

Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence¹⁻³

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ABSTRACT

Background: Observational evidence suggests that having been breastfed in infancy may reduce the prevalence of type 2 diabetes in later life.

Objective: The objective was to examine the influence of initial breastfeeding on type 2 diabetes and blood glucose and insulin concentrations.

Design: A systematic review of published studies identified 1010 reports; 23 examined the relation between infant feeding and type 2 diabetes in later life or risk factors for diabetes. Risk factors in infants were examined separately from those in children and adults. All estimates were pooled by using fixed-effect models; differences <0 and ratios <1 imply a beneficial effect of breastfeeding.

Results: Subjects who were breastfed had a lower risk of type 2 diabetes in later life than did those who were formula fed (7 studies; 76 744 subjects; odds ratio: 0.61; 95% CI: 0.44, 0.85; $P = 0.003$). Children and adults without diabetes who had been breastfed had marginally lower fasting insulin concentrations than did those who were formula fed (6 studies; 4800 subjects; percentage difference: -3%; 95% CI: -8%, 1%; $P = 0.13$); no significant difference in fasting glucose concentrations was observed. Breastfed infants had lower mean preprandial blood glucose (12 studies; 560 subjects; mean difference: -0.17 mmol/L; 95% CI: -0.28, -0.05 mmol/L; $P = 0.005$) and insulin (7 studies; 291 subjects; mean difference: -2.86 pmol/L; 95% CI: -5.76, 0.04 pmol/L; $P = 0.054$) concentrations than did those who were formula fed.

Conclusion: Breastfeeding in infancy is associated with a reduced risk of type 2 diabetes, with marginally lower insulin concentrations in later life, and with lower blood glucose and serum insulin concentrations in infancy. *Am J Clin Nutr* 2006;84:1043-54.

KEY WORDS Infant feeding, blood glucose, serum insulin, type 2 diabetes, systematic review

INTRODUCTION

The increasing prevalence of type 2 diabetes in both the developed and developing world during the past 2 decades represents a serious public health challenge (1). Considerable attention has focused on diet and physical activity patterns, both in childhood and adult life, and on the associated increases in the prevalence of obesity (1). However, it is increasingly recognized that nutrition in early postnatal life may have long-term physiologic effects in humans as well as in animals (2, 3), and it has been specifically suggested that breastfeeding may protect against the development of type 2 diabetes (4-6). The composition of breast

milk differs importantly from formula feeds (particularly in protein and energy content), and the volumes received during breastfeeding are normally smaller than those associated with formula feeding (5, 7, 8); earlier studies have suggested that breastfeeding may protect against later obesity (9). Thus, an effect of breastfeeding on glucose and insulin metabolism would be biologically plausible.

Evidence from individual epidemiologic studies relating breastfeeding to the risk of type 2 diabetes has been inconsistent. Some studies suggest that breastfeeding is associated with a lower risk of diabetes in later life (7), whereas others have reported nonsignificant associations (10) and others no effect (11). However, individual studies have been modest in size and lacking in statistical power to exclude even quite large effects on diabetes risk. We therefore conducted a systematic review and meta-analysis of the published literature to quantify the strength of the associations between breastfeeding and risk of type 2 diabetes in later life. We also examined the relation of breastfeeding to subsequent fasting glucose and to fasting insulin concentrations, which can be regarded as a marker of insulin resistance (12), an important precursor of type 2 diabetes (13). These studies have been examined separately in infancy (ie, at or shortly after the time of breastfeeding) and in later life (childhood and adulthood). The strength and consistency of reported associations, the extent of small study bias and publication bias, and the potential contribution of confounding factors were examined where possible.

METHODS

We searched EMBASE (1980 onwards), MEDLINE (1966 onwards), and Web of Science (1980 onwards) databases for published articles, letters, abstracts, and review articles on the

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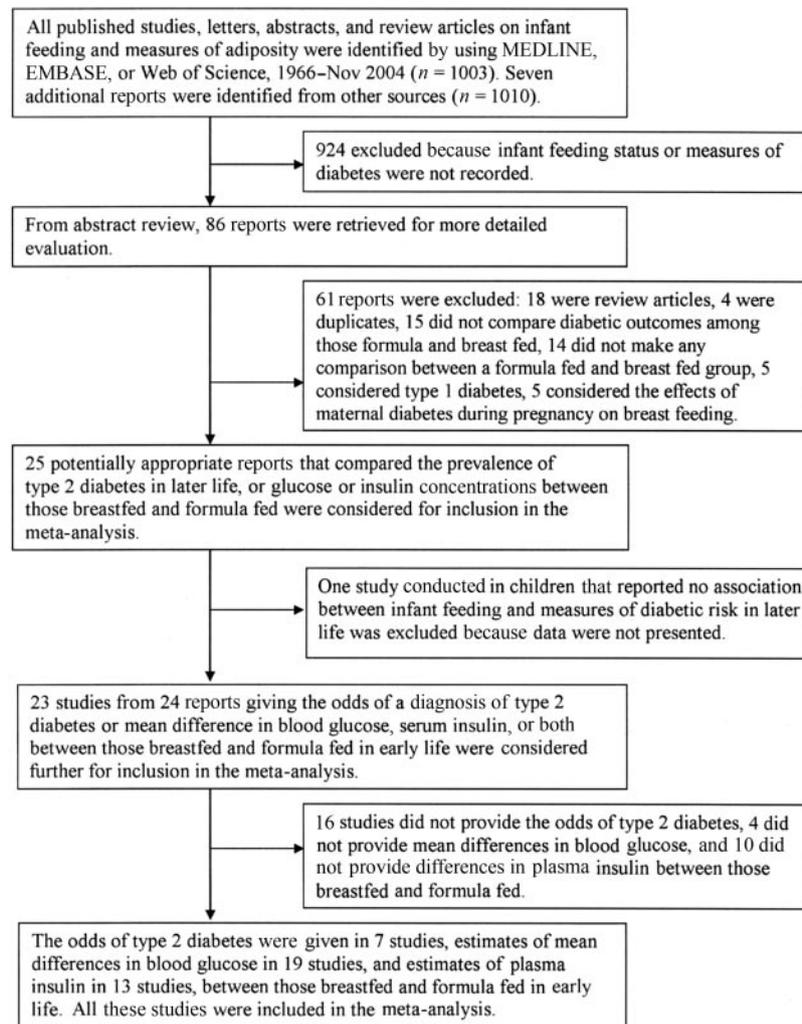


FIGURE 1. Flow diagram showing the number of studies included and excluded from the meta-analysis.

effects of infant feeding on type 2 diabetes and precursors for diabetes. References were identified by using combined text words; MESH and Subject headings were also used for MEDLINE and EMBASE databases, respectively (*see* Appendix under “Supplemental data” in the current online issue at www.ajcn.org).

The electronic search was completed in November 2004 and yielded 1003 unduplicated references. Seven additional references with relevant data were also included: 3 studies were identified by an ongoing OVID alert system for a related review (9, 14, 15), 2 were cited from reference lists of eligible studies (16, 17), 1 article was written by 2 of the authors (RMM and GDS) (18), and 1 meeting abstract was also identified (19).

Two authors (CGO and RMM) completed the literature search and extracted data from relevant studies. Abstract review suggested that 86 reports were potentially relevant. Sixty-one articles were excluded: 18 were review articles or letters, 4 studies duplicated data in other reports, 15 did not compare diabetic status or precursors for diabetes among those formula and breastfed, 14 did not compare formula and breastfed groups, 5 considered Type 1 diabetes, and 5 considered the effects of maternal diabetes during pregnancy on breastfeeding (Figure 1). A list of excluded studies is available from the authors. Hence, 24 studies

(25 publications) that compared risk factors for diabetes or the prevalence of type 2 diabetes in later life in those who were breast and formula fed were considered further. Although a null association between infant feeding and risk factors for diabetes was reported in 2 studies (10, 20), data were not presented. Although data were obtained directly from the first author for one of these studies (10), the other smaller study (with 109 control subjects) was excluded from the meta-analysis (20). Hence, 23 studies (24 reports) with data were considered further. The odds or prevalence of type 2 diabetes in those who were breastfed and formula fed were reported in 3 studies (14, 21, 22); odds ratios were provided by the study authors for an additional 4 studies (6, 10, 11, 18). Studies defined Type 2 diabetes in several ways. Three studies diagnosed diabetes from a 75-g oral-glucose-tolerance test (6, 21, 23), 3 from fasting plasma glucose concentrations (11, 22, 24), and one study used postload or fasting glucose concentrations (10). Two other studies diagnosed diabetes from data collected from participants in questionnaires (14, 18). The mean differences between breast and formula feeders (defined as breast minus formula throughout) in blood glucose were available for 20 studies (35 estimates, with 15 repeat measures including fasting and postload concentrations in older participants or pre- and postprandial concentrations in infants) (6, 10, 11,



15–18, 21, 25–36) and in plasma insulin for 13 studies (26 estimates, with 13 repeats; **Table 1**) (5, 6, 10, 11, 15, 18, 25, 26, 28, 31, 33, 35, 37). Preprandial measures in infants and fasting measures in adults were used preferentially in 5 studies with multiple measures of blood glucose or serum insulin (5, 6, 29, 31, 35, 36).

Initial feeding status was ascertained either from maternal recall at the time of infant feeding or retrospectively up to 28 y after birth (7, 21). In 2 studies, feeding status was ascertained from questionnaire data obtained directly from the participants 45 to 71 y after birth (14, 18). The World Health Organization defines exclusive breastfeeding as receiving “only breast milk from his/her mother or a wet nurse, or expressed breast milk, and no other liquids or solids with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines” (38). Few studies report this definition, and exclusive breastfeeding is rarely maintained for the first 4 to 6 mo of life as advised by the World Health Organization (38). Hence, the categorization of infant feeding as exclusive or nonexclusive is based on the classification given in each article and listed for each study in Table 1.

The feeding groups were defined as being mutually exclusive (ie, exclusively breastfed and exclusively formula fed) in 10 of the 23 studies that reported data (5, 10, 15, 26–29, 32, 34, 35, 37). In the remaining 13 studies, those who had received any breast-milk were compared with those exclusively formula-fed in 5 studies (11, 14, 18, 21, 22), the breastfed group were weaned early or offered other feeds in 4 studies (16, 25, 30, 33), exclusive breast-feeders were compared with formula-fed groups that included mixed feeders in 3 studies (6, 17, 31), and the exclusiveness of infant feeding could not be gauged in one study (36).

The use of standard commercial formulas was reported in 7 studies (5, 18, 25, 28, 29, 32, 35, 36), preterm or adapted formulas in 5 studies (16, 26, 31, 33, 37), and the type of infant formula was unclear in 11 studies (6, 10, 11, 14, 15, 17, 21, 22, 27, 30, 34). Five studies were conducted in populations from North America (2 from selected populations with exceptionally high levels of type 2 diabetes) (21, 22), 14 in populations from Western Europe (8 from the United Kingdom), and 4 in populations from other regions (Table 1).

Statistical analysis

Statistical analysis was performed using STATA/SE version 8.2 for WINDOWS software (Stata Corporation, College Station, TX). The main outcomes of the meta-analyses were based on the odds ratios of type 2 diabetes, mean differences in blood glucose, and mean differences in serum insulin (log insulin for children and adults). Odds ratios (with their variances) were used for analyses, which compared the odds of being diagnosed with type 2 diabetes in those who were initially breastfed with those who were formula fed (odds ratios <1 imply that breastfeeding is associated with a lower prevalence of diabetes). Age-adjusted odds ratios were selected; in some studies, odds ratios were also adjusted for birthweight, current body mass index (BMI), and familial and socioeconomic factors (*see* Table 1). Mean differences in blood glucose at all ages and serum insulin in infants were calculated mostly from reported means and measures of variance for each feeding group (*see* Table 1). Although this is appropriate for blood glucose, which exhibits a normal distribution, mean differences may underestimate the size of the difference between feeding groups for insulin, because insulin exhibits a positively skewed distribution. Hence, for 6 studies conducted in children and adults, the mean difference in log insulin and the

ratio of geometric means in fasting insulin expressed as a percentage difference were calculated (ratios <1 imply that breastfeeding is associated with lower insulin concentrations) (6, 10, 11, 15, 18, 33). Preprandial concentrations in infants and fasting concentrations in children and adults of blood glucose and serum insulin (excluding diabetic patients) were used throughout.

Fixed-effect models are reported throughout, because these reflect only the random error within each study and are less affected by small study bias (usually the result of selective publication of small studies with extreme results) (39). Heterogeneity across studies was examined using the chi-squared test (40). Data from infants and older age groups for glucose and insulin were examined separately. Funnel plots were used to assess whether small studies yield larger effect estimates than do bigger studies (39, 41). Begg and Egger tests for funnel plot asymmetry were performed throughout, but there was insufficient power for these to show any significant findings (39, 42). The effect of study size, year of birth, the method of ascertainment of infant feeding status (whether contemporary or recalled up to 71 y after birth), type of formula fed, study response rate (analyzed as a continuous variable), study design (randomized controlled trial, case-control, or cohort), and whether infants were born pre- or full-term was examined by using metaregression and sensitivity analysis. In most cases, there was insufficient power to find appreciable differences; only significant findings in infants are reported in the Results. Sensitivity analyses were used to examine the effect of adjustment for important confounders and of fasting status.

RESULTS

Type 2 diabetes in later life

Seven studies [6 conducted in adults (6, 10, 11, 14, 18, 21) and 1 conducted in adolescents (22); total of 76 744 subjects] provided odds ratios that related initial infant feeding methods and type 2 diabetes (Table 1 and **Figure 2**). Feeding status was reported as being exclusive in one of these studies (10). Three of these studies were carried out in North America and 4 in Europe. Two studies included native North Americans (21, 22) and one was conducted on the offspring of Dutch famine survivors (6). Six of the 7 studies related breastfeeding to a lower risk of type 2 diabetes, and there was no evidence of heterogeneity across studies (chi-square test $P = 0.4$). Overall, the subjects who were breastfed showed a lower risk of type 2 diabetes than did those who were formula fed (pooled odds ratio: 0.61; 95% CI: 0.44, 0.85; $P = 0.003$; **Table 2** and **Figure 2**). Three studies had information on relevant confounders (birthweight, parental diabetes, socioeconomic status, and individual or maternal body size). However, the odds ratio relating breastfeeding and diabetes risk was similar before (0.55; 95% CI: 0.35, 0.86; $P = 0.009$) and after (0.55; 95% CI: 0.34, 0.90; $P = 0.017$) adjustment (10, 21, 22). The method for ascertaining feeding exposure was unrelated to the odds ratio.

Blood glucose and serum insulin: studies in adults and children

All studies excluded subjects with known diabetes (6, 10, 11, 18). Seven studies [4 conducted in adults (6, 10, 11, 18) and 3



TABLE 1
Studies included in the meta-analysis in alphabetical order^a

Study	Design	Source	Source of information on feeding	Mean year born, age measured	No. of subjects breastfed, formula fed	Exclusive feeding groups	Fasting status	Mean difference in blood glucose ² mmol/L	Mean difference in serum insulin ² pmol/L	OR (95% CI) of type 2 diabetes	Adjustments for OR of type 2 diabetes
Baur et al (25) ³	CS	Infants recruited from the Royal Alexandra Hospital for Children, Sydney, Australia	In infancy	NS, 0.8 y	13, 12	No, sole or partially BrF vs FF	Fasting	-0.70 ± 0.28 ⁴	-1.20 ± 1.98	—	—
Calvert et al (26) ³	PC	Preterm infants recruited from the Special Care Unit, John Radcliffe Hospital, Oxford, UK	In infancy	NS, 18 d	10, 9	Yes, for 18 d	Preprandial	-0.21 ± 0.37	-0.28 ± 6.82 ⁵	—	—
Dewey et al (37) ³	CS	Infants recruited from Fairfield and Yacaville, California, USA	In infancy	NS, 5 mo	52, 62	Yes, exclusively fed	NS	—	-22.8 ± 5.48	—	—
Fall et al (10) ⁶	HC	Adults born in Hertfordshire, UK	In infancy	1920–1980, 1 y	498, 35 ⁷	Yes, exclusively fed	Fasting	-0.07 ± 0.09 ⁸	0.06 ± 0.10 ^{8,9}	0.67 (0.25, 1.84) 0.64 (0.22, 1.91)	None Age, current BMI, birth weight, social class
Hawdon et al (27)	CS	Born in Newcastle upon Tyne maternity units, UK	In infancy	NS, 7 d	71, 61	Yes, for 7 d	Preprandial	-0.40 ± 0.20 ¹⁰	—	—	—
Heck and Erenberg (16)	CS	Born in the University of Iowa Hospitals and Clinics, USA	In infancy	1983, 48 h	64, 50	No, BrF group offered other feeds	Nonfasting	-0.17 ± 0.08 ¹⁰	—	—	—
Lawlor et al (15) ⁶	CS	European Youth Heart Study, Estonia and Denmark	PQ at 9, 15 y	1986, 9 and 15 y	1340, 230	Yes, for ≥ 1 mo	Fasting	0.02 ± 0.03 ¹¹	-0.03 ± 0.05 ^{6,11}	—	—
Lommerdal and Havel (28) ³	PC	Born in Umea, Sweden	In infancy	NS, 6 mo	30, 38	Yes, for 6 mo	Nonfasting	0.20 ± 0.29	-27.0 ± 22.2	—	—
Lucas et al (5, 29) ¹²	PC	Infants recruited from the Special Care Unit, John Radcliffe Hospital, Oxford, UK	In infancy	NS, 6 d	11, 8	Yes, for 6 d	Preprandial 55 min postprandial 90 min postprandial 150 min postprandial 240 min postprandial	-0.20 ± 0.39 -0.10 ± 0.58 -0.20 ± 0.29 -0.30 ± 0.68 -0.20 ± 0.44	-4 ± 4.91 -5 ± 26.0 -72 ± 30.7 -21 ± 10.0 -3 ± 5.9	—	—
Martin et al (11) ⁶	HC	Carnegie (Boyd Orr) survey, UK	PQ at 0–19 y	1918–1939, 71 y	272, 90	No, BrF vs exclusive FF	Fasting	-0.04 ± 0.07	-0.02 ± 0.08 ⁹	0.97 (0.41, 2.30)	Age, sex
Martin et al (18) ⁶	CS	Males born in Caerphilly, UK	Personal questionnaire at age 45–59 y	1918–1939, 52 y	1159, 421	No, ever BrF vs exclusively FF	Fasting	0.01 ± 0.03	-0.01 ± 0.04 ⁹	2.75 (0.63, 12.06) 2.89 (0.65, 12.83)	Age Age, birth weight

(Continued)

TABLE 1 (Continued)

Study	Design	Source	Source of information on feeding	Mean year born, age measured	No. of subjects breastfed, formula fed	Exclusive feeding groups	Fasting status	Mean difference in blood glucose ²	Mean difference in serum insulin ²	OR (95% CI) of type 2 diabetes	Adjustments for OR of type 2 diabetes
Pettitt et al (21) ^{3,13}	CS	Pima Indians of Arizona, USA	PQ at 0–28 y	NS, 25 y	340, 344	NS	Postload	mmol/L –0.70 ± 0.36 ¹⁴	pmol/L —	0.51 (0.28, 0.93)	Age, sex, birth weight, parental diabetes, maternal diabetes in pregnancy
Plancoulaine et al (30) ³	CS	Fleurbaix Laventine Ville Sante study, France	PQ	NS, 8 y	212, 249 ⁷	No, BrF from 0 to 8 mo	Fasting	0.00 ± 0.07	—	0.56 (0.3, 1.03)	Age, sex, birth weight, parental diabetes, maternal diabetes in pregnancy, weight-for-height
Ravelli et al (6) ¹⁰	HC	Dutch Famine Birth cohort, Holland	In infancy	1945, 50 y	520, 105	No, exclusively BrF for 10 d vs partly FF	Fasting	–0.18 ± 0.07	–0.13 ± 0.05 ⁹	0.46 (0.23, 0.94) ⁶	Famine exposure, sex, age, birth weight, hospital duration in infancy
Rich-Edwards et al (14) ⁵	PC	Nurses' Health Study, USA	Personal questionnaire at 46–71 y	1921–1946, 59 y	46 921, 25 929	No, ever BrF or FF	—	—	—	0.44 (0.09, 2.05)	Famine exposure, sex, age, birth weight, hospital duration, neonatal care, parity, maternal education, family socioeconomic status
Salmenpera et al (31) ²	CS	Born in the Children's Hospital University of Helsinki, Finland	In infancy	NS, 9 mo	13, 7	No, exclusively BrF, FF group weaned at 3 mo	Preprandial 55 min postprandial 90 min postprandial 150 min	–0.20 ± 0.20 0.10 ± 0.35 –0.20 ± 0.32	0.00 ± 3.11 –16.0 ± 9.4 –12.0 ± 16.9	—	—
Schultz et al (32) ¹⁰	PC	Premature infants born at the University Medical School, Pécs, Hungary	In infancy	NS, 4 wk	10, 10	Yes, for 4 wk	postprandial Fasting, pre morning feed	0.00 ± 0.16 0.50 ± 0.24	—	—	—
Singhal et al (33) ³	RCT	Preterm infants recruited from centres in Norwich, Cambridge, Sheffield, Ipswich and King's Lynn	In infancy	1984, 15 y	66, 64	No, group fed banked breast milk also given milk supplement	Fasting	–0.02 ± 0.08	0.00 ± 0.11 ⁹	—	—

(Continued)

TABLE 1 (Continued)

Study	Design	Source	Source of information on feeding	Mean year born, age measured	No. of subjects breastfed, formula fed	Exclusive feeding groups	Fasting status	Mean difference in blood glucose ²	Mean difference in serum insulin ²	OR (95% CI) of type 2 diabetes	Adjustments for OR of type 2 diabetes
								mmol/L	pmol/L		
Sweet et al (34) ³	CS	Born at the Royal Maternity Hospital, Belfast, UK	In infancy	NS, 1 h	22, 24	Yes, for 1 h	22 min postprandial	-0.18 ± 0.26	—	—	—
Ugur et al (35) ^{2,16}	CS	Born in the Obstetrics Clinic of Cerrahpasa Medical Faculty, Istanbul, Turkey	In infancy	1983, 7 d	10, 15	Yes, for 7 d	Preprandial 30 min postprandial 60 min postprandial 90 min postprandial 120 min	-0.22 ± 0.49 -1.06 ± 0.54 -0.56 ± 0.54 -1.11 ± 0.50	-20.8 ± 38.2 -97.2 ± 54.5 -20.8 ± 54.5 -20.8 ± 48.4	—	—
Wallensteen et al (36) ¹²	CS	Selected from a Child Health Centre, Stockholm, Sweden	In infancy	NS, 3 mo	6, 6	NS	postprandial	-0.28 ± 0.44	6.94 ± 46.0	—	—
Wang et al (17) ³	PC	Born in the International Peace Maternity and Child Health Hospital, China	In infancy	1991, 48 hr	30, 30	No, exclusively BF for 3–6 mo, FF mixed fed	Preprandial 90 min postprandial 180 min postprandial Nonfasting	0.10 ± 0.42 0.10 ± 0.50 0.50 ± 0.42 -0.34 ± 0.24	—	—	—
Young et al (22)	CC	Cases from the Diabetes Education Resource Centre for Children and Adolescents, Health Sciences Centre, controls from Ambulatory Care Clinic at Winnipeg Children's Hospital, Canada	PQ	1988, 13 y	49, 47	No, ever BF or FF	—	—	—	0.56 (0.23, 1.38)	None ¹⁵

¹ HC, historical cohort; PC, prospective cohort; CS, cross sectional; CC, case control; RCT, randomized controlled trial; PQ, parental questionnaire up to 28 y after birth; BF, breastfed; FF, formula fed; NS, not stated; OR, odds ratio. OR < 1 corresponds to a protective effect of breastfeeding.

² Mean difference (±SE) was defined as breastfed - formula fed and was calculated from means and SEs (or SDs) for feeding groups.

³ Mean difference was given in the report.

⁴ $\bar{x} \pm SE$ (all such values unless stated otherwise).

⁵ Insulin concentrations (in $\mu\text{U/L}$) were multiplied by 6.945 to give pmol/L.

⁶ Data were provided by the author.

⁷ Male and female data were combined.

⁸ Adjusted for age, current BMI, birth weight, and social status.

⁹ In log insulin.

¹⁰ Calculated from means for feeding groups, total no. of participants, and *P* value for the difference.

¹¹ Adjusted for child's age and sex, country, birth weight, mother's education and income, father's education and income, maternal BMI, and family history of diabetes.

¹² Mean difference calculated from mean and SE (or SD) for feeding groups was extracted from graph given in the report (SE was calculated from the *P* value of the difference when given).

¹³ Data from Pima Indians was published in multiple sources—data from an abstract with measures of both glucose and ORs of diabetes before and after adjustment for important confounders was preferentially used.

¹⁴ Adjusted for age and sex.

¹⁵ OR was calculated from prevalence of diabetes in feeding groups given in the report cited.

¹⁶ Glucose concentrations (given in mg/dL) were divided by 18 to give mmol/L. Insulin was reported in $\mu\text{U/mL}$ and was assumed to be $\mu\text{U/L}$ in order to give probable values.

¹⁷ ORs were obtained by pooling ORs for 6–12 mo vs none and >12 mo vs none by using a fixed-effects model.

TABLE 2

Overall pooled differences for blood glucose, serum insulin, and odds of type 2 diabetes from studies conducted in infants, children, and adults: comparison between breastfed and formula-fed subjects¹

Variable	No. of studies	No. of subjects breastfed, formula fed	Mean difference		OR of type 2 diabetes	P for difference between breastfed and formula fed	P for test for heterogeneity ²
			Blood glucose	Serum insulin			
<i>mmol/L</i>							
Glucose							
Infants	12	290, 270	-0.17 (-0.28, -0.05) ³	—	—	0.005	0.169
Children and adults	7	4067, 1194	-0.01 (-0.04, 0.03)	—	—	0.679	0.245
Insulin							
Infants	7	140, 151	—	-2.86 pmol/L (-5.76, 0.04)	—	0.054	0.012
Children and adults	6	3855, 945	—	-3% (-8%, 1%)	—	0.127	0.402
Type 2 diabetes							
	7 ⁴	49 772, 26 972	—	—	0.61 (0.44, 0.85)	0.003	0.383
	5 ⁵	2579, 953	—	—	0.59 (0.40, 0.87)	0.008	0.280

¹ Combined estimates based on fixed-effects models throughout. Mean differences were used for glucose measurements in all age groups and for insulin measurements in infants. Percentage differences in insulin measurements and odds of type 2 diabetes were used for children and adults. Glucose and insulin measurements were made by using preprandial estimates for infants and fasting estimates for children and adults where possible. OR, odds ratio.

² Chi-square test for heterogeneity between the estimates.

³ OR; 95% CI of pooled estimates given in parentheses (all such values).

⁴ The studies were either unadjusted or adjusted.

⁵ Two of the studies were partially adjusted; 3 of the studies were fully adjusted.

conducted in children (15, 30, 33); 5261 subjects in total; 6 observational studies and 1 trial] reported on the association between infant feeding and fasting blood glucose in later life (Table 1 and Figure 3). Mean differences in glucose were unadjusted except for 2 studies: one was conducted in children and adolescents with adjustment for a number of individual, social, and familial factors, and the other study was conducted in adults with adjustment for birthweight, current BMI, and social class (see Table 1) (10, 15). All 7 studies showed little differences in mean glucose concentrations between feeding groups, and no marked evidence of heterogeneity was observed between estimates (chi-square test $P = 0.2$; Table 2). The overall pooled mean difference was -0.01 (95% CI: $-0.04, 0.03$; $P = 0.7$; Table 2).

Six studies [4 conducted in adults (6, 10, 11, 18) and 2 conducted in children (15, 33); 4800 subjects in total; 5 observational studies and 1 randomized controlled trial] reported on the association between infant feeding and fasting insulin (Table 1 and Figure 4). Four of the 6 studies showed lower serum insulin concentrations in the breastfed subjects than in the formula-fed subjects. No marked evidence of heterogeneity was observed between the study estimates (chi-square test $P = 0.4$). The overall pooled proportional difference in insulin was -3% (95% CI: $-8\%, 1\%$; $P = 0.13$; Table 2), a difference which was similar in adults and children.

Blood glucose and serum insulin: studies in infants

Twelve studies (560 subjects) reported on the association between breastfeeding and preprandial blood glucose concentrations in infants. Nine of these provided lower estimates in the breastfed subjects than in the formula-fed subjects. No strong evidence of heterogeneity was observed (chi-square test $P = 0.2$; Table 2). The pooled mean difference was -0.17 mmol glucose/L (95% CI: $-0.28, -0.05$ mmol glucose/L; $P = 0.005$;

Table 2 and Figure 3). The mean difference in infants was similar when the analysis was based on postprandial blood glucose concentrations (taken 60–180 min postprandially). The pooled mean difference was similar in the 8 studies that measured blood glucose within the first 4 wk of life (7 after exclusive breastfeeding) and in 4 studies conducted in infancy that measured blood glucose 3 mo to 1 y after birth (a group likely to have been weaned). It was also similar in 7 studies in which breastfeeding was exclusive (26–29, 32, 34, 35) and in the remaining 5 studies that were not.

Seven studies (291 subjects) reported on the association between breastfeeding and preprandial insulin concentrations in infancy. Six of these provided lower insulin estimates in breastfed subjects. Some evidence of heterogeneity was observed (chi-square test $P = 0.01$; Table 2). The pooled mean difference was -2.86 pmol/L (95% CI: $-5.76, 0.04$ pmol/L; $P = 0.054$; Table 2 and Figure 5). A similar pattern of differences was observed when postprandial measures (ie, 60 min after feeding), which were available in 3 studies, were used (mean difference: -4.07 pmol/L; 95% CI: $-7.51, -0.62$ pmol/L; $P = 0.021$) (5, 31, 35). The mean insulin difference was stronger in 5 studies (26, 28, 29, 35, 37) that reported exclusive infant feeding (-10.1 pmol/L; 95% CI: $-16.3, -3.9$ pmol/L) than in 2 studies (25, 31) that did not report exclusive feeding (-0.85 pmol/L; 95% CI: $-4.13, 2.42$ pmol/L; P for test for difference = 0.01). The pooled mean difference was similar in 3 studies that measured serum insulin within the first 18 d of life and in 3 studies that measured serum insulin 6 mo to 1 y after birth (a group likely to have been weaned).

Funnel plots and tests for small study bias and publication bias were carried out for all associations. None of the funnel plots showed a pattern of asymmetry that suggested publication bias. None of the Begg and Egger tests were statistically significant, although the power of these tests for detecting small study bias was low especially in the studies conducted in adults.

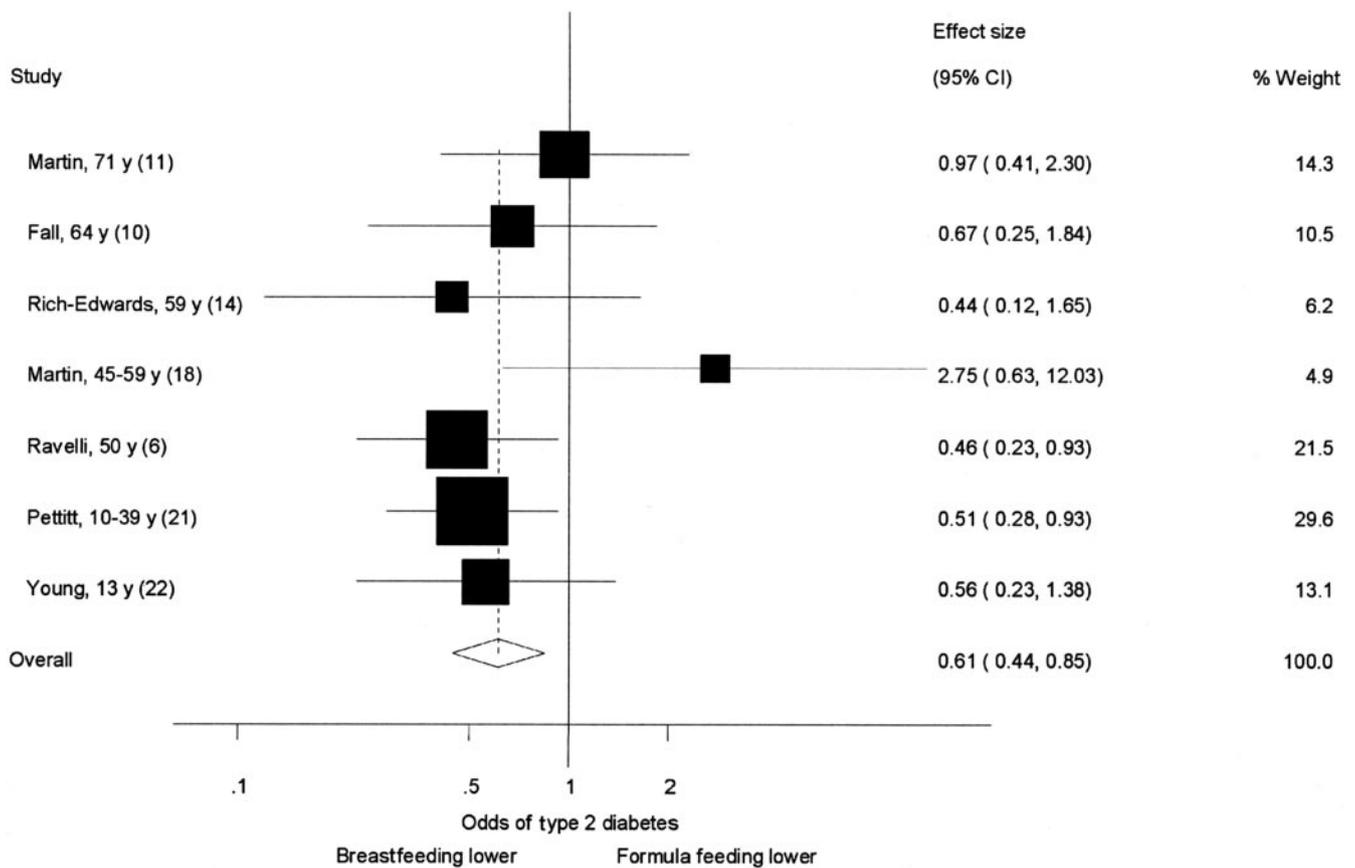


FIGURE 2. Odds ratios (95% CIs) of type 2 diabetes in a comparison of breastfed and formula-fed participants. Values <1 signify a protective effect of breastfeeding. Boxes are proportional to the inverse of the variance, with horizontal lines showing the 95% CI of the odds ratio. The first author of each study is indicated on the y axis. The mean age (in y) of each study's subjects is shown in ascending order of age at which type 2 diabetes was measured. Reference numbers are shown in parentheses. The dashed vertical line and diamond (95% CI) represent the pooled estimate calculated with a fixed-effects model. The solid vertical line is the null value.

DISCUSSION

In the present overview of published studies relating infant feeding and risk of diabetes, the pooled estimate from 6 studies conducted in adults and 1 study conducted in adolescents showed that early breastfeeding was consistently associated with a lower risk of type 2 diabetes in later life compared with those initially formula fed. In the studies where further analysis was possible, the association was unaffected by adjustment for potential confounders (10, 21, 22). In adults and children without diabetes, insulin concentrations were marginally lower in the breastfed subjects than in the formula-fed subjects, although glucose concentrations were similar. However, in infancy, breastfeeding was consistently related to lower concentrations of blood glucose and serum insulin than was formula feeding.

Because randomized controlled trials that assign participants to either breastfeeding or formula feeding are infeasible, except in the special circumstances of preterm birth (33), observational data form a crucial part of the evidence for the long-term health effects of different infant feeding approaches. The findings of the 7 published observational studies relating breastfeeding to reduced risks of diabetes were broadly consistent, despite the widely differing nature of the populations [including one study conducted in a population born during the Dutch Famine of World War II (6) and 2 conducted in Native American populations (21, 22)]. Although information on infant feeding exposure

in these studies was collected differently in the various studies, the ascertainment method (particularly the duration of recall) appeared to be unrelated to the associations observed. The association between breastfeeding and outcome is unlikely to be affected by whether infant feeding information is obtained by recall, which has been shown to be valid from 18 mo (43) to 20 y after birth (44). Knowledge of disease status at the point of ascertainment (particularly in the study of young Native Canadians) (22) did not appear to be related to the strength of association observed. Publication bias is an important potential explanation for the consistent associations observed in these published studies. The results provide no evidence of marked publication bias, although the statistical power of formal tests was limited by the small number of studies available for analysis. The presence of confounding is also an important possibility. Maternal social class, maternal weight, and low birthweight are all factors that may influence both the likelihood of breastfeeding and the risk of later diabetes. Size at birth may be an important confounder, especially because a lower mean birthweight is associated with formula feeding (11, 16, 18) and also with an increased risk of diabetes in later life (45). Low maternal social class and maternal obesity are related to a tendency to formula feed and to a greater risk of obesity in offspring (46, 47); obesity is a strong risk factor for glucose intolerance, insulin resistance, and diabetes in later life (48). Hence, it is possible that confounding by birthweight



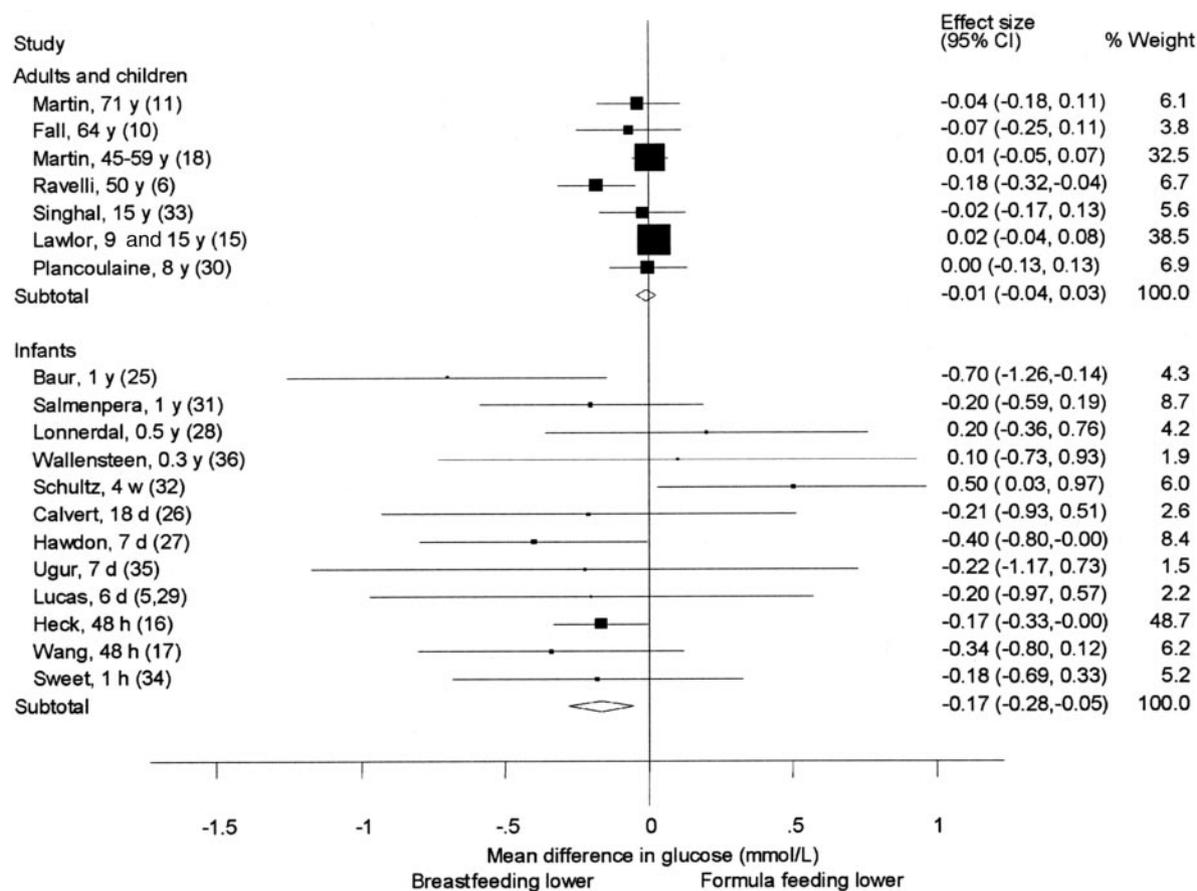


FIGURE 3. Mean (95% CIs) difference in blood glucose between breastfed and formula-fed participants. Boxes are proportional to the inverse of the variance, with horizontal lines showing the 95% CI of the mean differences. The first author of each study is indicated on the y axis. The mean age (in y, d, h, or wk) of each study's subjects is shown in ascending order of age at which glucose concentrations were measured. Reference numbers are shown in parentheses. The diamonds (95% CI) represent the pooled estimates calculated with a fixed-effects model for infants and older age groups separately. The solid vertical line is the null value.

and maternal factors could lead to overestimation of the association between breastfeeding and diabetes in later life. However, in 3 studies for which information on the effects of adjustment for a wide range of confounders was available, we were able to show that adjustment for such confounders had little effect on the association between breastfeeding and diabetes risk. However, 2 of these studies were both based on Native American populations living under Western influences. It is possible that the relation of the maternal decision to bottle-feed to subsequent exposure to risk factors for type 2 diabetes in the offspring is different in these particular populations from that of other populations. It will therefore be necessary to examine the influence of confounding in other population groups before this possibility is discounted.

The absence of any appreciable association between breastfeeding and fasting glucose concentration in children and adults (with confidence limits around the pooled estimate excluding any appreciable association) is not necessarily surprising or inconsistent with the observations on diabetes risk. Any effects of breastfeeding on glucose concentrations are likely to be greater in the subjects developing diabetes, who were excluded from these data. Moreover, measurement of fasting glucose concentrations within the normal range, particularly in childhood, will not necessarily provide a sensitive test for longer term disturbances of glucose metabolism. Published data on the relation

between infant feeding and postload glucose concentrations (which could provide a more sensitive marker of associations) are sparse (6, 21). Of possibly greater relevance are the observations on fasting insulin concentrations, which provide a useful marker of insulin resistance in population-based studies (12). Mean fasting insulin concentrations in children and adults showed a tendency to be lower in the breastfed subjects than in the formula-fed subjects, which raises the possibility of emerging differences in insulin resistance between the breastfed and formula-fed groups. However, these modest differences did not achieve statistical significance and could be, at least partly, the result of confounding; adjustment for potential confounding factors was not systematically possible with the available data. Studies conducted in infants however, in contrast to those conducted in children and adults, showed consistent associations between breastfeeding and lower glucose and insulin concentrations. These differences could reflect lower energy intake in breastfeeding infants than in formula-fed infants (7), differences between breast milk composition and formulas (particularly the amino acid and protein contents), or hormonal differences that result in lower levels of fat deposition in breastfed infants (5, 8). Additional studies are needed to establish whether such differences may be the result of confounding. However, the presence

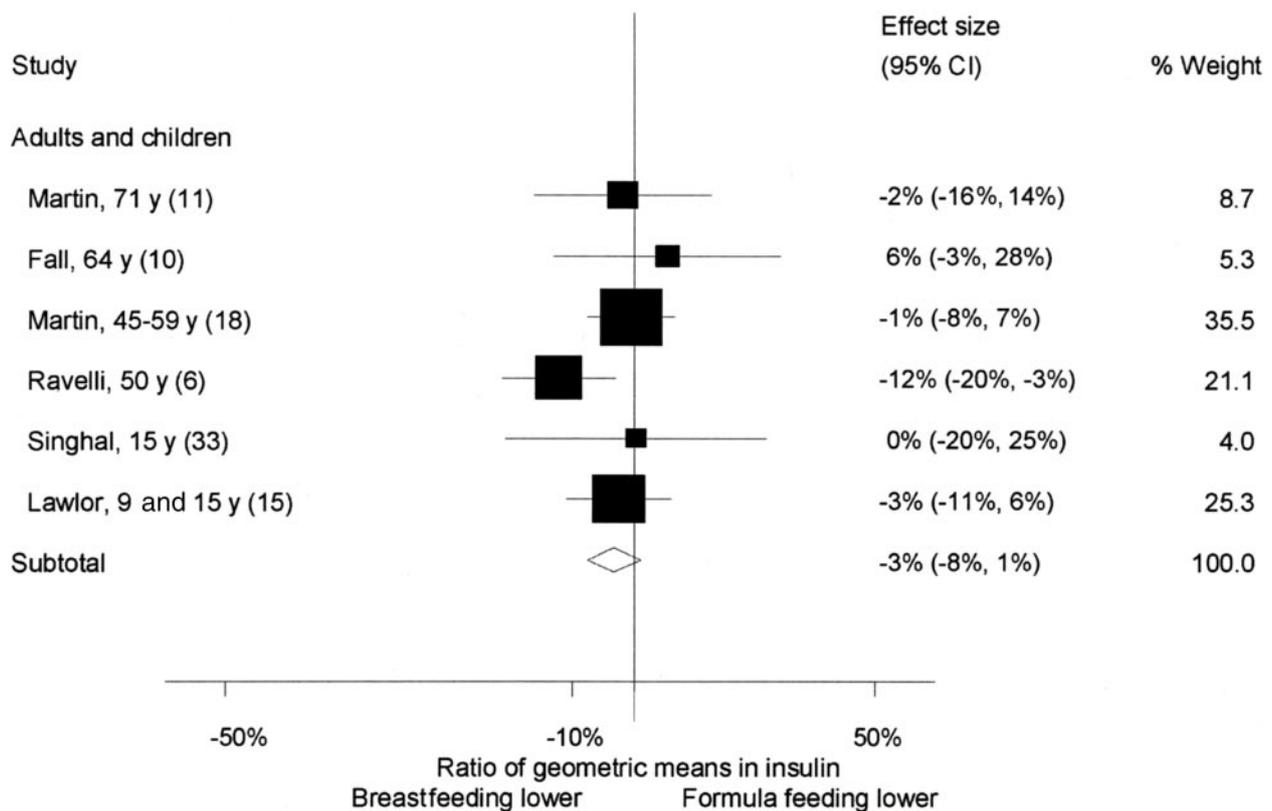


FIGURE 4. Percentage difference (for children and adults) in serum insulin (95% CIs) between breastfed and formula-fed participants. Boxes are proportional to the inverse of the variance, with horizontal lines showing the 95% CI of the differences. The first author of each study is indicated on the y axis. The mean age (in y) of each study's subjects is shown in ascending order of age at which serum insulin concentrations were measured. Reference numbers are shown in parentheses. The diamond (95% CI) represents the pooled estimate calculated with a fixed-effects model. The solid vertical line is the null value.

of detectable differences in glucose and insulin early in life increases the biological plausibility of longer term, possibly delayed, effects of breastfeeding on glucose and insulin metabolism. This raises the possibility that diabetes is nutritionally programmed (2) from early life. One possible mechanism for the effects of breastfeeding on diabetes risk is a protective effect of breastfeeding on obesity (49), which is itself a strong risk factor for type 2 diabetes. However, recent systematic reviews have suggested that the effect of breastfeeding on obesity prevalence and mean BMI is small (9, 50). The role of obesity as an intermediate mechanism therefore remains uncertain (9).

On the basis of the published evidence, breastfeeding may provide a degree of long-term protection against the development of type 2 diabetes, which could be of public health importance. If a reduction in type 2 diabetes risk of 15% (based on the conservative confidence limit) is associated with breastfeeding in Westernized populations where the prevalence of diabetes is $\approx 6\%$ and the proportion infants who are bottle-fed is at least one-third, the proportion of diabetes in the population that could be attributed to breastfeeding would be 5% (51). However, although important, this effect is modest compared with the potential benefits of reductions in obesity in later life (52, 53). Additional evidence is needed to establish definitively whether breastfeeding protects against diabetes, the extent of protection, and the duration of breastfeeding required, which were not examined in the present review. Replication of these findings in ethnic groups other than whites and Native Americans is also

needed. Many existing observational studies (particularly birth cohort studies and other longitudinal studies) have unpublished data on infant feeding and information on diabetes, glucose concentrations, and insulin in adult life that could help resolve this issue. On the basis of the published evidence reviewed here, it would be valuable to identify these studies systematically to establish whether the association between infant feeding method and type 2 diabetes is consistent and independent of publication bias and whether confounding is responsible for the association. If breastfeeding protects against type 2 diabetes, it will then be important to examine the extent to which duration of breastfeeding matters and whether this effect is explained by the protective effect of breastfeeding on the prevalence of obesity in adult life (9, 54). 

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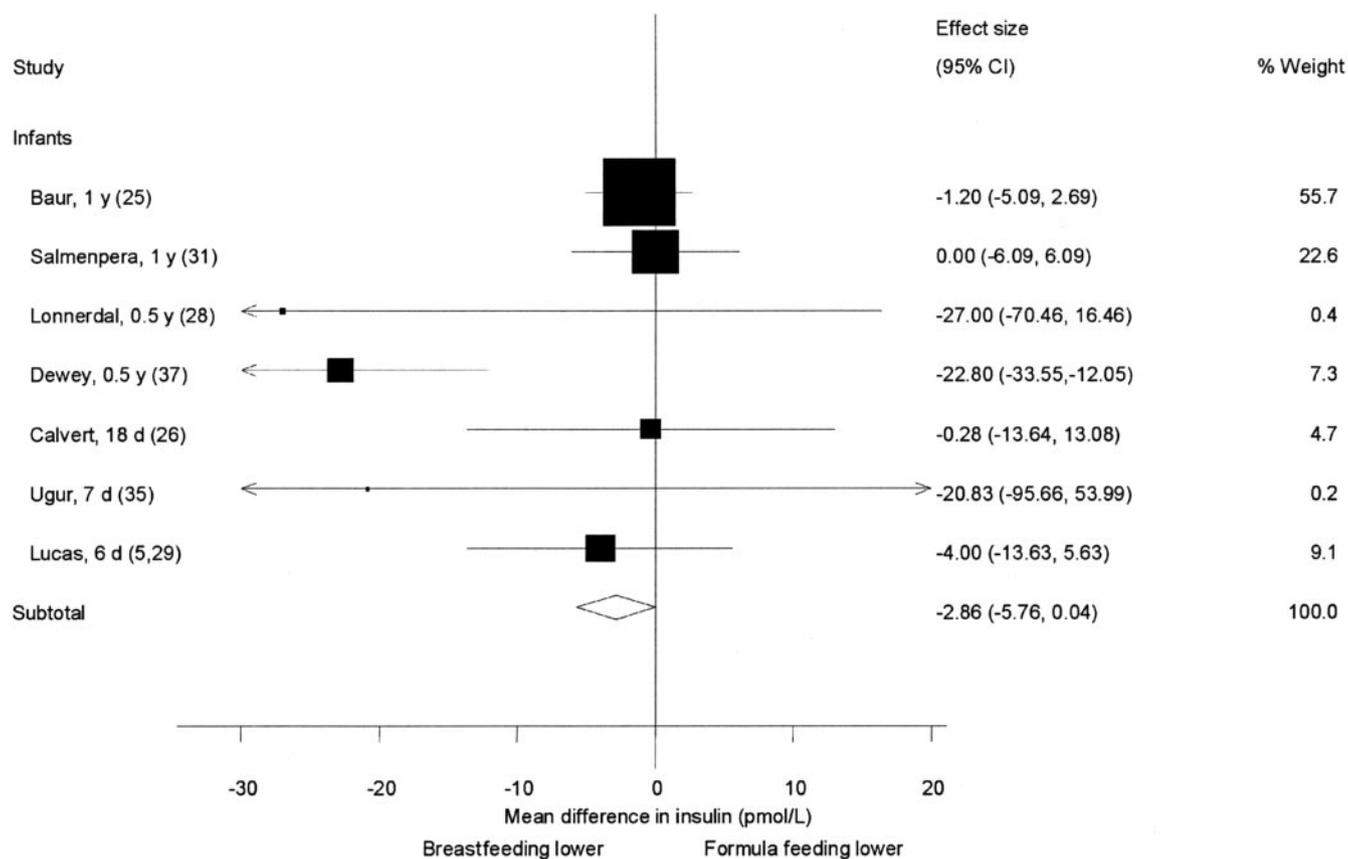


FIGURE 5. Mean (95% CI) difference in serum insulin between breastfed and formula-fed infants. Boxes are proportional to the inverse of the variance, with horizontal lines showing the 95% CI of the differences. The mean age (in y or d) of each study's subjects is shown in ascending order of age at which serum insulin concentrations were measured. Reference numbers are shown in parentheses. The diamond (95% CI) represents the pooled estimate calculated with a fixed-effects model. The solid vertical line is the null value.

REFERENCES

- Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782-7.
- Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, eds. *The childhood environment and adult disease*. Chichester, United Kingdom: Wiley and Sons Ltd, 1991:38-55.
- Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 2004;363:1642-5.
- Aynsley-Green A, Lucas A, Bloom SR. The effect of feeds of differing composition on entero-insular hormone secretion in the first hours of life in human neonates. *Acta Paediatr Scand* 1979;68:265-70.
- Lucas A, Sarson DL, Blackburn AM, Adrian TE, Aynsley-Green A, Bloom SR. Breast vs bottle: endocrine responses are different with formula feeding. *Lancet* 1980;1:1267-9.
- Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, Bleker OP. Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. *Arch Dis Child* 2000;82:248-52.
- Pettitt DJ, Forman MR, Hanson RL, Knowler WC, Bennett PH. Breast-feeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. *Lancet* 1997;350:166-8.
- Oakley JR. Differences in subcutaneous fat in breast- and formula-fed infants. *Arch Dis Child* 1977;52:79-80.
- Owen CG, Martin RM, Whincup PH, Davey Smith G, Cook DG. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. *Pediatrics* 2005;115:1367-77.
- Fall CH, Osmond C, Barker DJ, et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 1995;310:428-32.
- Martin RM, Ebrahim S, Griffin M, et al. Breastfeeding and atherosclerosis: intima-media thickness and plaques at 65-year follow-up of the Boyd Orr cohort. *Arterioscler Thromb Vasc Biol* 2005;25:1482-8.
- Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 1993;137:959-65.
- Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 1992;41:715-22.
- Rich-Edwards JW, Stampfer MJ, Manson JE, et al. Breastfeeding during infancy and the risk of cardiovascular disease in adulthood. *Epidemiology* 2004;15:550-6.
- Lawlor DA, Riddoch CJ, Page AS, et al. Infant feeding and components of the metabolic syndrome: findings from the European Youth Heart Study. *Arch Dis Child* 2005;90:582-8.
- Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 hours of life. *J Pediatr* 1987;110:119-22.
- Wang YS, Shen YH, Wang JJ, Yang MJ, Ding SW, Shi YY. Preliminary study on the blood glucose level in the exclusively breastfed newborn. *J Trop Pediatr* 1994;40:187-8.
- Martin RM, Ben Shlomo Y, Gunnell D, Elwood P, Yarnell JW, Davey Smith G. Breast feeding and cardiovascular disease risk factors, incidence, and mortality: the Caerphilly study. *J Epidemiol Community Health* 2005;59:121-9.
- Libby G, Chien PF, McEwan NF, et al. Birthweight and pre-eclampsia in the mother predict the development of early onset Type 2 diabetes. *Diabetic Medicine* 2003;20:14(abstr).
- Buinauskiene J, Baliutaviciene D, Zalinkevicius R. Glucose tolerance of 2- to 5-yr-old offspring of diabetic mothers. *Pediatric Diabetes* 2004;5:143-6.
- Pettitt DJ, Decourten MP, Nelson RG, et al. Lower prevalence of NIDDM in breast-fed Pima-Indians. *Diabetes* 1995;44:A6(abstr).
- Young TK, Martens PJ, Taback SP, et al. Type 2 diabetes mellitus in children: prenatal and early infancy risk factors among native Canadians. *Arch Pediatr Adolesc Med* 2002;156:651-5.
- World Health Organization. Prevention of diabetes mellitus. *World Health Organ Tech Rep Ser* 1994;844:1-108.

24. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-97.
25. Baur LA, O'Connor J, Pan DA, Kriketos AD, Storlien LH. The fatty acid composition of skeletal muscle membrane phospholipid: its relationship with the type of feeding and plasma glucose levels in young children. *Metabolism* 1998;47:106-12.
26. Calvert SA, Soltesz G, Jenkins PA, et al. Feeding premature infants with human milk or preterm milk formula. Effects on postnatal growth and on circulating concentrations of intermediary metabolites, amino acids, and regulatory peptides. *Biol Neonate* 1985;47:189-98.
27. Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. *Arch Dis Child* 1992;67:357-65.
28. Lonnerdal B, Havel PJ. Serum leptin concentrations in infants: effects of diet, sex, and adiposity. *Am J Clin Nutr* 2000;72:484-9.
29. Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. *Acta Paediatr Scand* 1981;70:195-200.
30. Plancoulaine S, Charles MA, Lafay L, et al. Infant-feeding patterns are related to blood cholesterol concentration in prepubertal children aged 5-11 y: the Fleurbaix-Laventie Ville Sante study. *Eur J Clin Nutr* 2000;54:114-9.
31. Salmenpera L, Perheentupa J, Siimes MA, Adrian TE, Bloom SR, Aynsley-Green A. Effects of feeding regimen on blood glucose levels and plasma concentrations of pancreatic hormones and gut regulatory peptides at 9 months of age: comparison between infants fed with milk formula and infants exclusively breast-fed from birth. *J Pediatr Gastroenterol Nutr* 1988;7:651-6.
32. Schultz K, Soltesz G, Mestyan J. The metabolic consequences of human milk and formula feeding in premature infants. *Acta Paediatr Scand* 1980;69:647-52.
33. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet* 2003;361:1089-97.
34. Sweet DG, Hadden D, Halliday HL. The effect of early feeding on the neonatal blood glucose level at 1-hour of age. *Early Hum Dev* 1999;55:63-6.
35. Ugur S, Haktan M, Cakir E, Senocak M, Telci A. Serum insulin and blood glucose levels in breast-fed and formula-fed infants in the first week of life. *Clin Ther* 1988;10:678-87.
36. Wallensteen M, Lindblad BS, Zetterstrom R, Persson B. Acute C-peptide, insulin and branched chain amino acid response to feeding in formula and breast fed infants. *Acta Paediatr Scand* 1991;80:143-8.
37. Dewey KG, Nommsen-Rivers L, Lonnerdal B. Plasma insulin and insulin-releasing amino acid (IRAA) concentrations are higher in formula-fed than in breastfed infants at 5 mo of age. *FASEB J* 2004;18:A843 (abstr).
38. World Health Organization. Indicators for assessing breast-feeding practices. Division of Diarrhoeal and Acute Respiratory Disease Control. Report of an Informal Meeting. Geneva, Switzerland: World Health Organization, 1991.
39. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
40. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic reviews in health care: meta-analysis in context*. London, United Kingdom: BMJ Books, 2001:285-312.
41. Light RJ, Pillemer DB. *Summing up: the science of reviewing research*. Cambridge, MA: Harvard University Press, 1984.
42. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.
43. Launer LJ, Forman MR, Hundt GL, et al. Maternal recall of infant feeding events is accurate. *J Epidemiol Community Health* 1992;46:203-6.
44. Kark JD, Troya G, Friedlander Y, Slater PE, Stein Y. Validity of maternal reporting of breast feeding history and the association with blood lipids in 17 year olds in Jerusalem. *J Epidemiol Community Health* 1984;38:218-25.
45. Forouhi N, Hall E, McKeigue P. A life course approach to diabetes. In: Kuh D, Ben-Shlomo Y, eds. *A life course approach to chronic disease epidemiology*. Oxford, United Kingdom: Oxford University Press, 2004:165-88.
46. Hediger ML, Overpeck MD, Kuczumski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. *JAMA* 2001;285:2453-60.
47. Li L, Parsons TJ, Power C. Breast feeding and obesity in childhood: cross sectional study. *BMJ* 2003;327:904-5.
48. Stumvoll M, Goldstein BJ, van Haften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;365:1333-46.
49. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, et al. Risk of overweight among adolescents who were breastfed as infants. *JAMA* 2001;285:2461-7.
50. Owen CG, Martin RM, Whincup PH, Davey Smith G, Gillman MW, Cook DG. The effect of breastfeeding on mean body mass index throughout life: a quantitative review of published and unpublished observational evidence. *Am J Clin Nutr* 2005;82:1298-307.
51. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-31.
52. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995;122:481-6.
53. Wannamethee SG, Shaper AG, Walker M. Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *J Epidemiol Community Health* 2005;59:134-9.
54. Harder T, Bergmann R, Kallischnigg G, Plagemann A. Duration of breastfeeding and risk of overweight: a meta-analysis. *Am J Epidemiol* 2005;162:397-403.

