

# Advantages and pitfalls of different types of studies for investigations of the impact of food on health

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**Abstract** – Several types of studies can be used to elucidate various aspects of the effect of food on human health. The main categories are:

- **Epidemiological (observational) studies with humans. These can be prospective, where the diet is recorded and health indicators are monitored after the first recording, or retrospective, where people who have a disease are identified and it is then investigated if their diet has been different from those who did not get the same disease.**
- **Intervention studies with animals or humans, where the outcome is differences in indicators of health between groups eating different controlled diets.**
- **In vitro studies, where specific aspects of the mechanisms of the effects of food or food components are studied in cell cultures, isolated organs or on enzyme activities.**

**Each type of study is useful for elucidation of certain types or aspects of hypotheses. They also differ in terms of sensitivity (precision) and accuracy (risk of confounding with other influences than the food itself). A thorough understanding of the effect of a food on human health requires that all three types of studies give corresponding and predictable results.<sup>1</sup>**

## INTRODUCTION

The relation between food and human health has been a subject of interest since prehistoric times, and the philosopher Hippocrates (4<sup>th</sup> century BC) specified a healthy diet as one of the primary prerequisites for a healthy life. In the 16<sup>th</sup> century Paracelsus challenged the prevailing dogma that all diseases were the result of divine intervention. He emphasised the concept of cause and effect, and encouraged independent observations rather than reliance only on literature studies. Since then ever increasing numbers of scientists have investigated how health or disease can be caused by dietary factors, with the ultimate aim to improve the diet's capacity for sustaining health.

Early nutritionists had great successes in discovering the essential nutrients: vitamins, minerals, amino acids and lipids, and by the early 20<sup>th</sup> century was it how to sustain animals on defined diets during several generations (Hartwell 1927). Already more than a hundred years ago it became clear that the composition of the diet could affect health aspects such as the susceptibility to cancer, even if it con-

tained all necessary nutrients and was not contaminated with toxins or pathogens (Braithwaite 1901).

A range of methods have been developed to study the many different types of impact of food on human health, with the ultimate aim to be able to predict the effect on the health of an entire population of a particular change in the diet.

## TYPES OF METHODS

Three broad categories of methods are relevant in this context: Epidemiology, interventions and in vitro experiments.

### *Epidemiological studies*

Epidemiology is to find out which factors in the life of people in a population are correlated with their risk to contract a disease, and therefore may be causing or promoting the disease.

Effects of diet on health almost always occur after a quite long period of time, and therefore epidemiological studies of food and health must be designed to compare diet at one point in time with health at a later time. There are two ways to make this feasible:

In prospective studies, diet is recorded among a group of healthy people (called the cohort). After the first recording of intake of various foods, the health status of each person is monitored. An example of a prospective study is the Parsifal study (Alfvén et al. 2006), which covered schoolchildren in anthroposophic and "standard" schools in several European countries. Their lifestyle including type of food was assessed by interviews with the children and their families, as well as cases of allergies, infections and other diseases.

Retrospective studies are based on people who have been diagnosed with a disease that may be diet related. The patients are interviewed about their background (age, gender, smoking, job description, postcode etc.), their diet and other risk factors before they became ill. For each patient, one or more control persons are identified, who match the patient for all the background factors, and these matched controls are then interviewed in the same way. It is then tested if there is a difference in the diet of the patients compared with the controls.

The main advantage of epidemiological studies is that they reflect differences in diet that actually occur in the population, also the costs per participating person is relatively low. The main disadvantages are that it is difficult to get precise information about diet, and it is impossible to test different effects of different food components that normally occur to-

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gether, in the same food or in the diets of the same people. For example, the Parsifal study found lower incidence of allergies among children in anthroposophic schools, and that these children ate more organic food and fermented vegetables, and had a lower number of vaccinations, when compared with the children in the "standard" schools. But since these lifestyle factors occurred together in the same children, the study could not determine which of them were important for the allergy. Some researchers are not aware of this, and declare that they have shown

#### *Intervention studies*

In intervention studies with food, human volunteers or experimental animals eat special diets decided by the researcher, and the health status is recorded during and sometimes after the intervention.

For practical and ethical reasons, intervention studies with humans often run for only a few weeks, or they control only a small part of the diet, for example a pill with a vitamin supplement or the type of bread.

In the study design, separate groups of volunteers can receive different experimental diets, alternatively the design can be a crossover study, where during different periods each volunteer receives every experimental diet. An example of a crossover study with completely controlled diets is the study by Grønder-Pedersen et al. (2003), where a group of 16 volunteers were provided with all their food during two three-week periods, one of the periods was with organic food and the other period with conventional. Intervention studies with animals are easier to carry out for longer periods, even several generations (Velimirov et al. 1992).

The assessments of health impact can be direct endpoints (how soon and how often a certain disease develops), or direct measures of well-being (sleep patterns, IQ tests). Biomarkers such as the cholesterol level in the blood can be used to assess very early stages of disease development, or it can be an ex vivo measurement, studying the development or reactions of living cells or organs after removing them from the animal or person. For example, Finamore et al. (2004) showed that spleen cells from rats fed organic wheat had a stronger immune response than when conventional wheat was used.

The greatest advantage of intervention studies is that it is possible to ensure that all other factors are kept constant, in particular if the volunteers do not know which treatment they are receiving. For human studies, the disadvantages are that short-term studies can only show short-term effects, and it is not feasible to control the diet of many people for many years. Intervention studies with animals can be fully controlled and cover the entire life cycle of the organism. However, not all animals react to a food in the same way as humans. For example, rodents have an enzyme that degrades any excess of the vitamin A-precursor  $\beta$ -carotene, and allow them to tolerate very high doses. So  $\beta$ -carotene was considered completely harmless, until moderately high doses of  $\beta$ -carotene increased the risk of cancer in human intervention studies (Omenn et al. 1996).

#### *In vitro studies*

Some aspects of the effect of food component on humans can be studied on isolated cells, organs or enzymes in vitro (latin for "in glass"). In vitro studies are extremely important for understanding the mechanisms of actions of essential nutrients as well as of toxins, and the general metabolism of all the components of cells and organs, including those of food origin.

The main advantages of in vitro studies are that they allow precise control of the concentrations of a studied compound at the cell surface, they provide rapid results and avoid ethical problems of animal (or human) suffering. The main disadvantages are the risk that compounds or other factors are introduced, which do not occur in the living body, and that this can make it difficult to interpret the results. For example, a study of the effect of extracts of organic and conventional strawberries on human cancer cell lines showed that some concentrations of the extract stimulated the growth of the cancer cells and other concentrations were inhibitory, with few correlations with the properties of the extracts (Olsson et al. 2006).

#### CONCLUSIONS

Each type of study has advantages and disadvantages, with a high risk that some effects of food on health are exaggerated, and other effects are overlooked. In particular effects resulting from long-term exposure to a food are difficult to measure. Whenever possible, an effect should be studied using several different methods. The results become more reliable when the same trends are found in different types of studies, in particular when this includes human epidemiological studies.

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