Chapter 10

METHODOLOGICAL CHALLENGES IN STUDYING LONG-TERM EFFECTS OF BREAST-FEEDING

M.S. KRAMER
Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University Faculty of Medicine, and the Institute of Human Development, Child and Youth Health, Canadian Institutes of Health Research, The Montreal Children’s Hospital, 2300 Tupper Street, Montreal, Quebec H3H 1P3, Canada. michael.kramer@mcgill.ca

1. INTRODUCTION

Many short- and long-term child health benefits have been reported with breast-feeding. Many of these alleged health benefits exhibit dose-response relationships, with greater exclusivity and duration of breast-feeding associated with greater degrees of benefit. The short-term benefits have included reduced morbidity and even mortality from infectious diseases, particularly gastrointestinal and respiratory infection.1-2 Atopic eczema and cow’s milk and other food allergies have also been reported to be less frequent in breast-fed infants. The clearest short-term benefits have been shown to accrue to infants during the actual period of breast-feeding, but a number of studies have suggested that breast-feeding, particularly exclusive and prolonged breast-feeding, may confer protection against such long-term health outcomes as asthma, other allergic diseases, type 1 diabetes, inflammatory bowel disease, lymphoma, leukemia, obesity, hypertension, and hypercholesterolemia, as well as lead to taller stature and improved neurocognitive development.1

It is unfeasible and probably unethical to randomise newborn human infants to breast-feeding vs formula-feeding, or even to more vs less...
exclusive, or to longer vs shorter durations of breast-feeding. Thus most of the evidence bearing on the child health benefits of breast-feeding is based on observational (nonexperimental) studies, with numerous potential sources of bias.\textsuperscript{3,4} This is true even for short-term benefits, but relating long-term health outcomes to feeding in infancy and early childhood presents even greater methodological challenges for epidemiological studies. Given the recent interest in “programming” and the early origins of adult chronic diseases,\textsuperscript{5,6} it is timely to reflect on these challenges and how they can be addressed in future studies.

The major methodological issues can be subdivided into those related to random vs systematic error. Systematic error, or bias, can be in turn subdivided into considerations of bias due to measurement, selection, confounding, and reverse causality. These issues will be discussed in turn in the remainder of this chapter.

2. RANDOM ERROR

Random error is due to sampling variation, i.e., chance variation in the observed association between “exposure” (breast-feeding vs formula-feeding, exclusive vs partial breast-feeding, prolonged vs short duration of breast-feeding) and the health outcome under study. No matter how representative the sample of the source population of interest, the observed magnitude of the association between feeding and health outcome may differ from the “true” magnitude merely by chance. The size of the error (i.e., the difference between the observed and true magnitude) reflects the degree of sampling variation and depends primarily on the sample size, with small samples being much more prone to random errors. This is a particularly important issue when using cohort (forward-directional) designs to study rare outcomes, such as type 1 diabetes, cancer, inflammatory bowel disease, and other autoimmune diseases, since very large samples are required to ensure an adequate number of cases of the outcome to detect differences in incidence due to feeding mode.

Random error is easily quantified by standard statistical theory based on known sampling distributions such as the normal, binomial, and Poisson distributions. It is these known distributions that enable quantitative estimates of sampling error by such well-known techniques as confidence intervals, hypothesis tests, and P values.

Table 10-1 provides an illustrative example of random error in a hypothetical cohort (follow-up) study of 500 breast-fed (BF) and 500 formula-fed (FF) infants for the development of a health outcome (O+) of interest. In the upper 2 x 2 table, the absolute risks in the BF and FF groups