Old Herborn University Seminar Monograph 23:
Intestinal microbiomics: novel indicators of health and disease.
Editors: Peter J. Heidt, Johannes Snel, Tore Midtvedt, and Volker Rusch.
Old Herborn University Foundation, Herborn-Dill, Germany: 87-91 (2010).

# THE DESIGN AND CONDUCT OF POPULATION STUDIES OF DIET AND HEALTH OUTCOMES

KARIN B. MICHELS

Obstetrics and Gynecology Epidemiology Center,
Department of Obstetrics, Gynecology and Reproductive Biology,
Brigham and Women's Hospital, Harvard Medical School,
Boston, Massachusetts, USA

## SUMMARY

The association between diet and health and disease outcomes is best explored in large population-based observational studies. While a number of designs are available to study this relation, the prospective cohort design is least affected by biases, as it is not subject to recall or selection biases that affect case-control studies, nor is it plagued by the compliance problems of a randomized clinical trial. The most challenging problem of studying the association between diet and disease is the assessment of diet itself. Diet assessment is affected by measurement error, and there is no perfect way to assess diet. All diet assessment instruments that employ self-reports have considerable measurement error. Few biomarkers are known that reflect dietary intake well. While the search for additional biomarkers is ongoing, other methods of diet assessment using the Internet, telephone, and/or cameras are explored.

## INTRODUCTION

The role of diet in health and disease has long been of interest and has been addressed in numerous studies. While much has been learned about the optimal diet from observational research during the past decades, the perfect study design to determine the role of diet in maintaining health is still debated. Since the assessment of diet remains challenging, numerous methods have been explored and new methods are under development.

## REVIEW AND DISCUSSION

Several epidemiologic study designs can be employed to study the association between diet and disease.

### Cross-sectional study

In a cross-sectional study, diet and disease are assessed at the same time. For example, in the National Health and Nutrition Examination Survey (NHANES) conducted in the United States, population-based samples of approximately 30,000 individuals are selected every few years and queried about their diet and other lifestyle factors (*Kant* et al., 1991). At the same time, the participants' health status is

assessed. In this cross-sectional approach, however, a time sequence cannot be established, i.e., it remains unknown whether an illness may be a consequence of the diet that is reported during the survey or whether the diet report may have been influenced by the disease.

**Case-control study**

In a case-control study, cases with the disease of interest and controls free of the disease of interest are sampled from the same source population. Cases and controls are asked to report their dietary intake typical for the time period preceding the disease in the cases. This study design is affected by two potential sources of error: Selection bias and recall bias. Since the cases report their past diet when they already have the disease, their disease status may affect the reporting of their diet. Differential reporting of diet by cases and controls introduces recall bias, which is a differential misclassification. Furthermore, if the controls are not appropriately selected, their diet may not be representative of the dietary intake of the source population that gave rise to the cases; this may introduce selection bias and distort the observed measure of association. Confounding by other dietary or lifestyle factors is an additional concern in an observational study.

**Prospective Cohort Study**

A prospective cohort study is not affected by the aforementioned biases. In a prospective cohort study, the diet of healthy individuals is assessed at the onset of the study and participants are followed over a substantial period of time until a certain number of them get the disease of interest. While a prospective cohort study is not affected by selection or recall bias, a problem arises if participants are lost to follow-up, i.e., contact with participants is not maintained during follow-up and therefore their health status is unknown. If a high participation rate over several years is accomplished, the cohort design is likely the best design available to study the association between diet and disease outcomes. An example of a prospective cohort study is the Nurses' Health Study, in which diet is assessed every four years and nearly 90% participation has been maintained for more than 30 years. Confounding remains a challenge also in cohort studies.

**Randomized Clinical Trials (RCT)**

While the role of nutrition in maintaining health could also be studied in a randomized clinical trial, which is not plagued by confounding, assigning a certain diet to individuals over a longer period of time is usually problematic. Even if individuals agree to adhere to a particular diet, maintaining such a diet over years, which would be necessary to study its effect on chronic disease outcomes, is virtually impossible. The recent example of the Women's Health Initiative demonstrates the difficulties of maintaining an assigned diet over several years (*Howard* et al., 2006). The successful randomization of diet is possible only if meals are provided to participants, which is practical only in the short term and with a limited number of participants. An example of a successful randomization of diet is the Dash Trial, which tested the effect of several diets on blood pressure (*Sacks* et al., 2001). Participants came to the hospital every day to consume one meal there and took the two remaining meals and between-meal snacks home. The Dash Trial was successful because all meals were provided and because a change in blood pressure with dietary intervention can be observed within a few weeks.

## Assessment of Diet

The assessment of dietary intake in a human population is difficult, as diet is composed of many foods and drinks and most individuals do not remember what they consumed on any given day. Hence, it is only possible to obtain either a snapshot of an individual's diet at one time or to assess dietary preferences over longer time periods. When validating diet assessment instruments, they should be compared to a gold standard not affected by the same (correlated) measurement error, preferably a biomarker.

## The 24-hour Recall

The 24-hour recall assesses diet during the previous 24 hours. While such a snapshot might capture a person's diet during one day, the previous 24 hours may or may not be typical in reflecting this individual's typical diet. A 24-hour recall is affected by measurement error if the individual does not remember all the items he/she consumed during the previous 24 hours and does not capture seasonal variation of diet. Obtaining several 24-hour recalls throughout a year might reduce this error component. Nevertheless, obtaining 24-hour recalls in a large population such as the NHANES study produces population means in the intake of dietary items that are approximately accurate (*Willett*, 1998).

## 7-day Diet Record

The 7-day diet record requires participants to maintain a diary of everything they consume and drink during a 7-day period. This approach has the advantage over the 24-hour recall that it captures diet during an entire week, including weekdays and weekends in which a person's diet usually varies. Moreover, maintaining a dietary record prospectively avoids the recall of diet and if carefully maintained can provide the best image of an individual's diet during one week. However, the 7-day diet record may not capture a person's typical diet if the diary week is not representative, and a one-week diary does not capture seasonal variation. Again, such measurement error may be reduced if the 7-day diet record is kept on four occasions throughout a year. Furthermore, some people may change their diet during the week of recording because they have to document everything they eat and drink. Hence, the 7-day diet record may not always accurately reflect a person's diet. In addition, computerization of the diet diaries for analysis in large observational studies is prohibitive (*Willett*, 2001).

## Food Frequency Questionnaire

The food frequency questionnaire (FFQ) is the most widely used dietary assessment instrument in observational research. It consists of a pre-structured questionnaire that includes approximately 160 food items and up to nine response options for frequency of intake. The semiquantitative FFQ also provides portion sizes for most food items such as 1 glass, 1 cup, or 1 slice. Study participants are asked to report their average intake of a food or beverage per day, per week, or per month during the past year, or sometimes during a different time period, e.g., 6 months or 1 month. While the FFQ does not attempt to measure consumption of foods or beverages with high precision and is affected by measurement error, it captures dietary preferences reasonably well and separates high from low intake (*Willett*, 1998).

## Alternative Diet Assessment Instruments

Attempts to improve on existing dietary assessment methods incorporate the use of existing technology. Recently, an Internet-based 24-hour die-

tary recall has been developed, which provides respondents with 8,000 foods to choose from enhanced by graphical display (National Cancer Institute). Information on time of consumption and preparation methods is also collected. Camera-assisted methods in which participants photograph all meals are not new (*Elwood* and *Bird*, 1983), but photos are now taken digitally and submitted to dieticians via mobile phone cards (*Wang* et al., 2006). Telephone-based methods are also being developed.

**Biomarkers of Dietary Intake**

Biomarkers that reflect dietary intake with high accuracy and precision are superior to self-reports that are prone to measurement error. Unfortunately, few such biomarkers for diet have been identified. Recovery biomarkers provide an estimate of absolute intake levels based on the metabolic balance between intake and excretion over a fixed period of time, and thus excretion levels are highly correlated with intake (*Bingham*, 2002). Examples of recovery biomarkers are doubly labelled water to measure energy expenditure and thus total caloric intake, urinary total nitrogen to estimate total daily protein consumption, and urinary total potassium to estimate total daily potassium intake (*Jenab* et al., 2009). Predictive biomarkers are also sensitive and time dependent, and show a dose-response relation with dietary intake, but their overall recovery is lower. The only known predictive biomarkers are 24-hour urinary sucrose and fructose levels, which are closely correlated with intake of sugars (*Tasevska* et al, 2005). Concentration biomarkers correlate with intakes of foods or nutrients, but the correlation is lower than that for recovery biomarkers and do not translate into absolute levels of intake (*Bingham* et al., 2008). Examples for concentration biomarkers are fatty acids, carotenoids, and other vitamins.

## CONCLUSIONS

Prospective cohort studies are the preferred study design to assess the association between diet and health and disease in free-living populations. While the search for additional biomarkers of diet is ongoing and alternative dietary assessment methods are explored, most observational research currently relies on the use of the FFQ.

## LITERATURE


Bingham, S.A.: Biomarkers in nutritional epidemiology. Public Health Nutr. 5, 821-827 (2002).

Bingham, S., Luben, R., Welch, A., Low, Y.L., Khaw, K.T., Wareham, N., and Day, N.: Associations between dietary methods and biomarkers, and between fruits and vegetables and risk of ischaemic heart disease, in the EPIC Norfolk Cohort Study. Int. J. Epidemiol. 37, 978-987 (2008).

Elwood, P.C. and Bird, G.: A photographic method of diet evaluation. Hum. Nutr. Appl. Nutr. 37, 474-477 (1983).

Howard, B.V., Van Horn, L., Hsia, J., Manson, J.E., Stefanick, M.L., Wassertheil-Smoller, S., Kuller, L.H., LaCroix, A.Z., Langer, R.D., Lasser, N.L., Lewis, C. E., Limacher, M.C., Margolis, K.L., Mysiw, W.J., Ockene, J.K., Parker, L.M., Perri, M.G., Phillips, L., Prentice, R.L., Robbins, J., Ros-

souw, J.E., Sarto, G.E., Schatz, I.J., Snetselaar, L.G., Stevens, V.J., Tinker, L.F., Trevisan, M., Vitolins, M.Z., Anderson, G.L., Assaf, A.R., Bassford, T., Beresford, S.A., Black, H.R., Brunner, R.L., Brzyski, R.G., Caan, B., Chlebowski, R.T., Gass, M., Granek, I., Greenland, P., Hays, J., Heber, D., Heiss, G., Hendrix, S.L., Hubbell, F.A., Johnson, K.C., and Kotchen, J.M.: Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295, 655-666 (2006).

Jenab, M., Slimani, N., Bictash, M., Ferrari, P., and Bingham, S.A.: Biomarkers in nutritional epidemiology: Applications, needs and new horizons. Hum. Genet. 125, 507-525 (2009).

Kant, A.K., Block, G., Schatzkin, A., Ziegler, R.G., and Nestle, M.: Dietary diversity in the US population, NHANES II, 1976-1980. J. Am. Diet Assoc. 91, 1526-1531 (1991).

Sacks, F.M., Svetkey, L.P., Vollmer, W.M., Appel, L.J., Bray, G.A., Harsha, D., Obarzanek, E., Conlin, P.R., Miller, E.R., 3rd, Simons-Morton, D.G., Karanja, N., Lin, P.H., and Group, D.A.-S.C.R.: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N. Engl. J. Med. 344, 3-10 (2001).

Tasevska, N., Runswick, S.A., McTaggart, A., and Bingham, S.A.: Urinary sucrose and fructose as biomarkers for sugar consumption. Cancer Epidemiol. Biomarkers Prev. 14, 1287-1294 (2005).

Wang, D.H., Kogashiwa, M., and Kira, S.: Development of a new instrument for evaluating individuals' dietary intakes. J. Am. Diet Assoc. 106, 1588-1593 (2006).

Willett, W.: Nutritional Epidemiology (Willett, W.,Ed.). 2nd edition. Oxford University Press, New York (1998).

Willett, W.: Commentary: Dietary diaries versus food frequency questionnaires-a case of undigestible data. Int. J. Epidemiol. 30, 317-319 (2001).