for nutrition researchers. Ultimately, nutrition researchers need to translate biomarker levels into g/day intake such as is the case with urinary nitrogen to determine protein intake. Unfortunately, many of the studies to date in the field do not test for specificity of the biomarkers in terms of being specific for a certain food and the majority have not tested whether the markers increase with increasing dose of the food. In order to answer these important aspects controlled intervention studies need to be performed where one has control on food intake and can then measure resultant biomarker levels. In recent literature two papers have emerged where the concept of such studies have been developed for metabolomics derived biomarkers and calibration curves for the determination of intake were developed.

In the first paper Gracia-Perez *et al.* used a controlled intervention to determine a biomarker for grape intake

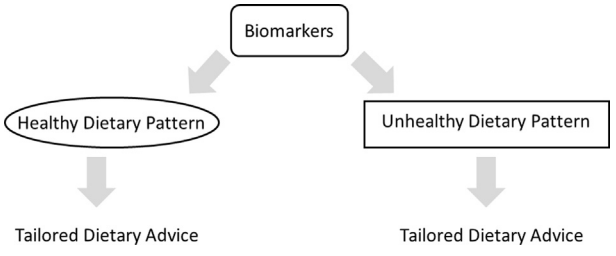
Figure 1



The strategy for successful implementation of dietary biomarkers. The discovery study involves a feeding study where participants consume known amounts of foods of interest. Metabolomic analysis of the collected biofluids leads to the identification of food intake biomarkers. Calibration curves can be developed and used in an independent cohort study to determine food intake.

[13••]. Using the data from the dose response aspect of the study the authors developed calibration curves for determination of red grape intake (g/day) from urinary tartaric acid. Bland–Altman analysis of the agreement between estimated intake based on the urinary biomarker and the actual intake of red grapes demonstrated that there was good agreement. This work is an important demonstration of the potential to estimate intake of a specific food from a urine sample. In the second paper, which originated from my group, a controlled dietary intervention was performed where participants consumed standardised breakfasts for three consecutive days over three consecutive weeks [14••]. The food of interest was orange juice and its consumption decreased over the three weeks (from 520 g/day to 30 g/day). The biomarker proline betaine was measured in urine samples and

Figure 2



Overview of the potential of food intake biomarkers in assessment of dietary patterns. The example here is limited to two dietary patterns. Combinations of biomarkers can be used to classify individuals into certain dietary patterns. Following this dietary advice can be developed tailored to the dietary pattern of the individual.

calibration curves were developed from the biomarkers levels and the know quantities of orange juice consumed. The novel aspect of this work was that we were able to use an independent cohort of 560 individuals to test the ability of the fasting biomarker levels to determine intake in g/day using the calibration curves developed in the controlled intervention study. We demonstrated that using the fasting samples we were able to determine intake (g/day) and the results had excellent agreement with the four-day food records. The importance of this work is that it demonstrates the potential use of the food intake markers for nutrition researchers: the use of a urine sample to determine intake of a specific food. The ability to use a fasting urine sample to determine intake of certain foods has immense potential. It is now imperative that similar work is performed for other food intake biomarkers to move the field forward. However, it is also important to realise that this will not be possible for all foods — thus in the near future it will be important to establish which foods have the potential of being measured in this fashion.

Dietary patterns

In recent years there has been an increased interest in nutritional epidemiology to classify subjects into dietary patterns [15,16]. This has emerged from the realisation that focusing on relationships between single nutrients and disease risk was ignoring the fact that individuals consume complex combinations of foods in different patterns with macronutrient, micronutrient and non-nutrient component interactions [17,18]. As a consequence of the importance of dietary patterns there has also been an interest in the use of dietary biomarkers to determine such dietary patterns.

Many of the earlier papers in this field examined the correlations between the dietary patterns and the metabolomics data [19–21]. They successfully demonstrated in a number of studies that there was positive relationships between dietary patterns and a number of metabolites in both urine and blood. These studies provided a significant evidence base for the potential of biomarkers in assessing dietary patterns. In the recent literature three examples have emerged where the concept has been developed further. Andersen and colleagues used an untargeted metabolomics approach to distinguish between two dietary patterns with the purpose of developing a compliance measure [22]. In this study the participants (n = 181) were randomly assigned to follow a New Nordic Diet (NND) or an Average Danish Diet (ADD): using a 24 hour urine sample a model was built that could distinguish the two dietary patterns.

Garcia-Perez *et al.* performed controlled interventions to develop models for classification of individuals into dietary patterns based on their NMR profiles using a highly controlled intervention [23••]. Applications of these