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REVIEW ARTICLE

EVIDENCE-BASED NUTRITION — REVIEW OF NUTRITIONAL EPIDEMIOLOGICAL STUDIES

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Results from epidemiological studies are often used to explore the relationships between nutrition and health. The objective of this paper is to provide guidelines for evaluating the quality and strength of evidence from different types of epidemiological studies (including ecological, cross-sectional, case-control, cohort and experimental studies) for conclusions about the relationship between nutrition and health.

The discussion include advantages and disadvantages of these different types of studies, exposures, outcomes, the role of chance, bias and confounding factors, recruitment and sampling procedures and criteria, study size and power, measurement error (random and systematic), time effects, observer and participant effects, compliance, as well as analysis and interpretation of results. A checklist for reviewing epidemiological studies is given as guide to assess the quality of the data and the suitability of the study results for specific conclusions.

In our previous paper (published in the July *SAJCN*) we described the broad principles of evidence-based nutrition, outlining the approach that should be taken when undertaking a systematic review of the relationship between nutrition and health. Once a specific and clear research question has been defined, the approach to gathering and reviewing all relevant papers should follow an *a priori* agreed protocol. The quality of any review, in terms of providing helpful insight into causal factors and justification for action, is influenced by the quality of the original studies included in the review. If the quality of original studies is poor, it will be difficult to draw clear and helpful policy conclusions. When compiling a review it is

important to differentiate between types of epidemiological studies (including observational and experimental studies) in humans and mechanistic studies (in humans and animals *in vivo*, and *in vitro* studies). In summarising the evidence it is not appropriate simply to count the number of positive and negative studies overall as a basis for drawing conclusions about the strength and direction of the evidence. Even when epidemiological studies are grouped by study design, it is important to have some measure of study quality and to assess whether the findings of studies that are well done differ from those that are poorly done.

In this paper we review the strengths and weaknesses of the different types of epidemiological studies that are used to explore the relationship between nutrition and health. The aim of this review is to provide the reader with a guide to the key methodological factors to look for when reading the original research paper. A number of texts are available that provide much greater detail.^{1,2}

TYPES OF EPIDEMIOLOGICAL STUDIES

Broadly, epidemiological studies can be divided into experimental and observational investigations either in individuals or populations (Table I and Fig. 1). Before going into any detail, it is important to be clear about the research question being addressed. Most commonly, studies are seeking to assess the relationship between what people eat or nutritional status (exposure) and some health outcome. The more precisely a question is formulated, the easier it will be to see whether the study has been properly designed to address that question. Sometimes measures can be described as exposure or outcome measures; for example, anthropometry is often used to describe exposure, and sometimes used as a marker (outcome) of the impact of poor diet (exposure). How to clarify exposure and outcome measures will be covered in more detail elsewhere.

Table I. Summary of study designs used in nutritional epidemiological research

Study design	Study group	
	Populations	Individuals
Experimental	Community trials	Clinical trials (therapeutic or secondary or tertiary prevention)
		Field trials (primary prevention)
		Field intervention studies
Observational	Ecological studies	Cross-sectional (prevalence) studies
		Case-control (referent) studies
		Cohort (longitudinal) studies
		Cohort (longitudinal) studies

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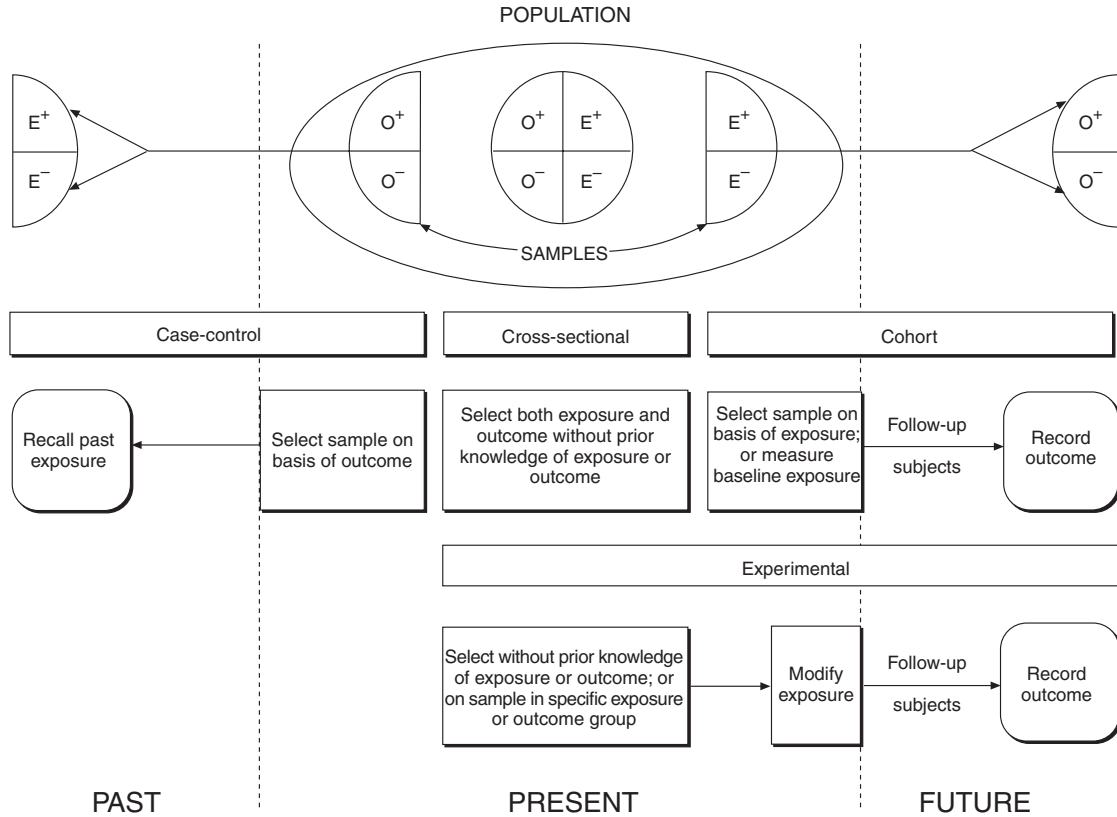


Fig. 1. Summary of sampling and time order of study designs used in nutritional epidemiological studies (O = outcome; E = exposure).

In the interpretation of any study a few key concepts are common and must be considered: chance, bias and confounding; and sampling, study size and power. For all studies the impact of information and selection bias needs to be considered. While there will always be measurement error in any study, it is important to differentiate between random and systematic error. Systematic error leads to bias, and bias can never be removed by increasing the size of a study. If there is random error, then a bigger sample will help improve the precision of the estimate of effect.

Ecological studies

In ecological studies of the association between nutrition and health, population or group indices of dietary intake or nutritional status (exposure) are related to population or group indices of health status (outcome). The unit of analysis is not an individual but a group defined by time (e.g. calendar year, birth cohort), geography (e.g. country, province, or city), or sociodemographic characteristics (e.g. ethnicity, religion, or

socioeconomic status). For example, national dietary cereal consumption for each country in Africa (from FAO food balance sheet data) can be plotted against infant mortality rates (taken from the State of the World's children annual report from UNICEF) for each country. This might show that countries that have higher cereal availability have lower infant mortality rates (IMRs). Another type of ecological analysis may be to plot within-country national trends for consumption of foods against trends for morbidity or mortality. This might show if there is any association between increasing (or decreasing) availability and increasing or decreasing IMR. These associations do not prove that there is a causal link between cereal consumption and IMR. All that can be asserted is that there may be an association. Ecological studies are helpful when within-group (country or region) variation in exposure is small compared with between-group variation. It is often difficult in ecological studies to control for other potentially confounding factors and to explore interactions. For example, countries where cereal consumption is higher may

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have better health care or more resources for sanitation, which may be more important in predicting IMR. When comparing national levels of exposure and outcome, it is important to consider the relevant time frame for comparison; there is likely to be some lag time between exposure and its effect on outcome. For example, with smoking and lung cancer there is about a 10-year lag.

Disadvantages and advantages of ecological studies

Ecological studies are ideal for exploring newly proposed hypotheses; this serves as a basis for developing more detailed individual-level studies in the future. Ecological studies are weak in terms of drawing causal inferences about the effects of factors operating at an individual level. In some situations individual level data are not available and an ecological approach is all that is available. Ecological studies may be very useful for monitoring national trends in health indicators and the wider social, cultural, economic and environmental factors that influence health that cannot be measured at an individual level.

Cross-sectional studies

Cross-sectional studies (sometimes described as prevalence surveys) measure both exposure and outcome in the present and at the same point in time in individuals. Generally, cross-sectional studies sample from the population in such a way as to reflect the population characteristics for both exposure and outcome, and thus can be used to describe the prevalence of nutrition problems in a community. If information on population characteristics (age, gender, income, education, etc.) is also collected, the effect these factors may have on the exposure-outcome relationship can also be assessed. When repeated in the same population, a cross-sectional survey can be used for surveillance and monitoring, provided the measure is sensitive and specific for the required measure.

Sampling, selection bias, sample size, and power

Selection bias and sample size will affect the generalisability of the findings in a cross-sectional study. If the source population and sampling frame are not clear in the description of the methods, it may be that the study sample will not reflect the source population and therefore the results of the study will not be generalisable. If a particular sector of the sample is excluded (for example malnourished children too sick to participate), the prevalence estimate and reported associations may be misleading. If the sampling frame is adequate, but the sample size is too small to provide a reliable estimate of the population prevalence, the study results will not be helpful. To ensure that enough participants are included, sample size should be calculated with available formulas and be reported in an article.

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Information bias

When you have read the methods, is it clear and are you confident that the authors have measured the relevant exposure and other variables with the required level of accuracy to answer the question? Is the dietary methodology clearly described and is it likely to be valid (have they assessed the validity of their instrument)? Do you think people will tell the truth about the behaviour being asked about? Is it likely that all the subjects in the study will use the instrument in the same way and provide the same quality and accuracy of information? For example, will the dietary assessment be used differently by better and worse educated participants (are they all literate and does the instrument assume literacy?), or by obese and thin participants? If the methods section does not answer these questions, you may not be able to believe the findings of the study.

Disadvantages of cross-sectional studies compared with other study designs

The main disadvantage of cross-sectional studies is that it is not possible to disentangle cause from effect because the exposure is not measured before the onset of the outcome. It may be that, for example, the outcome or illness may have altered the dietary patterns, rather than the other way around (for example, someone starts drinking milk after they get an ulcer to relieve symptoms). Although cross-sectional studies can take other potentially confounding factors into account, causal inferences cannot be drawn from such studies, primarily because the temporal sequence cannot be established.

Case-control studies

In case-control studies (sometimes termed case-referent studies) patients with a disease (cases) are compared with controls who do not have the disease. The study begins by recruiting people on the basis of their outcome status, and then explores past exposure measures. Case-control designs are efficient where the outcome (e.g. liver cancer) is rare (in an absolute sense) and all available cases can be recruited from the population of interest.

Population definition, recruitment of controls, and sample size

Ideally, a population is defined (for example, the catchment area of a hospital or the walking distance for mothers to bring malnourished children to a clinic) from which all cases of interest are identified over a specified period of time. This population must be sufficiently large to generate a statistically viable number of cases. Ideally all eligible cases arising in the catchment area should be recruited. If the cases are self-selected, for example based on people who turn up at the clinic, there may be some bias introduced, because the sickest children, or those furthest away, or those different in some

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other ways, may be left out. The paper should explain recruitment clearly.

Controls should be recruited at random from the same population from which the cases are drawn. All non-cases could be recruited for comparison, but it is more statistically efficient to take a sample of the population. Controls are often selected at random and matched on certain characteristics that are known to influence outcome, but of themselves are of no direct interest in the study (for example, age and gender).

Information bias

Case-control studies usually describe recalled past exposure. The aim should be to try to explore exposure at the time when it is thought that the behaviour (exposure) was affecting the process that leads ultimately to the outcome. For example, in most cancer case-control studies the aim is to describe diet at the time that diet either initiated the cancer process, or promoted the development of cancer. Often this will be 10 - 20 years ago. Most studies ask people to recall their usual diet over a fairly recent time frame, and then extrapolate backwards in time, often aided by questions about change in past diet. The key issue to consider when reviewing the paper is whether this recalled past exposure is reported with the same accuracy and precision in cases and controls. When assessing the impact of the exposure on outcome (usually expressed as an odds ratio), participants are usually ranked and intake grouped into, for example, thirds of the distribution (as high, medium and low) and risk of outcome is assessed across these thirds. The absolute intake is not necessary, and provided the ranking of intake is consistent between cases and controls, the estimate of risk will reflect the underlying risk of exposure on outcome. If, however, controls who are truly high consumers are misclassified as low consumers, and cases are not so misclassified (i.e. differential misclassification), then the wrong estimate of the true effect of intake on outcome will be derived from the analysis.

Disadvantages and advantages of case-control studies

The biggest problem with case-control studies is the potential for biased recall of past exposure.

Case-control studies are good for studying rare outcomes. Case-control studies are restricted to assessing one outcome (or at the most subsets of related outcomes), but may be able to assess many different exposures (but also depending on the measure of diet used).

Cohort studies

Cohort studies (sometimes called prospective studies) measure exposure in the present and outcome is assessed at some point in the future. Unlike cross-sectional surveys, a cohort study can be used to draw causal inferences about the effect of the exposure on outcome, as the exposure is measured before the

outcome is known, and therefore not influenced by knowledge of the outcome status.

Sample selection and follow-up

The sample for a cohort study is not always selected to represent the distribution within the whole population. The sample may be weighted to maximise the heterogeneity of exposure, or it might be selected to minimise loss to follow-up; both these factors may be considered to be of more importance than the representativeness of the sample. For both cohort studies the primary concern is to select a sample that is not going to be lost in the follow-up period. For example, a number of large cohort studies follow up health professionals who have to be registered to maintain their practice, and so can be traced through these registers.

Cohort designs can be an efficient way of sampling rare exposures from the population; the benefit here is that it is possible to maximise the range of dietary exposure that can be studied. For example, vegetarians with very different dietary habits from the general population can be recruited and compared with a sample of omnivores to explore the effects of the dietary differences on health outcomes. If one were to take a random sample of the population, only about 5% are vegetarians, so the sample would need to be very large to recruit sufficient vegetarians to have a statistically viable sample. It is important to consider how many people are required to be followed up over what length of time to have sufficient disease endpoints to calculate an estimate of the risk of disease in the vegetarian group compared with the omnivore group.

Exposure measurement

In a cohort study, the exposure measure is often divided into thirds or fourths of the distribution and the change of risk assessed across these categories (logistic regression). The requirement for the measure of exposure in this type of analysis is that the measured intakes of participants can accurately rank the true intake of the population (i.e. so that people with a high and low intake can be differentiated). The selection of the cut-off points used to define groups may critically affect the estimate of risk obtained. Some authors prefer to use a regression approach where, instead of grouping data, each individual observation contributes to the regression equation (multiple regression); what is then described is the change in outcome per unit change in exposure. Both approaches, logistic and multiple regression, allow for the adjustment of the effects of other factors.

Disadvantages and advantages of cohort studies

Potentially the biggest concern for a cohort study is loss to follow-up, particularly when this may be differential by level of exposure. When reviewing the paper make sure the authors

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have described the drop-out rate and loss to follow-up; if they haven't, be cautious, because it may be that only a small proportion of those who started the study could be traced at the end. It is very likely that those who were lost to follow-up differed in important ways to those who were not lost.

Cohort studies are often very large and may take many years to be conducted, and are usually expensive. However, of all the observational studies they provide the strongest evidence for a causal relationship because it is unlikely that the measure of exposure is biased and measured before the outcome is known, and may therefore predict a causal pathway.

Experimental studies

Experimental studies are the most robust test of a causal hypothesis. An experiment is the only study design where the exposure ('treatment') is actually manipulated by the researcher and the effect that manipulation has on outcome can be assessed. Experimental studies are most often conducted at the individual level, but are sometimes conducted at the population level.

There are a number of general principles that are relevant to all experimental studies. When reviewing an experiment, look in the methods for the following details:

- **Selection of the study population:** needs to be relevant to the study question; exclusion rules may apply, but these should be clear.
- **Allocation of treatment regimens:** randomisation is essential; a comparison group is essential (either placebo or other treatment). If a community population level experiment, ideally communities should also be randomised.
- **Length of observation:** the study needs to be long enough for the effect of the exposure on outcome to occur, if it is going to.
- **Observer effects:** ideally should be blinded
- **Participant effects:** ideally should be blinded
- **Compliance:** should be described to make sure participants did (or did not) get the treatment. In some studies the treatment may be inadvertently shared with the controls, so they may also 'benefit' from the treatment and the results would look as though there is no difference between treatment and control, and therefore that the treatment did not work (even though it really did!).
- **Ascertainment of exposure and outcome:** both need to be measured at baseline and follow-up with required accuracy.
- **Study size/statistical power:** the study needs to be big enough to reduce the potential of a chance null effect. The number required depends on the effect expected and the accuracy of the methods used. If this is not described, beware!
- **Analysis and interpretation:** the true measure of effect is the difference in change between the treatment and the control group. Make sure the study is analysed like this.

Often you will see the change in treatment group reported alone (usually when it is statistically significant), but this is the wrong way to present the results. The whole point of the control group is to assess change in background (confounding) factors.

Disadvantages and advantages of experimental studies

Most experimental studies change only one factor. However, in the real world people eat a combination of foods and the

Table II. Checklist for reviewing nutritional epidemiological studies

1. Does the literature review justify the study
2. Is there a clear study aim, with a clear hypothesis
3. Do the hypotheses clearly define exposure and outcome, and other variables that need to be measured

Sampling, study size and power

4. Is the sample recruitment process clear
 - a. How participants were selected
 - i. are exclusion/inclusion criteria clear
 - b. What was the population or sampling frame
 - c. Response rate (loss to follow-up)
 - d. Reasons for non-compliance
5. Sample characteristics
 - a. Are these adequately described
6. Sample size and power
 - a. Has sample size been justified

Information and quality of data

7. Methods of assessing exposure
 - a. Are the methods described clearly
 - i. could you repeat study based on information given
 - ii. if nutrients are derived, what data base has been used
 - iii. how have portion sizes been assessed
 - b. Have the methods been validated
 - i. what validation information has been given
 - ii. is it sufficient and specific to purpose for which measure is being used
8. Methods of assessing outcome
 - a. How has the outcome been measured
 - b. Are the methods valid (sensitive and specific, accurate and precise)
9. Analysis
 - a. Can you follow the analysis
 - b. Are the tables and text clear

Interpretation

10. Discussion
 - a. Is the discussion fair and balanced
 - b. Have they covered the strengths and weaknesses of their study
 - c. Have they compared their results with the published literature
11. Conclusions
 - a. Are they justified and appropriate to the results as presented

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effect of one factor in isolation may be quite different from that when studied in the whole-diet. It is difficult to design a whole-diet experiment that is blinded.

CONCLUSION

It is important in any review of nutrition and health to differentiate the review by study type and to judge the quality of the individual studies included. Table II provides a general summary checklist that may be helpful as a template for reviewing all studies. In addition, specific points will need to be considered for each study design.

In terms of drawing causal inferences, experimental studies are theoretically the best test of a hypothesis, but may be difficult to interpret and not relevant to the study of dietary patterns. Experiments are good for single factors such as drugs. Among the observational studies, a well-done cohort study is likely to be more robust than a case-control or cross-sectional study, primarily because there is less chance of information bias.

References

1. Margetts BM, Nelson M. *Design Concepts in Nutritional Epidemiology*. 2nd ed. Oxford: Oxford University Press, 1997.
2. Willett W. *Nutritional Epidemiology*. 2nd edition. New York: Oxford University Press, 1998.

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SAJCN CPD activity No 16 - November 2002

You can obtain 3 CPD points for reading the article: 'Evidence based nutrition: review of nutritional epidemiological studies' and answering the accompanying questions. This article has been accredited for CPD points for dietitians. (Ref number: DT 02/3/276/12)

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PLEASE ANSWER ALL THE QUESTIONS

(Mark the ONE correct choice)

- | | |
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| <ol style="list-style-type: none"> 1. Selection error can be removed by increasing the size of any epidemiological study.
[a] True
[b] False 2. Ecological studies may be useful for monitoring national trends in health indicators and factors that influence health but cannot be measured at an individual level.
[a] True
[b] False 3. Causal inferences can be drawn from either cross-sectional or experimental studies.
[a] True
[b] False 4. In case-control studies the impact of past exposure on outcome is expressed as an odds ratio.
[a] True
[b] False 5. In estimating diet-disease risk across strata of exposure levels, the ranking of dietary intake needs to be consistent between cases and controls.
[a] True
[b] False 6. The greatest limitation with case-control studies is the potential for biased recall of past exposure.
[a] True
[b] False | <ol style="list-style-type: none"> 7. Disease may influence exposure in case-control studies.
[a] True
[b] False 8. Cohort studies begin with the supposed cause and seek to determine the incidence of disease in those exposed and those not exposed to it.
[a] True
[b] False 9. An experimental study is a study where the exposure is modified by the researcher and the outcome assessed.
[a] True
[b] False 10. Experimental studies need to be long enough for the effect of the exposure on outcome to occur.
[a] True
[b] False 11. A true measure of effect in experimental studies is a difference in change between the treatment and the control group.
[a] True
[b] False 12. There is less chance of information bias in:
[a] Case-control studies
[b] Cohort studies |
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✂ Cut along the dotted lines and send to: SASPEN Secretariat, SAJCN CPD activity No 16, c/o Department of Human Nutrition, PO Box 19063, Tygerberg, 7505 to reach the office not later than 31 January 2003

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"Evidence based nutrition: review of nutritional epidemiological studies"

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Please color the appropriate block for each question

(e.g. if the answer to question 1 is a: 1) a b)

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