

4. EFFECT OF BREASTFEEDING ON CHRONIC DISEASES

Papers summarized in this section explore associations between infant feeding and chronic or noncommunicable diseases. Some observational studies suggest that suboptimal breastfeeding may be a factor in obesity, diabetes, cancer, and other conditions.

4.1 Effect of Breastfeeding on Obesity

Gillman MW, Rifas-Shiman SL, Carmargo CA Jr., Berkey CS, Frazier AL, Rockett HRH, et al. Risk of overweight among adolescents who were breastfed as infants. JAMA 2001;285:2461–7.

COUNTRY: United States

SETTING: Nationwide

DESIGN: Cohort study using participants from the Growing Up Today Study (on diet, activity, and growth), n = 15,341 (8,186 girls and 7,155 boys) 9–14 years old

BREASTFEEDING DEFINITION: Using a 5-point scale: breastmilk only, more breastmilk than infant formula, both equally, more infant formula than breastmilk, infant formula only

OUTCOME MEASURE: Overweight status defined as body mass index (BMI) exceeding the 95th percentile for age and sex from U.S. national data

RESULTS: There was an inverse association between duration of breastfeeding and risk of overweight; those who were breastfed for ≥ 7 months were 20% less likely to be overweight than those who were breastfed for ≤ 3 months. Similarly, adolescents who received mostly or only breastmilk in the first 6 months had 22% lower risk of being overweight. For mothers, those who exclusively breastfed for the first 6 months had the lowest BMI, and those who breastfed the longest had a lower BMI than mothers who breastfed for shorter periods. Time of introduction of solids had no effect on the outcomes.

METHODOLOGICAL ISSUES: Sex-specific questionnaires were used to collect self-reported information from the participants regarding their age, sex, race/ethnicity, height, weight, sexual maturity, age at menarche, diet, and physical activity. Mothers responded to a supplemental questionnaire with information about the children's birth weight and length, gestational age, childhood medical conditions, and infant feeding practices. Comparisons were made between subjects who were mostly or only breastfed and those who were mostly or only formula-fed, and between subjects who were breastfed ≥ 7 months and those breastfed for ≤ 3 months. Co-variables included sexual maturity, sex, energy intake, total physical activity, hours of TV watching, and mother's body mass index (in 1995). Potential confounders included social and economic factors, including birth weight. All participants were children of registered nurses who participated in the Nurses Health Study II, and 93.6% of them were white.

Hediger ML, Overpeck MD, Kuczmariski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. *JAMA* 2001;285:2453–60.

COUNTRY: United States

SETTING: Nationwide

DESIGN: Data obtained from the cross-sectional National Health and Nutrition Examination Survey III (NHANES III) study: n = 2,685 (1,310 boys and 1,375 girls) 3–5 years old

BREASTFEEDING DEFINITION: Fully breastfed if no liquids other than breastmilk or water were received daily, partially breastfed if daily supplements with formula or milk were received

OUTCOME MEASURE: Body mass index (BMI) between 85th and 94th percentile was considered “at risk” of overweight; body mass index \geq 95th percentile was considered overweight

RESULTS: Children who were ever breastfed were 37% less likely to be at risk of overweight and 16% less likely to be overweight than children who were never breastfed. There was no clear dose-dependent effect of duration of full breastfeeding with risk of overweight or with overweight. Although there was a slight reduction in child body mass index with duration of full breastfeeding, the difference was not statistically significant. Eleven percent of the children were determined to be at risk of overweight, while 8.2% were classified as overweight. Girls showed a trend toward increasing overweight between 3 and 5 years of age. Ethnic differences were observed regarding ever having been breastfed, with non-Hispanic black infants being the least likely ever to have been breastfed. Maternal BMI influenced breastfeeding patterns: underweight mothers breastfed for shorter periods of time than normal-weight mothers, while overweight and obese mothers were more likely not to breastfeed at all. The strongest predictor of overweight among children was the mother’s present BMI; children of overweight and obese women were 3 and 4 times more likely to be at risk of overweight, respectively, than children of normal-weight mothers.

METHODOLOGICAL ISSUES: Ethnically diverse, U.S.-born children 3–5 years old were studied. Weighted sample statistical analyses and standard error estimations were done. Multiple regression was used to estimate the effect of duration of full breastfeeding on child body mass index. Odds and adjusted odds ratios were estimated for risk of overweight and for overweight using normal body mass index as the reference. Confounding variables were taken into account, and unweighted analyses were performed to confirm the significance of the findings.

von Kries R, Koletzko B, Sauerwald T, et al. Breast feeding and obesity: Cross sectional study. *Br Med J* 1999;319:147–50.

COUNTRY: Germany

SETTING: Bavaria (southern Germany, rural regions)

DESIGN: Cross-sectional survey: n = 9,357 children aged 5–6 years

BREASTFEEDING DEFINITION: Exclusive breastfeeding was defined as giving no food other than breastmilk to the child.

OUTCOME MEASURE: Body mass index (kg/meter²); obesity was defined as body mass index > 97th percentile and overweight as body mass index > 90th percentile.

RESULTS: There was a clear dose-response relationship between the duration of breastfeeding and the prevalence of overweight or obesity. Children who had been breastfed for ≥ 6 months were more than 30% less likely to be overweight and more than 40% less likely to be obese.

METHODOLOGICAL ISSUES: Anthropometric data were obtained from mandatory school entrance examinations and dietary habits, and complementary feeding information was gathered from questionnaires sent to parents. Chi-square tests were used to compare children who were and were not breastfed, and logistic regression models were used to assess the impact of variables associated with breastfeeding and being overweight or obese.

4.2 Effect of Breastfeeding on Diabetes

Jones ME, Swerdlow AJ, Gill LE, et al. Pre-natal and early life risk factors for childhood onset diabetes mellitus: A record linkage study. Int J Epidemiol 1998;27:444–9.

COUNTRY: United Kingdom

SETTING: Urban

DESIGN: Case-control study using data from the Oxford Record Linkage Study (ORLS)

BREASTFEEDING DEFINITION: Breastfed or nonbreastfed infants

OUTCOME MEASURE: Incidence of diabetes mellitus

RESULTS: There was a significant 33% increased risk of diabetes among infants who were not breastfed at discharge. Maternal diabetes was a strong predictor of diabetes in children. Maternal preeclampsia was associated with increased risk for early and later onset of diabetes.

METHODOLOGICAL ISSUES: Conditional logistic regression for matched case-control studies was used for calculating adjusted relative risk of diabetes among 0- to 20-year-olds. Breastfeeding status was obtained before the actual diagnosis of diabetes in the children.

Pettitt DJ, Forman MR, Hanson RL, Knowler WC, Bennett PH. Breastfeeding and the incidence of non-insulin-dependent diabetes mellitus in Pima Indians. Lancet 1997;350:166–8.

COUNTRY: United States

SETTING: Not reported

DESIGN: Longitudinal: breastfeeding data obtained retrospectively but before most of the subjects had developed diabetes

BREASTFEEDING DEFINITION: Exclusive breastfeeding (EBF), partial breast-feeding, exclusive formula-feeding (FF) during the first 2 months of life

OUTCOME MEASURE: Noninsulin-dependent diabetes mellitus (NIDDM) measured by a glucose tolerance test

RESULTS: The rate of NIDDM for those exclusively breastfed was lower than for those who were exclusively bottle-fed. At age 10–19 years, none of the EBF children had developed NIDDM, whereas 3.6% of the FF children had. At ages 20–29 years, 8.6% of the EBF and 14.7% of the FF subjects had developed NIDDM, and at ages 30–39 years, 20% of the EBF and 29.6% of the FF subjects had developed NIDDM. The odds ratio for NIDDM for subjects who were EBF was 0.44 (95% CI: 0.43–0.96).

METHODOLOGICAL ISSUES: Breastfeeding data were collected before the onset of most cases of noninsulin-dependent diabetes. Recall consistency was checked in a subsample, showing that most women were consistent.

Norris JM, Scott FW. A meta-analysis of infant diet and insulin-dependent diabetes mellitus: Do biases play a role? Epidemiology 1996;7:87–92.

COUNTRY: Multicountry (Europe and the United States)

SETTING: Not reported

DESIGN: Meta-analysis of 17 case-control and 2 ecological studies

BREASTFEEDING DEFINITION: Ever having been breastfed compared with never having been breastfed and duration of breastfeeding; age at introduction of breastmilk substitutes (any milks or foods other than breastmilk in the infant's diet).

OUTCOME MEASURE: Insulin-dependent diabetes mellitus (IDDM)

RESULTS: The summary odds ratio of never having been breastfed and IDDM was 1.13 (95% CI: 1.04–1.23). Subjects who were breastfed for less than 3 months compared with those who were breastfed for at least 3 months had a summary odds ratio for IDDM of 1.23 (95% CI: 1.12–1.35). The summary odds ratio showed elevated risks for IDDM associated with age at first introduction of any breastmilk substitute before the age of 6 months. The incident odds ratio for the risk of IDDM associated with exposure to a breastmilk substitute before 3 months of age compared with ≥ 3 months was 1.54 (95% CI: 1.17–2.03).

METHODOLOGICAL ISSUES: Recall bias may be an issue in case-control studies, particularly if the recall time is large.

Samuelsson U, Johansson C, Ludvigsson J. Breast-feeding seems to play a marginal role in the prevention of insulin-dependent diabetes mellitus. Diabetes Research and Clinical Practice 1993;19:203–10.

COUNTRY: Sweden

SETTING: Southeast region

DESIGN: Case-control: cases (n = 297) were diabetic children < 15 years; controls (n = 792) were matched by age, sex, and place of residence

OUTCOME MEASURE: Childhood insulin dependent diabetes

BREASTFEEDING DEFINITION: Duration of exclusive breastfeeding and any breast-feeding

RESULTS: There was no significant effect of breastfeeding history on risk of developing diabetes. In a subgroup analysis, it was found that children diagnosed during the winter tended to have older mothers and to have been breastfed for a shorter period of time than controls. The authors suggest that, among these “epidemic” type cases, breastfeeding might have a weak protective effect.

METHODOLOGICAL ISSUES: The authors examined the data for many different subgroup effects and found a slight association for one of these (winter diagnosis, older mothers, and shorter duration of breastfeeding). They did not discuss the mechanism by which the subgroup with these characteristics might be at greater risk. Overall, this study does little to establish an association between diabetes and breastfeeding.

4.3 Effect of Breastfeeding on Later Risk of Cancer

Shu XO, Linet MS, Steinbuch M, et al. Breast-feeding and risk of childhood acute leukemia. J Natl Cancer Inst 1999;91:1765–72.

COUNTRY: Multicountry (United States, Canada and Australia)

SETTING: Not reported

DESIGN: Case-control study design with 2,200 childhood acute leukemia cases (1,744 cases with acute lymphoblastic leukemia [ALL], and 456 cases with acute myeloid leukemia [AML]) obtained from the Children’s Cancer Group and 2,418 controls (1,879 for ALL and 539 for AML) obtained through random digit dialing and matched for age at diagnosis, geographic location, and race. Children in the ALL groups were aged 1–14 years and children in the AML groups were aged 1–17 years.

BREASTFEEDING DEFINITION: Breastfeeding for 6 months or longer, breastfeeding for 1–6 months, or not breastfeeding

OUTCOME MEASURE: Acute lymphoblastic leukemia and acute myeloid leukemia

RESULTS: Overall, there was an inverse association between ever having been breastfed and a reduced risk of childhood acute leukemia, for both ALL (odds ratio = 0.80; 95% CI: 0.69–0.93) and AML (odds ratio = 0.77; 95% CI: 0.57–1.03). A reduction in the risk of childhood acute leukemia was particularly strong among children who were breastfed for more than 6 months. The odds ratio of children who were breastfed for longer was 0.72 (95% CI: 0.60–0.87) for ALL and 0.57 (95% CI: 0.39–0.84) for AML.

METHODOLOGICAL ISSUES: Mothers of children with acute leukemia were more likely to be nonwhite and, on average, less educated. More ALL cases were from lower-income families or had birth weights greater than 4000 g, than were controls, possibly introducing confounding variables or bias.

Titus-Ernstoff L, Egan KM, Newcomb PA, Baron JA, Stampfer M, Greenberg ER, et al. Exposure to breast milk in infancy and adult breast cancer risk. *J Natl Cancer Inst* 1998;90:921–4.

COUNTRY: United States

SETTING: Three states: Massachusetts, New Hampshire, Wisconsin

DESIGN: Population-based case-control study of 8,299 women aged 50 or more. A total of 205 cases and 220 controls were premenopausal, and 3,803 cases and 4,071 controls were postmenopausal.

BREASTFEEDING DEFINITION: Ever having been breastfed

OUTCOME MEASURE: Breast cancer

RESULTS: After adjusting for breast cancer risk factors, there was no relationship between having been breastfed as an infant and breast cancer occurrence in either pre- or postmenopausal women.

METHODOLOGICAL ISSUES: The authors discuss a number of sources of bias, such as recall bias, and rule them out.

Potischman N, Brinton LA, Coates RJ, Malone DE, Schoenberg JB. Letter re: *Fruedenheim et al., Epidemiology* 1995;6(2):198–200.

COUNTRY: United States

SETTING: Georgia, Washington, New Jersey (urban)

DESIGN: Case-control: cases (n = 380) were newly identified with premenopausal breast cancer; controls (n = 311) were selected randomly from the community

BREASTFEEDING DEFINITION: Any breastfeeding (yes, no); breastfeeding histories were obtained from subject's mothers.

OUTCOME MEASURE: Breast cancer

RESULTS: This study examined whether having been breastfed as an infant reduced a woman's risk of premenopausal breast cancer. Having been breastfed as an infant was associated with reduced risk. The magnitude of the reduction in risk was identical to that found in Fruedenheim et al. (1994), for premenopausal women (odds ratio = 0.76; 95% CI: 0.54–1.08).

METHODOLOGICAL ISSUES: The response rate for cases and controls was low.

Freudenheim JL, Marshall JR, Graham S, Laughlin R, Vena JE, Bandera E, et al. Exposure to breastmilk in infancy and the risk of breast cancer. Epidemiology 1994;5:324-1.

COUNTRY: United States

SETTING: Western New York

DESIGN: Case-control: cases (n = 528) were women newly diagnosed with breast cancer; age-matched controls (n = 602) were randomly selected from the community

BREASTFEEDING DEFINITION: Any breastfeeding (yes, no); breastfeeding histories as an infant were obtained from the subjects

OUTCOME MEASURE: Breast cancer

RESULTS: This study examined whether having been breastfed as an infant reduced a woman's risk of breast cancer. Having been breastfed was associated with a significantly decreased risk. The adjusted odds ratio was 0.74 (95% CI: 0.56-0.99). The difference was found for both pre- and postmenopausal women. The authors conclude that being bottle-fed as infants may predispose women to the development of breast cancer.

METHODOLOGICAL ISSUES: The participation of eligible cases and controls was low (about 50%), and only about half of the cases and controls knew whether they had been breastfed as infants. Thus, results may have been biased by low participation and poor recall. The authors controlled for many known confounding factors.

Davis MK, Savitz DA, Gaudard BI. Infant feeding and childhood cancer. Lancet 1988;August 13:365-8.

COUNTRY: United States

SETTING: Statewide (Colorado)

DESIGN: Case-control: cases (n = 201) were children diagnosed with childhood cancer; controls (n = 181) of similar age, sex, and area of residence were randomly selected from the community.

BREASTFEEDING DEFINITION: Duration of any breastfeeding categorized as follows: no breastfeeding, breastfed < 6 months; breastfed > 6 months

OUTCOME MEASURE: Childhood cancer

RESULTS: This study examined whether having been breastfed was associated with a decreased risk of childhood cancer. Compared with children who had been breastfed > 6 months, children who were not breastfed or breastfed for < 6 months had significantly higher risk of developing cancer (p = 0.023). Compared with breastfeeding > 6 months, the crude odds ratios for no breastfeeding and breastfeeding < 6 months were 1.8 and 1.9, respectively. Adjusted odds ratios were similar. Increased risk was largely the result of increased risk for lymphoma. Compared with children who had been breastfed > 6 months, children not breastfed or breastfed < 6 months had a 5 to 8 times greater risk of developing lymphoma (unadjusted p value = 0.023). However, when adjusted for maternal education, the p value increased to 0.1.

METHODOLOGICAL ISSUES: Young cases < 1.5 years of age were excluded from the study to avoid the possibility of reverse causality. The small number of cases made it difficult to evaluate the effect of maternal education, which was associated with breastfeeding and cancer risk.

4.4 Effect of Breastfeeding on Other Outcomes

Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: Two cohorts after randomised trials. Lancet 2001;357:413–9.

COUNTRY: United Kingdom

SETTING: Five neonatal units in the UK and follow-up 13–16 years later

DESIGN: Randomized with prospective follow-up of children 13–16 years old born preterm (n = 926). Two parallel studies were conducted: trial 1 consisted of preterm infants randomized to receive either breastmilk (from a breastmilk bank) or preterm formula, and trial 2 consisted of preterm infants receiving either normal-term or preterm formula.

BREASTFEEDING DEFINITION: Banked breastmilk, preterm formula, standard term formula

OUTCOME MEASURE: Systolic, diastolic, and mean arterial blood pressure

RESULTS: Mean arterial and diastolic blood pressure were significantly lower in children aged 13–16 years who received banked breastmilk than in those who received preterm formula. No significant differences were found among infants who received either term or preterm formula. The proportion of enteral intake of breastmilk was significantly related to mean arterial and diastolic blood pressure, even after adjustment for confounding factors, but not to systolic blood pressure. Neither energy nor protein intake was related to mean arterial blood pressure.

METHODOLOGICAL ISSUES: Multiple linear regression analyses were performed for the observational epidemiological data.

Ravelli ACJ, van der Meulen JHP, Osmond C, et al. Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. Arch Dis Child 2000;82:248–52.

COUNTRY: The Netherlands

SETTING: Urban (Amsterdam)

DESIGN: Population-based observational study: n=625

BREASTFEEDING DEFINITION: Exclusive breastfeeding, partial breastfeeding (PB), exclusive formula feeding (FF)

OUTCOME MEASURE: Glucose tolerance, plasma lipid profile, blood pressure, and body mass in 48- to 53-year-olds

RESULTS: Adults who had been bottle fed (PBF and FF) had higher fasting insulin,

higher LDL cholesterol and apolipoprotein B concentrations (fasted), higher LDL:HDL ratios, and lower HDL concentrations than adults who had been exclusively breastfed in infancy. No effects of infant feeding mode were found for blood pressure, body mass index, or body fat distribution.

METHODOLOGICAL ISSUES: All subjects were born during the Dutch Famine, so they were exposed to malnutrition in utero. Infant feeding methods were separated into exclusive breastfeeding, partial bottle feeding, and exclusive bottle-feeding. Eighty-three percent of the subjects were exclusively breastfed, close to 16% were partially bottle fed, and only 1% were exclusively bottle-fed. Multiple regression was used for analyses of the continuously distributed variables, and logistic regression was used to assess the dichotomous outcome (impaired glucose tolerance). All analyses were adjusted for sex, period of prenatal exposure to famine (early, mid, or late gestation), maternal age, length of hospital stay, maternal characteristics, birth outcomes, and adult characteristics.

Saarinen UM, Kajosarri M. Breastfeeding as prophylaxis against atopic disease: Prospective follow-up study until 17 years old. *Lancet* 1995 (October 21);346:1065–9.

COUNTRY: Finland

SETTING: Helsinki (southern Finland)

DESIGN: Prospective: n = 236, 150 of whom were followed until 17 years of age

BREASTFEEDING DEFINITION: Breastfeeding duration categorized as follows: > 6 months, 1–6 months, < 1 month or no breastfeeding

OUTCOME MEASURE: Atopic eczema, food allergy, respiratory allergy. A child was considered atopic if any of these 3 measures was diagnosed.

RESULTS: This study examined the association between infant feeding mode and various atopic diseases. Children were followed from birth, seen frequently during infancy and again at ages 1, 3, 5, 10, and 17 years. The prevalence of atopy throughout the follow-up period was significantly higher in the group that had little or no breastfeeding. The prevalence of eczema at ages 1 and 3 years was lowest in the group breastfed the longest. The prevalence of food allergy between 1 and 3 years was highest in the group that had little or no breastfeeding. Respiratory allergy was most prevalent in the group that had little or no breastfeeding. The prevalence of respiratory allergy at 17 years of age for children breastfed the longest was 42%, compared with 65% among children breastfed the shortest or not at all. The authors conclude that breastfeeding protects against atopic disease throughout childhood and adolescence.

METHODOLOGICAL ISSUES: The prevalence of respiratory allergy is very high even among the breastfed children, which the authors do not discuss but which suggests that being born just before the birch pollen season may have contributed to the high prevalence that developed later in the children.

Wingard DL, Criqui MH, Edelstein SL, Tucker J, et al. Is breast-feeding in infancy associated with adult longevity? *Amer J Public Health* 1994;84(9):1458–62.

COUNTRY: United States

SETTING: Statewide (California)

DESIGN: Prospective population-based: subjects (n = 1,170) were followed more than 65 years and cause-specific mortality was documented

BREASTFEEDING DEFINITION: Duration of breastfeeding categorized as follows: 0, 1–5, 6–11, 12–36 months. Breastfeeding information was obtained from the subject's parents within 10 years of the child's birth.

RESULTS: This study examined whether breastfeeding is associated with increased longevity in adulthood. After adjustment for all known confounding factors, there was a weak association between having been breastfed and increased longevity among men. No association was found among women. Breastfeeding was not associated with death from cardiovascular disease for either sex. Death from accidental injury was inversely associated with breastfeeding and showed a dose-response with duration of breastfeeding in men only. No biologically plausible explanation is offered for why having been breastfed as an infant would reduce risk of death from injury. Overall, the results do not provide strong evidence that breastfeeding is related to adult longevity.

METHODOLOGICAL ISSUES: This sample was restricted to middle-class children with access to health care, so differences in health care are unlikely to explain the findings. The study controlled for many potentially confounding factors.

Koletzko S, Griffiths A, Corey M, Smith C, Sherman P. Infant feeding practices and ulcerative colitis in childhood. *Br Med J* 1991;302:1580–1.

COUNTRY: Canada

SETTING: Not reported

DESIGN: Case-control: cases (n = 93) were children with ulcerative colitis; controls (n = 138) were unaffected biological siblings

BREASTFEEDING DEFINITION: Duration of exclusive breastfeeding and any breastfeeding, and age of introduction of solids

OUTCOME MEASURE: Ulcerative colitis

RESULTS: The study examined whether having been breastfed was associated with decreased risk of ulcerative colitis. Infant feeding practices were not associated with risk of disease development.

METHODOLOGICAL ISSUES: The small sample size may have precluded finding meaningful differences; however, the authors did not perform ex post power calculations to determine the power of their study to have detected a significant difference.

Koletzko S, Sherman P, Corey M, Griffiths A, Smith C. Role of infant feeding practices in development of Crohn's disease in childhood. *Br Med J* 1989;298:1617-8.

COUNTRY: Canada

SETTING: Not reported

DESIGN: Case-control: cases (n = 114) were children < 18 years with Crohn's disease; controls (n = 180) were unaffected biological siblings

BREASTFEEDING DEFINITION: Duration of exclusive breastfeeding or any breastfeeding

OUTCOME MEASURE: Crohn's disease

RESULTS: This study examined whether having been breastfed as an infant was associated with the risk of developing Crohn's disease. Lack of breastfeeding was a significant risk factor for disease development. Compared with children who had been breastfed, children who had not been breastfed had 3 times the risk ($p < 0.002$). Having had diarrhea in infancy was an independent risk factor.

METHODOLOGICAL ISSUES: The authors did not control for the possibility of reverse causality, e.g. that the disease could influence infant feeding patterns. Biological siblings were used as controls, and women tend to have similar infant feeding patterns across their children. Thus, the issue of why infants who later became ill were fed differently from their siblings merits investigation and discussion, which was lacking in the article.
