PROBIT IV

Breastfeeding Promotion RCT:

PROTOCOL OF RESEARCH PROJECT

1. Specific Aims

Breastfeeding improves health outcomes in infancy, including risks for atopic eczema (syn. ‘atopic dermatitis’, ‘eczema’) and gastrointestinal infections, but the long-term physiological effects of breastfeeding on child health are less clear. Among the most controversial purported benefits of breastfeeding are long-term effects on adiposity, blood pressure, neurocognitive function and asthma. Existing evidence is largely based on observational studies, which are prone to measurement error, publication bias and reverse causality. In addition, substantial differences between mothers who do and do not choose to breastfeed may confound results from observational studies, so it is difficult to determine whether the observational associations of breastfeeding duration with child health outcomes are causal or have alternative explanations.

The unbiased effects of breastfeeding can probably only be convincingly demonstrated in a randomized controlled trial (RCT). While it is not feasible to randomize healthy term infants to be breast or bottle fed, it is possible to randomize mother-child pairs to a breastfeeding promotion intervention. The Promotion of Breastfeeding Intervention Trial (PROBIT, ISRCTN37687716), the largest randomized trial of breastfeeding ever conducted, successfully increased breastfeeding duration and exclusivity among over 17,000 mother-infant pairs. The PROBIT intervention resulted in high rates of prolonged and exclusive breastfeeding; for example at 3 months, 43% of intervention mothers were exclusively breastfeeding compared with 6% of mothers in the control arm. The most plausible mechanism for any observed differences between the intervention groups is that the increased breastfeeding, caused by the breastfeeding promotion intervention, is the cause of differences between the intervention groups. Previous phases of PROBIT have demonstrated high rates of follow-up and valid, research-standard measurement of outcomes. The PROBIT trial thus offers a unique opportunity to obtain un-confounded estimates of the influence of breastfeeding on child health outcomes.

Our current proposal is based on the 15-16 year follow-up of children enrolled in PROBIT. Our hypotheses build on important findings from a previous follow-up of PROBIT children. In an intention-to-treat analysis, 6.5-year olds in the intervention arm had a 7.5 point advantage in verbal intelligence quotient (IQ) and higher teacher rated reading and writing vs. controls. At that age, most children had recently started school, but IQ is sensitive to environmental factors such as length of schooling. Thus, it remains unclear whether breastfeeding has an enduring effect on IQ. Furthermore, the pediatricians administering the IQ tests were not blinded to the children’s randomization status. In our current proposal, we plan to use self-administered tests of cognition and language, which will minimize any administrator bias. Also at age 6.5 years, the PROBIT intervention was not associated with asthma assessed by questionnaire (odds ratio: 1.2; 95% CI: 0.7-1.9), but the wide confidence interval does not exclude potentially important protective or adverse effects. In the current proposal, we include spirometric lung function measures, which index susceptibility to, and consequences of, asthma. Spirometry provides objective and continuous outcome measures, increasing study power. The PROBIT intervention was associated with a reduced risk of atopic eczema at 12 months (odds ratio: 0.54, 95% CI, 0.31-0.95), but was not associated with eczema assessed by questionnaire at 6.5 years (odds ratio: 1.0, 95% CI, 0.5-1.8). However, the reported prevalence of eczema at age 6.5 was also extremely low (1%). We hypothesized that parents may not have reported cases of eczema that were not diagnosed by a doctor. In this proposal, we plan to minimize such underreporting by training the study pediatricians to conduct physical examinations of participant’s skin to identify atopic eczema around the participant’s eyes, neck, elbows, knees or ankles. Such examinations should provide a more systematic approach to identifying true cases of atopic eczema.

Also at age 11.5 years, the PROBIT intervention was not associated with measured obesity (odds ratio: 1.17 (95% CI, 0.97 to 1.41) or blood pressure (mean difference between intervention vs control arms:...
1.0 mmHg (95% CI: -1.1 to 3.1) for systolic and 0.8 mmHg (-0.6 to 2.3) for diastolic blood pressure, but the wide confidence interval does not exclude potentially important protective or adverse effects.

The specific aims of the current proposal are to perform an intention-to-treat analysis comparing the randomized intervention vs. control arm. We will estimate the unconfounded, causal effects of breastfeeding promotion for the following hypotheses:

1. Prolonged, exclusive breastfeeding improves neurocognitive outcomes, including verbal and non-verbal cognitive ability and vision at age 15-16 years.
2. Prolonged, exclusive breastfeeding improves spirometric lung function and reduces rates of atopic eczema at age 15-16 years.
3. Prolonged, exclusive breastfeeding reduces adiposity and blood pressure at age 15-16 years.

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3. Prolonged, exclusive breastfeeding reduces adiposity and blood pressure at age 15-16 years.

We will also use data already collected as part of the PROBIT study to perform observational analyses examining associations of early life exposures, including birth characteristics and infant growth and feeding, with child health outcomes at age 6.5, 11 and 15-16 years, including cognition, asthma, atopy, dental health, adiposity, blood pressure, bloodspot measures of cardiometabolic health, neurocognitive outcomes, and lung function.

Furthermore, we will analyze associations of treatment assignment and breastfeeding duration with maternal health and adiposity at 11 years postpartum, using data already collected as part of PROBIT III.

The proposed research will provide an estimate of the causal effect of breastfeeding on outcomes meaningful for health in childhood and throughout the lifecourse. Understanding the causal effects of breastfeeding is important to maximize the population-wide impact of guidelines focusing on early nutrition, by providing robust data, ensuring consistent conclusions, and minimizing potential harms. Although different in many socioeconomic, cultural, and economic respects from the United States, Belarus is a relatively developed country, with strict hygienic standards, high immunization rates, low incidence of infection, low rates of infant and child mortality, similar types of formula feeds and accessible health care services. The results of this current proposal are therefore likely to inform policy in the US and many other countries.

2. Research Strategy

2.1. Significance

Breastfeeding is widely promoted as a cornerstone of public health. Observational studies, including several involving co-applicants on the current proposal, suggest that being breastfed reduces risks for obesity, hypertension, diabetes, heart disease, asthma and atopy. Yet mothers who breastfeed differ from mothers who formula feed: they are wealthier, better educated, less likely to smoke, and more likely to engage in other beneficial health behaviors. Thus, residual or unmeasured confounding, rather than breastfeeding itself, may explain observed associations between breastfeeding and health outcomes. To disentangle the health effects of breastfeeding from the characteristics of mothers who choose to breastfeed, we will perform an intention-to-treat analysis of a breastfeeding promotion intervention on neurocognitive and lung function outcomes in a large, well-characterized population of children followed from birth. Each of the outcomes to be studied are known to be sensitive to early life exposures, which can permanently program organ structure and function resulting in profound influences on health, function, and mortality risks throughout the lifecourse. In the sections below, we summarize the current evidence for associations of breastfeeding with each of the primary outcomes of this proposal, and highlight areas needing further study.

2.1.1. Neurocognitive function

Brain development is fastest in the 3rd trimester of gestation and the first 4 years after birth and is influenced by nutrition. Observational studies report consistently higher intelligence quotient (IQ) scores of 2 to 5 points in breast- vs formula-fed term infants. However, although many observational studies control for socioeconomic status and maternal intelligence, uncontrolled confounding by subtle differences in the mother’s...
behavior or her interaction with the infant are possible. In the 6.5 year follow-up of PROBIT, IQ was measured by the Wechsler Abbreviated Scales of Intelligence (WASI).\textsuperscript{17} Children randomized to the breastfeeding promotion arm had a 7.5 (95% CI: 0.8 to 14.3) point advantage in verbal IQ, 2.9 (-3.3 to 9.1) point difference for performance IQ and 5.9 (-1.0 to 12.8) point difference for full-scale IQ, vs controls.\textsuperscript{17} Smaller, but consistently positive, differences of 2 to 3 IQ points were seen in a blinded audit of 190 children and blinded teacher rated academic performance. Our experimental data, based on strict randomization and intention-to-treat analysis, is therefore consistent with observational data\textsuperscript{16} and suggests that associations in term infants are causal.\textsuperscript{17,18}

Nevertheless, these findings have been controversial and merit further investigation. Our current proposal maintains the strengths of earlier work within PROBIT, i.e. the large sample size and randomized design, while improving on the prior limitations, namely the young age at outcome assessment and imprecisely measured outcomes. An observational study and meta-analysis\textsuperscript{19} found that a positive association of breastfeeding with child IQ became negligible after controlling for parental IQ. Other studies that controlled for maternal IQ, however, report persistent, albeit attenuated, IQ benefits.\textsuperscript{16,20} In an RCT like PROBIT, parental IQ should be distributed randomly between treatment groups, as demonstrated for other measured baseline characteristics,\textsuperscript{21} and thus should not confound the intervention effect. The effect sizes for IQ at age 6.5 in PROBIT were imprecisely measured, due to high within-pediatrician clustering of IQ values across the 31 trial sites.\textsuperscript{22} While analyses based on the blinded audit and teacher ratings suggest the direction of the observed differences is robust, we do not know whether the large difference in verbal IQ arose by chance or a systematic overestimate of verbal IQ in the experimental group. The smaller differences seen in the blinded audit and teacher ratings may more closely estimate the true effect. All pediatricians were trained, monitored, and audited in their administration of the WASI, and no beneficial intervention effects were observed for other outcomes,\textsuperscript{23-25} equally subject to systematic error, providing some reassurance that the pediatricians' assessments of outcomes were unbiased. Nevertheless, the pediatricians who administered the WASI were not blinded to the trial arm of the children they examined, as many had contributed to the original intervention by providing postnatal support and encouragement of prolonged, exclusive breastfeeding.\textsuperscript{21} It is possible that the pediatricians at the intervention sites may have differentially administered or scored the WASI. In addition, about 20% of children seen at age 6.5 years had yet to start school, and they may have had difficulty completing the IQ test, potentially generating random measurement error.

Our current proposal builds on earlier findings by determining, in an intention-to-treat analysis that preserves the original random assignment, the magnitude of effect of the intervention on child cognition at age 15-16 years. We will use a computerized cognitive assessment battery that each child will self-complete with minimal instruction and automated scoring. This approach will counter the potential subjectivity in scoring WASI assessments, which could have compounded both the lack of blinding among pediatricians (leading to systematic error) and random error (thus reducing power\textsuperscript{22}). The children will be older and better able to participate in testing. Few studies involve follow-up into adolescence, when IQ is nearing its peak and inter-individual differences are enhanced.\textsuperscript{16,19} Associations of IQ in young adulthood are particularly strongly associated with socioeconomic and mortality outcomes, indicating the social and potential clinical importance of IQ in young adulthood.\textsuperscript{26}

In addition to assessing cognition, for the first time we will also include an assessment of vision. Vision is a neurocognitive outcome that is immature at birth and programmed by visual stimuli and nutrition in early life.\textsuperscript{27} Inadequate infant nutrition may alter visual development,\textsuperscript{28} and the absence of a clear retinal image may lead to myopia.\textsuperscript{29} Evidence suggests that breastfeeding promotes visual development, and hence less susceptibility to myopia,\textsuperscript{28,30-32} findings attributed to the long-chain polyunsaturated fatty acids (LCPUFAs) present in breast milk. However, although LCPUFAs occur in high concentrations in retinal photoreceptors, trials comparing LCPUFA-supplemented with un-supplemented formula milk are equivocal about their role in visual development.\textsuperscript{33} Inconsistencies may be due to differences in statistical power and/or the degree of adjustment for confounders.\textsuperscript{28,30} An intention-to-treat analysis in PROBIT would provide robust evidence on the association of breastfeeding with visual outcomes.

\textbf{2.1.2 Atopic eczema}
Breastfeeding is considered an important strategy to prevent the development of atopic eczema and other allergic diseases. Many allergy organizations, ministries of health, and the World Health Organization recommend between four and six months of exclusive breastfeeding to aid allergy prevention. These recommendations are largely based on cross-sectional studies. A meta-analysis of 21 observational cohort studies found no convincing evidence for a protective effect of exclusive breastfeeding for at least 3 months on atopic eczema risk up to 4.5 years age, but we are aware of no study that has assessed the impact of prolonged and exclusive breastfeeding on atopic eczema risk during adolescence or later in life.

Methodological shortcomings might explain some of the above contradictions. Observational studies are prone to confounding, in particular due to substantial differences between mothers who do and do not choose to breastfeed, making it difficult to determine whether the observational associations of breastfeeding duration with child health outcomes are causal or have alternative explanations. Observational studies may also be vulnerable to reverse causality, because a mother’s feeding behaviour (whether or not to continue breastfeeding) may be influenced by an infant’s having developed atopic eczema. That may be the reason why some observational studies have found higher atopic eczema risk with longer duration of exclusive breastfeeding.

The PROBIT breastfeeding promotion intervention reduced examination-based atopic eczema incidence in infancy (cluster-adjusted OR, 0.54; 95% CI, 0.31-0.95). In contrast, no evidence of a protective effect was observed at 6.5 years of age, but that result was based on questionnaire-based outcomes, rather than physical examination. Relying on questionnaire-derived outcomes for atopic eczema has previously been shown to be inadequate for risk factor analyses, as it attenuates associations; skin examination, using validated diagnostic criteria, is the gold standard, even for large population-based studies. In this proposal, we will conduct intention-to-treat analysis of PROBIT participants by standardized skin examination, conducted by trained study pediatricians, to provide further experimental evidence on whether increased breastfeeding duration and exclusivity protects against atopic eczema diagnosed over the long term.

### 2.1.3. Lung function

Childhood asthma, a leading cause of excess emergency visits, hospitalizations and missed school, is strongly influenced by exposures in early life. At birth, the lungs are immature. The number of alveoli increases rapidly during infancy, a period when lung function and growth may be particularly sensitive to nutritional or environmental exposures. Lung function subsequently tracks along percentiles from childhood into adulthood. There is evidence that lung function shortly after birth is associated with later asthma. Asthma inflammation can in turn affect lung function, and although lung function may be normal between flares in individuals, at a population level asthma is associated with reduced forced expiratory volume (FEV1). Reduced lung function may be an intermediate phenotype of asthma, but also might also be an outcome independent of asthma status. Thus, early-life adverse exposures have been associated with lung function throughout life.

A protective effect of breastfeeding on asthma has been observed and attributed to various potential biological mechanisms. For example, reduced exposure to cow milk and other foreign antigens may ameliorate the atopic immune response, or abundant cytokines (e.g. TGF-β1) in breastmilk may benefit lung and airways growth and development. A reduced frequency or severity of respiratory infections in infancy, which has been observed with breastfeeding in most studies, may, in turn, protect the development of lung function in childhood. However, some studies report an increased asthma risk with breastfeeding, particularly in older children of atopic mothers, in line with animal studies suggesting that breastmilk substances (e.g. IgE or interleukins) may trigger airway hyper-responsiveness and allergic inflammation. Other studies are null, and some indicate that the apparent protection of breastfeeding may arise by reverse causality, whereby early signs of atopic disease lead to earlier discontinuation of exclusive breastfeeding.

In PROBIT, wheezing, atopic symptoms and asthma diagnoses were more prevalent in the experimental versus control group at 6.5 years, although the wide confidence intervals could not exclude an important protective or adverse effect. Asthma symptoms and diagnoses were ascertained with the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire and an asthma diagnosis was rare (1%). Thus, potential measurement error and small numbers limited study power. The potential biological mechanisms...
outlined above imply that any link of breastfeeding with asthma may be mediated via effects on lung function during the sensitive period of lung growth in infancy. Furthermore, children with asymptomatic lung function impairment are at increased risk of chronic respiratory disease in later life, so lung function measures are a clinically relevant intermediate phenotype. Breastfeeding has been associated with substantially higher lung volumes in adolescence, with some evidence of a possible beneficial effect on airflow obstruction. Using spirometry, we propose to measure lung volumes (FEV₁ and FVC) and flow rate (PEFR), objective outcomes on a continuous scale that will provide greater power to detect effects compared to binary, self-reported outcomes such as asthma symptoms and diagnosis.

2.1.4 Adiposity and blood pressure

The prevalence of childhood obesity has risen substantially in recent decades around the world. In turn, obese children are more likely to become obese adults and suffer obesity-related chronic illnesses. However, few interventions to prevent childhood obesity have proven effective. Promoting greater uptake and duration of exclusive breastfeeding is a suggested public health measure to reduce childhood obesity and its metabolic consequences (e.g. high blood pressure, BP). This is based on mechanistic studies, for example those finding that the lower protein content of breastmilk (in comparison to formula milk) may reduce adipocytes development and a body of observational human data suggesting inverse associations of breastfeeding and its duration with later obesity. However, observational studies are prone to confounding by social patterning of both breastfeeding and growth, the epidemiological evidence is inconsistent and publication bias is a concern. Weight and blood pressure change dynamically during development, but most previous studies measure these outcomes on a single occasion, rather than on multiple occasions at different ages among the same individuals.

2.1.5. Summary

Our proposed research will provide an estimate of the causal effect of breastfeeding on important child health outcomes. Understanding the causal effects of breastfeeding is important to maximize the population-wide impact of guidelines focusing on early nutrition by providing robust data, ensuring consistent conclusions, and minimizing potential harms. These results will also inform social policies to promote breastfeeding and reduce its socioeconomic inequalities. For example, the recent health care overhaul does not reimburse women for breast pumps, as the Internal Revenue Service has ruled that breastfeeding does not have proven health benefits. Our findings may also drive further research to understand underlying mechanisms that could inform the diet of lactating women and the development of infant milk formula. For example, if future work determines that LCPUFAs explain any real long-term effects of breast milk on the studied outcomes, prenatal and infant nutrition could be optimized to include these nutrients. We focus on adiposity, blood pressure, neurocognitive and lung function at 15-16 years because these outcomes in childhood are linked to future psychological and social functioning, cardio-respiratory disease and mortality. Experimental data suggest a long-term benefit of breastfeeding on cognition is plausible, but the link and effect-size remain controversial. For lung function an adverse effect of breastfeeding has not been ruled out, despite decades of research. Research suggests that breastfeeding may reduce atopic eczema among infants, but there is limited evidence that this benefit extends into adolescence. As we are already assessing other major child health outcomes of breastfeeding, namely metabolic and cardiovascular risk, in PROBIT III at 11.5 years, neurocognitive and lung function are the most important remaining outcomes requiring further study.

2.2. Innovation

The long-term follow-up of PROBIT, with intention-to-treat analysis, provides a unique opportunity to robustly test whether breastfeeding causally influences long-term adiposity, blood pressure, neurocognitive outcomes and lung function. Instrumental variable analysis will provide unconfounded estimates of the effect of breastfeeding on the outcomes. A recent meta-analysis of the effects of breastfeeding on maternal and child health noted that the breastfeeding literature is comprised primarily of observational studies. No other study
of the magnitude and scope of PROBIT exists, and no prior randomized trials of breastfeeding have included outcomes past infancy.

2.3. Approach

2.3.1. People and track record

The study team unites expertise in the US, UK, Canada and the Republic of Belarus, and has already established a successful working relationship, having collaborated on the recent follow-up of PROBIT children at 11.5 years (PROBIT III). Under the leadership of Drs. Martin, Oken, and Kramer, the study team maintained the keen interest and active involvement of the participating Belarusian pediatricians and scientists, and obtained a remarkable 82% response rate for PROBIT III. For the proposed project we will employ similar strategies to ensure communication and productivity, including regular conference calls and twice-yearly joint visits to Minsk to meet with Belarusian pediatricians, research scientists and staff. Drs. Kramer, Martin and Oken have detailed knowledge of the project infrastructure in Belarus and a successful working partnership with the Minsk-based coordination centers (Ministry of Health; National “Mother and Child” Center, director Dr. Vilchuck, collaborator). We will employ this comprehensive knowledge and a network of key contacts to facilitate the project’s smooth running. We further detail the roles and expertise of study PI’s Drs. Oken and Martin, and senior co-I Dr. Kramer, in the Multiple PI leadership plan.

In addition to their work together on PROBIT, each of the study key personnel has led important research in the child health effects of early nutrition. Dr. Martin has authored several papers on the long-term effects of breastfeeding that have influenced clinical guidelines, including a series of influential meta-analyses. He is co-PI on the Boyd Orr cohort that has completed over 65 years of follow-up of children born in the 1930s, providing experience with cohort maintenance, questionnaire design and assessment and analysis of cognitive outcomes and lung function (spirometry). Dr. Oken has led or collaborated on studies and authored influential reviews and commentaries examining associations of maternal prenatal fatty acid status and other nutritional factors with child neurocognitive and immune development. She is co-PI of Project Viva, a longitudinal pre-birth cohort study that has followed women and children in the Boston area for over a decade. Through her work on Project Viva she has experience with questionnaire design, and assessment and analysis of child vision, cognition, and lung function via spirometry. The PI’s are thus well-qualified to lead the proposed study.

Other co-Investigators contribute extensive breadth and depth of experience. In addition to leading the first two phases of PROBIT, senior co-Investigator Dr. Kramer has had a long career investigating aspects of birth outcomes, infant feeding and infant growth. He has written about the difficulties of interpreting observational data on the association between breastfeeding and later health outcomes, and has authored influential papers on the association between breastfeeding and obesity. On behalf of the World Health Organization, he completed an extensive systematic review of the relationship between duration of breastfeeding and later health in childhood. Dr. Gillman is an internationally recognized expert in the developmental origins of health and disease. As PI of the Project Viva cohort and through his experience leading follow-up of children in the Framingham Children’s Study, the Growing Up Today Study, and the Early Determinants of Adult Health study, he has extensive experience in conducting and analyzing data from epidemiologic studies across the age spectrum. Professor Davey Smith is an eminent epidemiologist who led the establishment of an MRC Centre for Causal Analyses in Translational Epidemiology at the University of Bristol with a specific aim of developing methods to establish causality from population studies, including the long-term follow-up of RCTs. Dr. Henderson is a pediatric respiratory physician with extensive experience in measuring lung function in large population studies. Dr. Oken initially trained as an optometrist and has a longstanding interest in ophthalmic epidemiology. He has co-authored with Dr. Martin several papers examining the effect of infant feeding on health and is involved in 3 UK studies measuring refractive status in children. Dr. Carsten Flohr is trained in both pediatrics and dermatology; his research examines how genetic, immunological and environmental factors contribute to the development of atopic eczema and other atopic conditions. Dr. Yang is a social epidemiologist with a background in psychology and a research focus on determinants of cognitive ability in children and young adults, including collaborations with PROBIT. Dr. Kleinman is a senior biostatistician with extensive experience analyzing data from cluster randomized trials and longitudinal cohort studies including specific expertise in analysis of
repeated longitudinal measures and other clustered data, missing data problems, and Bayesian techniques.\textsuperscript{118,134-138} Thus, we have assembled an experienced team with a track record of productive, influential research and a long history of collaborative relationships that will ensure the successful completion of the proposed aims.

2.3.2. Environment

Each of the study key personnel comes from an academic setting with extensive experience in the design, conduct, and analysis of longitudinal studies of child health. The Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care is internationally recognized for its influential research in population health, including studies of the lifecourse influences on later health and disease risk. Bristol’s School of Social and Community Medicine demonstrates similar excellence in epidemiological research, including in early-life risk factors for chronic disease. In the 2008 UK Research Assessment Exercise, 70\% of the School’s epidemiology research was rated as world leading/internationally excellent. The School houses the MRC Centre for Causal Analyses in Translational Epidemiology, which will be available to provide methodological expertise, and the Avon Longitudinal Study of Parents and Children (ALSPAC) which has provided Drs. Martin, Henderson and Davey Smith with enormous experience of detailed phenotyping in large-scale prospective birth cohorts.

2.3.3. The PROBIT study

a. Study Population

Thirty-four maternity hospitals and one each of their affiliated polyclinics (the clinics where children are followed for routine health care) were randomly assigned to receive a breastfeeding promotion intervention (experimental group) or to continue the prevailing maternity hospital and polyclinic practices at the time of randomization (control group). Cluster randomization was preferred over individual randomization because randomizing individual women within the same maternity hospital to different interventions would probably have led to contamination and a dilution of the effect of the intervention. After randomization, two hospitals from two different pairs refused to participate and a third randomized site was removed from the trial because of documented falsification of outcome data.\textsuperscript{139} This left 16 intervention and 15 control sites in the trial.

Recruitment for PROBIT began in June 1996 and continued until the end of December 1997. Mothers were eligible for participation if they initiated breastfeeding on admission to the postpartum ward, had no illnesses that would contraindicate breastfeeding or severely compromise its success, and had given birth to a healthy singleton infant of 37 weeks or more gestation, 2500 g or more birth weight, and Apgar score 5 or higher at 5 minutes. Study staff estimated that only 1-2\% of eligible women declined participation. Since all women initiated breastfeeding, the experimental intervention was designed to increase the duration and exclusivity of breastfeeding. A total of 17,046 mothers (n=8865 intervention and n=8930 controls) had surviving infants. The randomization procedure produced groups with similar distributions of potentially confounding sociodemographic and clinical characteristics\textsuperscript{21} (Table 1).

b. The PROBIT Intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=8181)</th>
<th>Experimental (n=8865)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age 20-34 (%)</td>
<td>82.3</td>
<td>81.4</td>
</tr>
<tr>
<td>University education (%)</td>
<td>13.0</td>
<td>14.1</td>
</tr>
<tr>
<td>No other children in the household (%)</td>
<td>56.1</td>
<td>59.8</td>
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<tr>
<td>Gestational age (weeks)</td>
<td>39.3</td>
<td>39.4</td>
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<tr>
<td>Birth weight (g)</td>
<td>3446</td>
<td>3448</td>
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<tr>
<td>Birth length (cm)</td>
<td>52.2</td>
<td>51.9</td>
</tr>
<tr>
<td>Birth head circumference (cm)</td>
<td>34.8</td>
<td>35.1</td>
</tr>
<tr>
<td>Apgar score at 5 minutes (%)</td>
<td>8.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>51.6</td>
<td>51.8</td>
</tr>
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</table>

PROBIT IV STUDY – Promotion of Breastfeeding Intervention Trial IV
PROTOCOL (Revised 17 January 2012)
The experimental intervention included 10 steps that maternity hospitals must implement to become certified as ‘Baby Friendly’ (Table 2).140 Participants, usually the chief obstetrician and pediatrician from each of the intervention maternity hospitals and polyclinics, respectively, received the 18-hour Baby Friendly Hospital Initiative (BFHI) lactation management training course, which was organized by the European Regional Office of the WHO. The course emphasized methods to maintain lactation, promote exclusive and prolonged breastfeeding, and resolve common problems. Full implementation of the experimental intervention required 12 to 16 months to train all midwives, nurses, and physicians providing care to study mothers and infants during labor, delivery, and the postpartum hospital stay, and all pediatricians and nurses working at the polyclinics. Monitoring visits were conducted before and during recruitment and follow-up to ensure compliance with and maintenance of the study protocols.

### c. Data collection and validation at enrollment and in infancy

Sociodemographic and clinical information was recorded on an enrollment form completed during the postpartum stay. In Belarus, infants are seen monthly for routine well-child visits and whenever they are ill. Classification of the degree of breastfeeding was based on WHO definitions.140 An infant was considered to be exclusively breastfed at three months if the feeding information obtained at one, two, and three months indicated that he or she was being breastfed and that no solids, non-breast milk, or water or other liquids (other than vitamins or medications) were being administered to the infant. An infant was considered to be exclusively breastfed at 6 months if, in addition to the above criteria, he or she was not receiving any other liquid or solid foods at the 6-month visit. An infant was considered to be predominantly breastfed if he or she received no solids or non-breast milk; juices, water, teas, and other liquids were permitted in this category. Because the clinical outcomes were measured by the same pediatricians involved in implementing the experimental intervention or usual care, they could not be blinded to the intervention or control status of the study infants. A routine audit of data validity was therefore carried out at each study site. Twenty polyclinic charts were selected at random and the data on breastfeeding and infant outcomes at three months were compared with the data on these outcomes recorded on the PROBIT polyclinic visit forms. Of the 20 audited polyclinic charts, maternal interviews were also carried out for 10. For breastfeeding at three months, agreement was considered present if the date of weaning in the polyclinic chart or by maternal interview was within 15 days of the date recorded on the PROBIT polyclinic visit forms. For continued breastfeeding at three months, the kappa values for maternal interviews were 0.89 (95% CI: 0.81-0.97) in the experimental group and 0.94 (0.89-0.99) in the control group. Information about the outcome data collected at each PROBIT follow-up visit is summarized in Table 3 and detailed below.

### Table 2: The Ten Steps of the WHO’s Baby Friendly Hospital Initiative (BFHI).

1. Maintain a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within one hour of birth.
5. Show mothers how to breastfeed and maintain lactation, even if they are separated from their infants.
6. Give infants no food or drink other than breastmilk, unless medically indicated.
7. Practice “rooming in” – allow mothers and infants to remain together 24 hours a day.
8. Encourage unrestricted breastfeeding.
9. Give no pacifiers or artificial nipples to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge.

### Table 3. Visit schedule and previous funding for the PROBIT studies

<table>
<thead>
<tr>
<th>PROBIT phase</th>
<th>Funding source</th>
<th>PI</th>
<th>Funded components</th>
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<td>PROBIT I</td>
<td>Canadian Institutes of Health Research</td>
<td>Kramer</td>
<td>Baseline characteristics at enrollment</td>
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<tr>
<td>(Infant follow-up through 1 year)</td>
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<td></td>
<td>Infant growth, infectious diseases, and atopic eczema</td>
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<tr>
<td>PROBIT II</td>
<td>Canadian Institutes of Health Research</td>
<td>Kramer</td>
<td>Child adiposity, asthma, allergy, dental caries,</td>
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PROBIT IV STUDY – Promotion of Breastfeeding Intervention Trial IV
PROTOCOL (Revised 17 January 2012)
<table>
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<tr>
<th>PROBIT IV Study</th>
<th>Current proposals</th>
<th>Oken &amp; Martin</th>
<th>Focus of study</th>
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</thead>
<tbody>
<tr>
<td>PROBIT IV (Child follow-up through 6.5 years)</td>
<td>Health Research</td>
<td>Kramer</td>
<td>Child cognition, vision, atopic eczema, lung function, adiposity measures and blood pressure</td>
</tr>
<tr>
<td>PROBIT III (Child follow-up through 11.5 years)</td>
<td>Canadian Institutes of Health Research</td>
<td>Martin</td>
<td>Biomarkers of growth and heart disease risk in children (IGF-I, insulin, glucose, apoA1, apoB)</td>
</tr>
<tr>
<td></td>
<td>European Union (EARNEST Project)</td>
<td></td>
<td>Child adiposity and blood pressure</td>
</tr>
<tr>
<td></td>
<td>NICHD (R01 HD050758)</td>
<td>Oken</td>
<td>Child adiponectin and child metabolic syndrome</td>
</tr>
</tbody>
</table>
d. Outcomes in infancy (PROBIT I)

The first phase of follow-up (PROBIT I) assessed intervention effects on: breastfeeding duration/exclusivity; gastrointestinal and respiratory infection; and atopic eczema among infants. As seen in Figure 1, infants from intervention sites were 7 times more likely to be exclusively breastfed at 3 months (43.3% vs. 6.4%; P<0.001) and 13 times more likely at 6 months (7.9% vs. 0.6%; P = 0.01). Nearly twice as many intervention women were predominantly breastfeeding at 3 months (51.9 vs. 28.3%, p < 0.05) and nearly 7 times as many at 6 months (10.6% vs. 1.6%; P = 0.003). These differences were large enough to cause an appreciable reduction in gastrointestinal tract infections (9.1% vs. 13.2%) and atopic eczema (3.3% vs. 6.3%).

e. Outcomes at age 6.5 years (PROBIT II)

In PROBIT II, associations of breastfeeding promotion with child outcomes, including atopic disease, cognitive development, behavior, growth, obesity and blood pressure, were investigated. When the children were approximately 6.5 years of age, pediatricians invited them to the polyclinics for a study visit lasting about 1.5 hours. The participation rate was 13,889 (85%) of the 16,442 followed-up at 12 months (82% of the original cohort of 17,046). Outcomes included atopy, behavior, growth and blood pressure, and dental caries. Results for the IQ and asthma outcomes are described in detail above (Section 2.1).

f. Outcomes at age 11 years (PROBIT III)

At 11.5 years (PROBIT III), we investigated effects of breastfeeding on growth and cardio-metabolic risk factors. Pediatricians performed anthropometric measurements on mothers and children, and collected fasting blood via fingerstick. We have completed all study visits and await final data entry and results of laboratory assays. The participation rate - 13,891 children were seen - attests to our ability to maintain excellent follow-up and thus minimize retention bias. Intra-class correlation coefficients were extremely low for all measured outcomes (Table 4), indicating valid measurements with a low degree of clustering.

In an interim intention-to-treat analysis (n = 12,374), cluster-adjusted mean differences in experimental vs. control groups were essentially null: 0.16kg/m² (95% CI: -0.08, 0.40) for BMI; 0.43% (-0.15, 1.01) for body fat; 0.33cm (-1.25, 1.92) for waist circumference; 0.11mm (-1.53, 1.74) for triceps skinfold thickness; 0.62cm (-0.40, 1.64) for height; and 1.12mmHg (-1.06, 3.30) for systolic blood pressure. The odds ratio for obesity (experimental vs. control arms) was 1.19 (0.95, 1.50). We found similar null results for maternal postpartum adiposity. We now have a number of papers in progress presenting results of the intention-to-treat analysis of the anthropometric and biochemical study outcomes. Our joint experience leading PROBIT III yields several important messages: we have demonstrated our successful collaboration in leading a PROBIT outcome visit; we achieved high rates of follow-up with little evidence for bias in follow-up or clustering in outcome assessments; and we require 4 years of funding to allow for complete data collection and analysis.

Table 4: Intra-class correlation coefficients (ICC) for measurements taken in PROBIT III

<table>
<thead>
<tr>
<th>Measurement</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing height</td>
<td>0.03</td>
</tr>
<tr>
<td>Sitting height</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight</td>
<td>0.02</td>
</tr>
<tr>
<td>Bioimpedance</td>
<td>0.01</td>
</tr>
<tr>
<td>Mid-upper arm circumference</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.12</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.07</td>
</tr>
<tr>
<td>Hip circumference</td>
<td>0.03</td>
</tr>
<tr>
<td>Head circumference</td>
<td>0.10</td>
</tr>
<tr>
<td>Triceps skinfold thickness</td>
<td>0.12</td>
</tr>
<tr>
<td>Subscapular skinfold thickness</td>
<td>0.04</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.08</td>
</tr>
</tbody>
</table>
g. Summary

The PROBIT intervention successfully improved the duration of total and exclusive breastfeeding in a large population of mothers and infants. Participant characteristics were evenly balanced at study enrolment, suggesting that randomization was successful and confounding by measured and unmeasured characteristics is unlikely. At every phase of follow-up (I, II & III), those followed up (> 80%) had similar baseline characteristics vs. non-responders, providing reassurance against follow-up bias. Data collection through 11.5 years suggests high follow-up rates and uniform, high-quality outcome data, minimizing the likelihood of bias. The experienced and productive team will build upon established relationships to accomplish the proposed aims of this project.

2.3.4. PROBIT IV (current proposal)

a. Eligible population

We will attempt to follow-up all participants enrolled in PROBIT I, most of whom were seen at age 11.5 years (PROBIT III). Follow-up will commence in June 2012 when the oldest child will be 16 years. We will "front load" recruitment so that virtually all children are evaluated as near as possible to their 15th birthday and as few children as possible will be of school-leaving age (17 years). We again plan to follow up 14,000 children (82% of the original cohort). Given 97% follow-up in PROBIT I and 82% follow-up in both PROBIT II and III, we feel this goal is achievable; furthermore, the follow-up protocol will be shorter (1 vs. 2 hrs) and does not involve fasting or blood sampling, so will be more convenient for both children and clinicians; and we have recently updated contact information on the large majority of children seen between 2008-2010 for PROBIT III. Emigration levels are low and few families move their residence, except within Minsk. However, it is critical that we begin data collection soon, as after age 17 many children leave home to attend university, and we may lose the opportunity for further contact.

b. New data

As in PROBIT I-III, polyclinic pediatricians will locate and invite children to attend the follow up clinic examination where the pediatricians will collect the measures described below.

Informed consent. As we have done at each stage of data collection, pediatricians will obtain verbal informed consent via telephone or written informed consent from a parent for each participating child. They will also obtain verbal assent from children. Belarusian law disallows minors from providing written informed consent.

Neurocognitive function. Cognition will be assessed using the Mindstreams Global Assessment Battery (NeuroTrax Corp), a software package that is installed onto PCs and contains a validated computerized cognitive battery with multiple domains. After detailed review of available instruments, we chose Mindstreams because it tests a breadth of cognitive function; is brief (≈ 45 mins); includes a verbal domain (the domain most strongly associated with breastfeeding in PROBIT II); is self-administered; has an available, validated Russian language version; requires little computer literacy (only mouse clicks and number pad entries); and includes built-in trial tests with feedback before starting, to ensure comprehension. Other available tests are longer (> 1 hour); do not include verbal ability or have existing verbal tests that may not be generalizable to Russian; or are administered by trained personnel, so are not practical/cost-effective in our large trial. The Mindstreams non-verbal ability domain tests reaction time, immediate and delayed non-verbal memory (geometric figures), motor skills (e.g. hand-eye coordination; spatial recognition) and visual-spatial processing. The verbal ability domain tests immediate and delayed verbal memory (words; pictures) and word recognition. Aggregate outcome parameters will be computed from raw data using automatic algorithms, blind to intervention, standardized by age and fitted to an IQ-style scale (mean 100, SD 15). Standardized parameters that measure similar cognitive functions will be averaged to produce 7 'index scores', each summarizing performance in a single domain: memory; executive function; visual-spatial perception; verbal function; attention; information processing; and motor skills. A global cognitive score, reflecting general cognitive status, will be computed as the average of the index scores.

Vision. We will use the LogMAR-Crowded test (http://www.keeler.co.uk) to measure vision without optical correction, visual acuity with optical correction (if present) and pinhole acuity in each eye, to determine if any deficit in vision is refractive. A vision cut-off (LogMAR 0.2, equivalent to worse than 6/9 Snellen acuity) will be
used to define myopia; this threshold has high sensitivity (>90%) and specificity in identifying myopia,\textsuperscript{126,147} and that 91% of those with this level of vision at 16 years will be myopic in later life.\textsuperscript{148} The definition of myopia will be validated in a subset of children from the largest polyclinic (n=1000) using open field auto-refraction with a distant fixation target (Maltese cross at 5 meters) to stabilize accommodation without need for pharmaceutical cyclopia (which could otherwise compromise participation).

\textbf{Atopic eczema.} We will identify cases of atopic eczema through physical skin examinations conducted by the PROBIT study pediatricians, and collect additional data on eczema symptoms and skin health through questions from the International Study of Allergy and Asthma in Children (ISAAC) questionnaire. Study pediatricians will examine PROBIT participants for signs of flexural dermatitis around the eyes, the back of the neck, the front of the elbows, the back of the knees, and the front of the ankles. Evidence of flexural dermatitis upon exam at any of the 5 examination sites is sufficient for a diagnosis of atopic eczema.

\textbf{Lung function.} We will measure peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV\textsubscript{1}), forced vital capacity (FVC), and FEV\textsubscript{1}/FVC ratio using the 'Micro spirometer Plus' (Micromedical, www.micromedical.co.uk), which meets American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria.\textsuperscript{149} ATS/ERS guidelines will be followed in performing the measures and assessing acceptability and reproducibility.\textsuperscript{150} Room temperature and barometric pressure will be recorded. Children will be asked to complete the maneuver 5 times and the results and technical acceptability (i.e. maximum inspiration, a good start, a smooth continuous exhalation and maximal effort)\textsuperscript{150} of each blow recorded. We will aim for 3 acceptable and 2 repeatable (two largest values of FVC/FEV\textsubscript{1} within 0.15 liters of each other) maneuvers.\textsuperscript{150} Pediatricians will also measure child height using existing PROBIT stadiometers as they have done previously.\textsuperscript{23} The child will self-complete the European Community Respiratory Health Study questionnaire,\textsuperscript{151} which includes measures of respiratory symptoms, self-reported asthma/allergy, smoking, indoor exposures and asthma treatment.

\textbf{Adiposity and blood pressure.} Systolic and diastolic blood pressure readings will be measured using the semi-automated oscillometric Omron 705IT; (Omron Health Care, UK) using appropriate cuff size. The time of taking the measurement and room temperature (measured with an electronic thermometer) will be recorded. Standing height will be measured in duplicate (and averaged) using a wall-mounted. Waist circumference will be measured in duplicate at the mid-point between the iliac crest and the lower edge of the ribs in the mid-axillary line using a nonstretchable cloth tape measure. The Tanita TBF 300 GS body-fat analyzer (Tanita Corp, Tokyo, Japan) will be used to measure leg-to-leg bioimpedance from which weight, percent body fat, fat mass, and fat free mass are calculated.

\textbf{c. Training of pediatricians}

To ensure that high quality data are collected and that repeatable measurements can be obtained, we will hold a training workshop prior to starting fieldwork (as we have done in all past follow-ups). We will re-certify pediatricians in height measurement and certify them in the spirometry, cognitive and vision measures. Spirometry training will include an instruction session (Prof Henderson), followed by practical sessions to assess each pediatrician’s coaching technique and data outputs, with individual feedback. As we have done in the past (e.g. in PROBIT II for IQ) we will practice spirometry on consenting local children who are not study participants. Training for the cognitive function test will be minimal as the pediatricians only need to provide standardized, simple instructions to the children regarding how to execute the test from the software. Dr. Yang will advise on administering the cognitive function test and related analyses. Dr. Flohr will provide training in conducting the skin examinations, followed by a written, skills-based test to confirm that the pediatricians can accurately identify signs of flexural dermatitis. Dr. Owen will provide training in vision assessment, by lecture with follow-on practical and individual feedback. Subsequent workshops will be held 6 monthly to monitor follow-up, clarify procedures and re-standardize measurements.

\textbf{d. Quality control}

\textit{Monitoring.} Once the data collection process is underway, we will initiate data monitoring visits to each polyclinic. Trained Belarusian monitors will observe pediatricians and repeat key measurements during study visits on one full day.
Auditing. Once data collection is complete at each polyclinic, we will schedule auditing visits in order to assess the inter-observer reproducibility, an important step given that the pediatricians are not blinded to randomization status.23 The Belarusian auditors (likely the same individuals who will serve as monitors) will conduct duplicate (repeat) visits on a subset of randomly chosen PROBIT IV participants. We will perform 4 audit visits at each polyclinic with a single pediatrician, and a total of 6 audit visits (3 per pediatrician) for each polyclinic with two pediatricians. The auditors will be blinded to the initial measurements. We will calculate correlation coefficients with 95% confidence intervals for the initial vs. repeat measurements.

e. Data management

Using standard protocols for the questionnaire, measures and data coding, polyclinic pediatricians will be responsible for data collection. We have established a robust data management system and will build on the expertise gained in earlier follow-ups of the trial. There will be a peripherally located Microsoft Access database at the Data Center in Minsk for administration of follow-up invitation letters, appointment information, and monitoring conformity with other study procedures.

Data flow will be as follows. Copies of data forms containing the results of the physical examination and the questionnaires will be transported by driver from each polyclinic on a monthly basis to the Data Center in Minsk. Carbon copies of the forms will be kept at the polyclinic in case of loss in transit. Data will be entered into a Microsoft Access database, with built in logic checks, by trained data entry staff. Spirometric and cognitive data will be downloaded onto encrypted USB sticks, transported to Minsk by the driver and automatically uploaded into the database to prevent transcription errors. On a weekly basis, the Minsk-based data coordinator will run a program to identify logical errors and missing values, with corrections/completions requested by telephone and/or mail. Each month, a copy of the database will be e-mailed to the master database in Bristol, and subsequently to the analyst in Boston, who will perform ongoing analyses of data quality (blind to trial arm). She will calculate intra-class correlations to evaluate clustering, and will feed results back to the pediatricians at workshops held every 6 months.

f. Organization of study operations

Study operations will mirror the procedures we have successfully applied to PROBIT III, and are detailed more fully in the Multiple PI Leadership Plan. Drs. Oken and Martin together will be responsible for the scientific direction and overall conduct of the project. Dr. Martin will work with the UK-based Research Coordinator (Ms. Patel) to oversee day-to-day study logistics, including importation of equipment, planning workshops, developing training materials, creation and maintenance of the study databases. Ms. Patel will communicate with the Minsk-based co-ordination center and data entry team. Dr. Oken will supervise the US-based Project Manager (Ms. Andrews) to plan and oversee the data monitoring and data auditing visits. Ms. Andrews is also an experienced statistical analyst. She will receive monthly data downloads from Minsk, which she will use to create data summaries and identify missing, implausible, or outlying values, and will communicate these potential data errors back to the data entry team in Minsk. She will be the lead analyst for all analyses of the PROBIT age 15-16 year outcome data. With Dr. Oken’s supervision, Ms. Andrews will handle all communications with the Harvard Pilgrim Health Care IRB, and will track all expenses on the project.

Drs. Oken and Martin will communicate regularly with the study leadership in Minsk, including Konstantin Vilchuk, Director of the Belarusian Maternal and Child Health Center and Scientific Director for PROBIT in Minsk, and Natalia Bogdanovich, Director of Epidemiologic Studies at the Maternal and Child Health Center and Study Coordinator for PROBIT. To minimize any potential for confusion or miscommunication, Dr. Martin will be responsible for communicating via email with Dr. Vilchuck and Dr. Bogdanovich, with the help of an experienced Russian-English interpreter as has been done to date. At each twice-yearly visit to Minsk, the entire study leadership team (Drs. Oken, Martin, Kramer, Vilchuck, and Bogdanovich) will meet as a group to discuss operational issues.
2.3.5. Analysis Plan

a. Overall Analytic Plan

Prior to formal analysis, we will construct tables, histograms, and box-and-whisker plots of the collected data to
search for missing data and implausible or extreme values that may suggest error in measurement, recording
or data entry. Where possible we will return to paper records to find missing data and determine if errors can
be corrected. Histograms of residuals will be investigated for normality and outcomes transformed when
necessary to satisfy normality and other model assumptions, e.g., constant variance or linearity of effect.
Because this is a randomized trial, the primary approach will be an intention-to-treat (ITT). All analyses will
allow for the clustered nature of the data.

b. Exposure, outcomes, and covariates

The exposure will be randomization to the breastfeeding promotion intervention or to the control group. The
expected sample size is 14,000 children from 31 polyclinics.

The main neurocognitive outcomes will be the Mindstream scores standardized to an IQ scale (mean 100, SD
15) for memory; executive function; visual-spatial accuracy; verbal function; attention; information processing;
motor skills; and a global cognitive score. Vision will be assessed using LogMAR acuity, analyzed as a
continuous variable (given its more normal distribution compared to Snellen acuity measures); prevalence of
reduced LogMAR visual acuity will also be considered between intervention groups. Atopic eczema outcomes
will be evidence of flexural dermatitis around the eyes, the back of the neck, front of the elbows, back of the
knees, or ankles, as identified by a trained PROBIT pediatrician; secondary atopic eczema outcomes will
include responses to the skin questions from the ISAAC questionnaire. Respiratory function outcomes will be
PEFR, FEV1, and FVC, each expressed as internal z-scores adjusted for height, age and sex. Adiposity
outcomes will be body mass (BMI), fat mass (FMI), and fat-free mass (FFMI) indices, waist-to-height ratio and
overweight as BMI between the 85th to <95th percentiles and obesity as BMI at or above the 95th percentile,
based on the Centers for Disease Control and Prevention (CDC) 2000 age- and sex-specific reference data.
Blood pressure outcomes as continuous measures of systolic and diastolic blood pressure.

Since the number of polyclinics randomized in PROBIT (31) was relatively small, imbalances in baseline
covariates sufficient to confound the effect estimates may have occurred. We will therefore conduct a
secondary analysis in which we control for any predictors of our outcomes (unadjusted P<0.1) that are also
found to be associated (P<0.1) with randomization status. To date, PROBIT analyses suggest that this
circumstance is unlikely to occur (see Table 1); no evidence of confounding by individual-level covariates was
evident in PROBIT I, II or III.17,21 The main hospital-level potential confounders are geographic region and
urban versus rural location.

c. Statistical Analysis.

All analyses will allow appropriately for the clustering. We will use random effects models to account for
correlation within polyclinic, as is recommended for cluster randomized trials. Results will be reported as mean
differences. We will derive 95% confidence intervals and Wald tests of the null hypothesis of no association
between intervention groups. Effect modification will be addressed by stratification and by formally testing for
statistical interaction by introducing appropriate cross-product terms. We will initially examine results stratified
by sex to ensure comparability, before we consider combining results for boys and girls.

It is well known that “per-protocol” analyses of randomized trials, in which participants are grouped according
to the intervention they received, rather than that to which they were randomized, may be seriously biased. It is
for this reason that the primary analyses for this study will be based on intention-to-treat. However, this
approach may substantially underestimate the effect of the true exposure of interest (breastfeeding exclusivity
and duration), since there was not complete contrast of breastfeeding status between the randomized groups:
many intervention mothers did not exclusively breastfeed for 6 months, whereas some control mothers did.
There is a substantial statistical literature showing that causal effects of interventions may be validly estimated
from randomized trials, allowing appropriately for non-compliance with the intervention.152-155 Thus, in
secondary analyses, we will apply instrumental variable methods to estimate the causal effect of the difference
in breastfeeding exclusivity and duration achieved between the two randomized groups on our outcomes. In
this approach, we will use randomization status as the ‘instrument’ that is independent of any confounders of the exposure-outcome relationship, and is related to the outcomes only via the exposure. We will thus validly estimate the unbiased effect of breastfeeding itself on cognition, vision, and lung function. Although these analyses will address the attenuation of the effect of breastfeeding that is inevitable in intention-to-treat analyses, they are unlikely to increase the power of the study, so sample size calculations are not affected.

2.3.6. Power

Based on follow-up in PROBIT I-III, we expect 14,000 participants in PROBIT IV. We calculated detectable differences based on this number of subjects in 31 clusters, an intention-to-treat (ITT) analysis, 80% power, 5% significance, and used a realistic value (0.01) of the intra-cluster correlation coefficient (ICC) based on the ICCs of outcomes in PROBIT I-III. The effective sample size in PROBIT IV, allowing for the clustered design, is the total number of anticipated participants (14,000) divided by the design effect ($Deff$), where $Deff = 1+(n-1)\times ICC$ and $n$ is the average number of individuals per cluster ($n=14,000/31=451$). Thus, the design effect for an ICC of 0.01 is $1+4.5=5.5$ and the effective sample size is 2,500 children $(14,000/5.5)$. Expected means and SDs for each outcome were taken from childhood cohorts of similar age. Mean detectable differences, assuming exposure groups are dichotomized at the midpoint, are calculated as the product of the SD of each variable and the standardized difference (i.e. 0.1 given an effective sample size of 2,500). For the categorical atopic eczema outcome at the 16-year follow-up (flexural eczema on skin examination), the study has 94% power at the 5% significance level to detect a 50% reduction in atopic eczema prevalence between the two study groups, similar to PROBIT I.

Table 5 shows the mean differences that can be detected in the comparison of the two randomized arms by ITT and the corresponding effect due to breastfeeding that would have to be present to achieve those ITT differences. The breastfeeding effect is based on the difference in exclusive breastfeeding at 3 months of 43% in the intervention arm and 6% among controls, and is derived by dividing the ITT differences by 0.37=37% (the difference in exclusive breastfeeding in the 2 arms). For comparison, published differences are shown. The sample size is adequate for detecting important differences in the outcomes (Table 5). If we fail to find associations in the ITT analysis, the study is powered to have narrow confidence intervals (CIs) around null estimates. The 95% CIs for zero mean differences, assuming an effective sample size of 1250 in each arm ($(14,000/Deff)÷2$) and means/SDs in Table 2, would be: cognitive score $\pm 1.2$; FEV, $\pm 40$mls; FVC: $\pm 45$mls; PEFR: $\pm 60$mls/s.

<table>
<thead>
<tr>
<th>Continuous Outcomes</th>
<th>Mean</th>
<th>SD</th>
<th>Mean detectable differences: ITT</th>
<th>Breastfeeding effect to produce detectable effect</th>
<th>Differences observed in other studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognitive score</td>
<td>100</td>
<td>15</td>
<td>1.5</td>
<td>4.1</td>
<td>2-5-15</td>
</tr>
<tr>
<td>FEV₁ (mls)</td>
<td>3345</td>
<td>480</td>
<td>48</td>
<td>130</td>
<td>40-103</td>
</tr>
<tr>
<td>FVC (mls)</td>
<td>3700</td>
<td>575</td>
<td>58</td>
<td>150</td>
<td>54-103</td>
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<tr>
<td>PEFR (mls/s)</td>
<td>6200</td>
<td>800</td>
<td>80</td>
<td>200</td>
<td>180-200</td>
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<tr>
<td>LogMar visual acuity</td>
<td>0.02</td>
<td>0.2</td>
<td>0.02</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>99.9</td>
<td>9.6</td>
<td>1.15</td>
<td>3.11</td>
<td>Meta-analysis: 1.4; Max difference: 6.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>57.0</td>
<td>6.8</td>
<td>0.82</td>
<td>2.22</td>
<td>Meta-analysis: 0.5; Max differences: 3.4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>16.2</td>
<td>2.0</td>
<td>0.024</td>
<td>0.06</td>
<td>0.4-0.28-0.57</td>
</tr>
</tbody>
</table>

Data from ALSPAC, standardized for height; Northern Ireland Childhood Errors of Refraction study (personal communication); Estimates of means and SDs obtained from ALSPAC.
2.3.7. Timeline

As summarized in Figure 2, we anticipate completing all proposed work during the 4 year duration of the project. During the first 6 months we will finalize the training materials, DVD’s, and manual of procedures. We will hold our initial training workshop midway through Year 1, after which the pediatricians will commence data collection. Monitoring visits will begin a few months after the first visits are conducted. Based on experience in PROBIT III, we anticipate all 14,000 children will be seen over 2.5 years, after which we will complete the audit visits, data analysis, and manuscript writing. Although the NIH grant supporting PROBIT III operations was a 3-year grant, we required a fourth no-cost-extension year to complete data collection and analysis. Thus, we believe that 4 years is a reasonable timeline for the proposed work.

Figure 2: Project Timeline

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Year 01</th>
<th>Year 02</th>
<th>Year 03</th>
<th>Year 04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td></td>
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</tr>
<tr>
<td>Workshops</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Data collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audit visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis and writing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calendar Year 2011 2012 2013 2014 2015

Year 00 Year 01 Year 02 Year 03 Year 04

2.3.8. Strengths and limitations.

**Significance.** This study is significant because it will yield results that can directly influence breastfeeding promotion policies and thereby influence child health.

**Approach.** Our proposal combines the strength of a randomized design, minimizing confounding, and high rates of follow-up, minimizing selection bias. This project thus offers a unique opportunity to determine the long-term effect of a breastfeeding promotion intervention on child neurocognitive and lung function, adiposity and blood pressure. In the PROBIT trial, we successfully randomized units of medical care (hospitals and affiliated outpatient clinics) to breastfeeding promotion or usual care, resulting in large contrasts in breastfeeding experience between the two groups. In contrast to observational epidemiologic studies, in which residual confounding remains a concern even after adjustment for identified confounders, this intention-to-treat analysis will provide un-confounded estimates of the influence of breastfeeding on maternal adiposity. Breastfeeding was ascertained at regular intervals during infancy, with definitions of exclusive breastfeeding based on strict WHO criteria, minimizing measurement error. Modern alternatives to breastfeeding form the reference exposure, providing results of contemporary relevance.

The large sample size limits potential type 2 error for effect sizes of clinical and public health importance. We already have strong evidence supporting the internal validity of the conduct of the study, which would not be guaranteed if a study were established de novo. The stringent random allocation procedure produced intervention and control groups with similar baseline characteristics. Measurement error will be minimized by the use of standard, calibrated equipment. Pediatricians will be rigorously trained and retrained to obtain valid, reproducible measurements. Data monitoring and the extremely low intra-class correlations in previous phases of PROBIT (Table 4) support the precision of the outcome data collected to date.

We will minimize potential bias in outcome assessment by using self-administered, computer-scored measures of cognitive function. Although the polyclinic pediatricians cannot not be blinded to the intervention or control status, the pattern of results in previous phases of PROBIT follow-up (i.e. no effect seen for respiratory infections in infancy or child adiposity21,23), do not suggest systematic bias towards better outcomes in the intervention group. The duplicate audit visits will provide additional evidence against bias due to non-blinding. Losses to follow up and incomplete data are potential sources of bias. We expect similar high rates of follow-up as we achieved in PROBIT III. We will be able to compare and account for characteristics at baseline and at earlier follow-up visits between children who do and do not present for assessment at age 15-16. Compared
with observational cohorts, registered trials are less prone to problems of selective submission and publication bias. Generalizability is a concern. As the study is in Belarus, all participants are white. However, PROBIT includes an economically diverse population, and fewer than 2% of eligible mothers refused initial participation in the study. Belarus resembles Western developed countries in both basic health services and sanitary conditions. An uncontaminated water supply is ensured and monitored throughout the Republic by public health authorities, and clinics and physicians are abundant and readily accessible, even in rural areas. Therefore, we believe it will be reasonable to generalize results to children in the US.

This proposal represents good value. Previous grants have already supported recruitment, collection of baseline characteristics, and delivery of the intervention. As detailed in the budgets, the Canadian Institutes of Health Research will provide substantial co-funding (~$1.2m). We require funding only for the collection and analysis of outcome measures. In addition to the proposed aims, great potential exists for the conduct of other epidemiologic research based on earlier follow-ups and stored blood, including genetic analyses.

Innovation. This study will fill a crucial gap in the literature linking breastfeeding with important health outcomes in adolescence. Most previous studies have been observational. Additional limitations of the available literature include short duration of follow-up, recalled breastfeeding history, and assessment of asthma outcomes via questionnaire rather than objective measures such as spirometry. We will determine the causal effects of breastfeeding in the largest RCT in the field of human lactation ever, and by adding these 3 outcomes will complete analyses on a large range of outcomes over the 4 phases of PROBIT.

Investigators and environment. We have assembled an outstanding team of investigators with appropriate expertise and proven collaboration and productivity. We build upon an innovative cluster randomized controlled trial that successfully increased breastfeeding duration and exclusivity. The high quality of data collection is established. The environments will provide strong support to ensure the success of the study.
References


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PROmotion of Breastfeeding Intervention Trial

Plain English Summary

Background and study aims
The Promotion of Breastfeeding Intervention Trial (PROBIT) is a study in the Republic of Belarus involving 31 maternity hospitals and affiliated clinics across the country. The study was designed to help scientists, health care providers, and the general public understand the effects of infant feeding on child health and development.

In 1995, 16 hospitals and clinics were randomly allocated to a breastfeeding promotion intervention based on World Health Organization materials and procedures, while 15 continued breastfeeding practices in place at the time of random allocation. Mothers and babies were recruited from June 1996 to December 1997. In total, 17,046 mothers and their babies were recruited into the study. Of these, 16,492 (97%) were followed at regular intervals until the infants were 12 months of age. Detailed information was recorded at each followup visit about infant feeding, digestive and lung infections, and rashes.

When PROBIT children were six and a half years old, 13,889 (81%) were examined for height, weight, body fat, blood pressure, behaviour, dental health, intelligence quotient (IQ), asthma and allergy. At age 11 and a half years, 13,879 (81%) were again examined for height, weight, body fat, blood pressure, and also had blood tests to measure diabetes and heart disease risk factors. Currently we are seeing the children at age 16 years.

Who can participate?
Recruitment is complete. Mothers and their babies joined the study during their delivery hospital stay. Mothers could take part if they started breastfeeding, and they and their baby were healthy.

What does the study involve?
At the current visit, when the child is 16, the pediatrician:

1. Measures the child’s height, waist, blood pressure, weight and body fat.
2. Tests the child’s vision by asking him/her to read letter charts. A small number of children are also tested using an instrument that assesses whether they need glasses.
3. Examines the child’s skin for rashes.
4. Tests the child’s lung health by asking him or her to blow into a tube three to eight times to measure the capacity of the lungs.
5. Asks the child to take a computer-administered test of brain development (including memory, ability to solve problems, attention, perception, verbal skills, information processing and motor skills).
6. Administers a questionnaire to assess other aspects of the child’s health and physical development.

What are the possible benefits and risks of participating?
The lung function assessment involves blowing hard into a tube several times. Repeated blowing may cause some people to become wheezy. The pediatrician has asthma medication on hand to relieve these symptoms if they occur. None of the other measures or tests carries any risk to the child. As a result of the examination, the pediatrician may identify previously undiagnosed eye, lung or blood pressure problems in the child, which will then be followed up appropriately.

Where is the study run from?
The study is run from the The National Research and Applied Medicine Mother and Child Centre (Minsk, Belarus), in collaboration with the School of Social and Community Medicine, University of Bristol (Bristol, UK), Departments of Pediatrics and of Epidemiology, Biostatistics and Occupational Health, McGill University Faculty of Medicine (Montreal, Canada), and Harvard Medical School and Harvard Pilgrim Health Care Institute (Boston, USA).

When is the study starting and how long is it expected to run for?
The study started in January 1995 and is expected to run until December 2015. We hope the study will extend beyond this time as we intend to look at the children’s health over many years.

Who is funding the study?
This study is supported by a grant from the Canadian Institutes of Health Research (CIHR) and the US National Institutes of Health (NIH). The study has previously been funded by the National Health Research and Development Program (NHRDP) Health Canada, European Union’s project on Early Nutrition Programming: Long-term Efficacy and Safety Trials, the Thrasher Research Fund (USA), the United Nations Children’s Fund (UNICEF), and the European Regional Office of the World Health Organization (WHO).

Who is the main contact?
Professor Michael S Kramer
Michael.Kramer@mcgill.ca

website
Contact information
Type
Scientific
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Additional identifiers
EudraCT number ClinicalTrials.gov number
NCT01561612
Protocol/serial number
MOP-53155

Study information
Scientific title
Breastfeeding duration and exclusivity: impact on child health and development
Acronym
PROBIT

Study hypothesis
Current study hypothesis as of 11/03/2009:
Experimental intervention will lead to increased exclusivity and duration of breastfeeding, and hence to improved infant and child health.

Initial information at time of registration:
Experimental intervention will lead to increased exclusivity and duration of breastfeeding, and hence to reduced infection and eczema in infancy.

As of 25/03/2009, this record has been updated to include an updated anticipated end date; the initial end date at the time of registration was 31/03/2008.

As of 09/01/2013, the following changes were made to the record:
1. The anticipated end date for this trial was updated from 01/12/2011 to 31/12/2015
2. Belarus was added to the countries of recruitment, and Canada was removed

As of 02/09/2013, the anticipated start date was changed from 01/04/2002 to 01/01/1995.

**Ethics approval**
Research Ethics Board of McGill University Health Centre approved on 28/11/2001
Added 02/09/2013: Research Ethics Board of McGill University Health Centre approved on 18/06/2012 (Ref: 11-190-PED)

**Study design**
Randomised controlled trial

**Primary study design**
Interventional

**Secondary study design**
Randomised controlled trial

**Trial setting**
Hospitals

**Trial type**
Prevention

**Patient information sheet Condition**
Healthy, full-term, breastfed infants

**Intervention**
Experimental group: breastfeeding promotion intervention at maternity hospitals and affiliated polyclinics
Control group: continuation of maternity hospital and polyclinic practices existing at time of randomisation

**Intervention type**
Other

**Phase**
Not Applicable
Drug names Primary outcome measures
One or more episodes of gastrointestinal infection in first 12 months of life.

Secondary outcome measures
Current secondary outcome measures as of 09/01/2013:
1. Respiratory infections in first 12 months
2. Atopic eczema in first 12 months
3. Weight, length, and head circumference at 1, 2, 3, 6, 9, and 12 months
4. Blood pressure (BP) at age 6.5 and 9 years
5. Asthma, hay fever, atopic eczema, and allergy skin tests at age 6.5 years
6. Intelligence quotient (IQ) and behaviour at age 6.5 years
7. Oral/dental health at age 6.5 years
8. Anthropometry, lipoproteins, glucose, insulin, adiponectin, and IGF at age 11 years
9. Maternal height and weight at 6.5 and 11.5 years postpartum
10. Maternal body composition at 11.5 years postpartum
11. Maternal blood pressure at 11.5 years postpartum
12. Child metabolic syndrome at age 11.5 years
13. Eating attitudes at age 11.5 years
14. Child blood pressure at age 6.5, 11.5 and 16 years
15. Child body composition at age 11.5 and 16 years
16. Eczema, asthma, cognition, vision and lung function at age 16 years
17. Length/height and weight throughout childhood

Amended as of 11/03/2009:
8. Anthropometry, lipoproteins, glucose, insulin, adiponectin, and IGF at age 11 years

Initial information at time of registration:
1. Respiratory infections in first 12 months
2. Atopic eczema in first 12 months
3. Weight, length, and head circumference at 1, 2, 3, 6, 9, and 12 months
4. Blood pressure (BP) at age 6.5 and 9 years
5. Asthma, hay fever, atopic eczema, and allergy skin tests at age 6.5 years
6. Intelligence quotient (IQ) and behaviour at age 6.5 years
7. Oral/dental health at age 6.5 years
8. Lipids, lipoproteins, glucose, insulin, and HbA1c at age 9 years

Overall trial start date
01/01/1995

Overall trial end date
31/12/2015

Reason abandoned
Eligibility

Participant inclusion criteria
1. Birth weight equal and above 2500 g, either sex
2. Gestational age equal and above 37 weeks
3. Maternal intention to breastfeed

Participant type
Patient

Age group
Neonate

Gender
Both

Target number of participants
17046

Participant exclusion criteria
1. Neonatal disease or condition contraindicating breastfeeding
2. Neonatal disease or condition making breastfeeding difficult or impossible
3. Maternal psychosis
4. Maternal human immunodeficiency virus (HIV) or active tuberculosis (TB)
5. Maternal chemotherapy or radioisotopes

Recruitment start date
01/01/1995

Recruitment end date
31/12/2015

Locations
Countries of recruitment
Belarus

Trial participating centre
The Montreal Children's Hospital
Montreal
H3H 1P3 Canada

Sponsor information
Organisation
Sponsor details

McGill University (Canada)
845 Sherbrooke Street West James Administration Bldg.
Suite 429 Montreal
H3A 2T5
Canada

Sponsor type

University/education

Website

http://www.mcgill.ca/

Funders

Funder type

Research organisation

Funder name

Canadian Institutes of Health Research (CIHR) (Canada) - http://www.cihr-irsc.gc.ca
(Ref: MOP-53155)

Alternative name(s) Funding Body

United Nations Children's Fund (UNICEF)

Alternative name(s) Funding Body

Thrasher Research Fund (USA)

Alternative name(s) Funding Body

Type Funding Body Subtype Location Funder name

private sector organisation

Funding Body Subtype

foundation
Location
United States of America

Funder name
National Health Research and Development Program (NHRDP) - Health Canada (Canada)

Alternative name(s)
National Institutes of Health (NIH) (USA)

Funding Body Type
government organisation

Funding Body Subtype
federal/national government

Location
United States of America

Results and Publications
Publication and dissemination plan
Not provided at time of registration

Intention to publish date
Participant level data
Not provided at time of registration

Results - basic reporting
Publication summary
Publication citations

1. Results


- Full Text [http://doi.org/10.1136/bmj.39304.464016.AE]

2. Results


3. Results


- Full Text [http://doi.org/10.1542/peds.2007-1248]

4. Results

5. Results


6. Results


7. Results


8. Results


- Full Text [http://doi.org/10.3945/ajcn.113.079590]

11. Cohort profile


- Full Text [http://doi.org/10.1093/ije/dyt003]
Promotion of Breastfeeding Intervention Trial (PROBIT)

This study has been completed.

**Sponsor:**
Harvard Pilgrim Health Care

**Collaborators:**
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- Canadian Institutes of Health Research (CIHR)
- European Union Early Nutrition program
- University of Bristol

**Information provided by (Responsible Party):**
Emily Oken, Harvard Pilgrim Health Care

**ClinicalTrials.gov Identifier:**
NCT01561612

**First received:** March 20, 2012
**Last updated:** October 9, 2013
**Last verified:** October 2013

**Purpose**

The overall goal of the PROBIT study is to investigate the influence of a randomized breastfeeding promotion intervention designed to increase the duration and exclusivity of breastfeeding ("the breastfeeding promotion intervention") on the development of maternal and child health outcomes. The hypothesis is that randomization to the intervention will be associated with lower child adiposity, lower risk of asthma and atopy, improved lung function, and improved cognitive outcomes.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of Breastfeeding on Maternal and Child Health Outcomes</td>
<td>Behavioral: Breastfeeding promotion and support</td>
</tr>
</tbody>
</table>

**Study Type:** Interventional

**Study Design:** Allocation: Randomized
- Intervention Model: Parallel Assignment
- Masking: Open Label
- Primary Purpose: Prevention

**Official Title:** Breastfeeding Promotion RCT and Child Metabolic Syndrome

**Resource links provided by NLM:**
- MedlinePlus related topics: Breastfeeding, Children's Health
- U.S. FDA Resources

**Further study details as provided by Harvard Pilgrim Health Care:**

**Primary Outcome Measures:**
- Gastrointestinal tract infection [Time Frame: 12 months of age]
- Occurrence of 1 or more episodes of gastrointestinal tract infection

**Secondary Outcome Measures:**
- Maternal adiposity [Time Frame: 6.5 and 11.5 years postpartum]
- Child adiposity [Time Frame: Throughout childhood]
- Asthma [Time Frame: 6.5 and 16 years]
- Cognition [Time Frame: 6.5 and 16 years]
- Dental caries [Time Frame: 6.5 years]
- Child behavior [Time Frame: 6.5 years]
- Vision [Time Frame: 16 years]
- Lung function [Time Frame: 16 years]
- IGF-1 [Time Frame: Age 11.5 years]
IGF from dried bloodspots

child height [Time Frame: throughout childhood] Research measures of length/height

adiponectin [Time Frame: age 11.5 years] adiponectin from dried bloodspot


glucose [Time Frame: child age 11.5 years] fingerstick glucose measured by glucometer

insulin [Time Frame: child age 11.5 years] insulin measured on dried blood spots

Apo B [Time Frame: Child age 11.5 years]
Apo B measured in dried blood spots

Child blood pressure [Time Frame: throughout childhood]
Research measures of blood pressure at ages 6.5, 11.5 and 16 years

Maternal blood pressure [Time Frame: 11.5 years postpartum]
Research measure of maternal blood pressure

Child metabolic syndrome [Time Frame: Age 11.5 years]

Child growth [Time Frame: Throughout childhood]
Growth in weight, length, weight for length, BMI, and other measures

Respiratory tract infections [Time Frame: to age 12 months and throughout childhood]
Number of respiratory infections, from review of medical record

Atopic Eczema [Time Frame: Throughout childhood]
Eczema from review of medical record, parent report, and direct examination

Atopy [Time Frame: Age 6.5 years] Skinprick tests for allergy

Eating Attitudes [Time Frame: Age 11.5 years]
Children's Eating Attitudes Test (ChEAT) Questionnaire

Enrollment: 17046
Study Start Date: June 1996
Primary Completion Date: December 1998 (Final data collection date for primary outcome measure)
### Arms and Interventions

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental: Intervention</td>
<td>Breastfeeding promotion according to World Health Organization's Baby Friendly Hospital Initiative</td>
</tr>
<tr>
<td>Behavioral: Breastfeeding promotion and support</td>
<td>Breastfeeding promotion and support according to the World Health Organization's Baby Friendly Hospital Initiative</td>
</tr>
<tr>
<td>No Intervention: Control</td>
<td>Usual care</td>
</tr>
</tbody>
</table>

### Eligibility

#### Ages Eligible for Study:
Child, Adult, Senior

#### Sexes Eligible for Study:
All

#### Accepts Healthy Volunteers:
No

### Inclusion Criteria:
- Birth at one of 34 Maternity Hospitals in Republic of Belarus
- Breastfeeding initiated at birth, with no contraindications to breastfeeding
- Apgar score >=5 at 5 minutes
- Full term gestation
- Birth weight > 2500g

### Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01561612

### Locations

Belarus
- Maternal and Child Health Center
  - Minsk, Belarus

### Sponsors and Collaborators

- Harvard Pilgrim Health Care
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- Canadian Institutes of Health Research (CIHR)
- European Union EarlyNutrition program University of Bristol

### Investigators

- Principal Investigator: Emily Oken, MD Harvard Pilgrim Health Care Principal
- Investigator: Richard M Martin, MD University of Bristol

### More Information

Additional Information:

Related Info

Publications:


Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):


Responsible Party: Emily Oken, Associate Professor, Harvard Pilgrim Health Care
ClinicalTrials.gov Identifier: NCT01561612  History of Changes
Other Study ID Numbers: 190250  R01HD050758  FOOD-DT-2005-007036  G0600705  K24HD069408  MOP-53155 Study First Received: March 20, 2012
Last Updated: October 9, 2013

Keywords provided by Harvard Pilgrim Health Care:
Breastfeeding  Cognitive Development
Child Health  Behavior
Obesity  Eczema
Blood Pressure  Lung Function
Asthma  Spirometry

ClinicalTrials.gov processed this record on February 10, 2017