Breastfeeding and Cardiometabolic Profile in Childhood:
How Infant Feeding, Preterm Birth, Socio-Economic Status, and Obesity
May Fit into the Puzzle

Running title: Kuklina; Breastfeeding and cardiometabolic profile

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Introduction

Although the observed association between breastfeeding and cardiometabolic profile in childhood and adolescence in previous studies (refs) has biological plausibility, the precise mechanism and magnitude remains far from being fully understood. Early nutrition and epigenetic programming, anti-inflammatory properties, and cardiorespiratory fitness are among numerous hypotheses that are currently being actively investigated.

In this issue of Circulation, Martin et al. reported in the paper “Effects of promoting longer term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial”. The intervention study started in 1996-1997 in 31 Belarussian maternity hospitals and affiliated outpatient clinics with an enrollment of 17,046 breastfeeding mothers of healthy term infants. The trial was originally designed to assess the effects of a breastfeeding promotion and support intervention on duration of breastfeeding. Duration of both exclusive (infant only receives breast milk without any additional food or drink, not even water) and any breastfeeding (includes non-exclusive and exclusive) were assessed in the intervention and non-intervention groups. The planned 11.5 year follow-up of about 80% of study participants who had fasted for the follow-up assessment and did not have diabetes allowed authors to test whether an intervention to improve breastfeeding duration and exclusivity also influenced cardiometabolic risk factors in childhood. No significant differences between intervention and control groups were found in levels of blood pressure, fasting insulin, adiponectin, glucose, apolipoprotein A1, and metabolic syndrome.

Original study design and assumptions applied in the follow-up analysis

The results of the study Martin R et al. should be interpreted taking into account several considerations. First, all women enrolled in the trial expressed an intention to breastfeed on
admission to the postpartum ward and they initiated breastfeeding. The intervention successfully increased the proportion of women who were exclusively breastfeeding at 3 months (43.3% vs. 6.4%) and 6 months (7.9% vs. 0.6%) post partum. Although a significantly larger proportion of infants in the intervention group were breastfed during the first year of life (49.8% and 19.7% at 6 and 12 months of age, respectively), 36.1% and 11.4% of infants from the no-intervention group were also breastfed at 6 and 12 months of age. Thus, the results of this study in which longer durations of breastfeeding were compared to shorter durations of breastfeeding cannot be equated to results from studies comparing breastfeeding to formula-feeding.

In addition, the conclusions in this study are based on the implicit assumption that the characteristics of two groups of participants formed a decade ago remain the same. Many events may have occurred in every individual participant in the trial that may have changed the comparability of randomized groups. For instance, diet and physical activity are important determinants of cardiovascular risk profile in childhood and adolescence. Although the authors noted that it is unlikely that the intervention group had a poorer diet than the control group, the authors cannot rule out the possibility that changes in the socio-demographic and environmental factors took place during the study follow-up period.

**Is it breastfeeding or variations in study populations?**

Even in studies comparing breastfed infants with formula-fed infants, the effects of breastfeeding on measurements of CVD risk profile are usually small and their clinical significance remains unclear. Thus, even smaller differences are expected in the trial given the study design. Indeed, in systematic reviews/meta-analyses of observational studies comparing breastfed to formula-fed infants the effect of breastfeeding on systolic blood pressure (BP) was very moderate: 1.1 mm Hg and 1.4 mm Hg, respectively. Another point to consider is that only full-term singleton
infants weighing at least 2500 g and their healthy mothers were enrolled in the intervention study. It has been shown that the beneficial effects of breast milk on cardiovascular disease (CVD) risk factors may be larger and, thus, are more likely to be detectable in preterm infants. For instance, in a cohort of preterm children in two parallel randomized trials in five neonatal units in the UK, mean arterial blood pressure at age 13–16 years was 6.5 mm Hg lower in the 66 children fed breast milk obtained from a human milk bank (alone or in addition to mother's own milk) than in the 64 children fed preterm formula. The authors of the UK preterm trial also reported lower levels of C-reactive protein and low-density lipoprotein (LDL) to high density lipoprotein (HDL) cholesterol ratio in adolescents who had been randomized to receive banked breast milk compared to those given preterm formula. Finally, Belarus has a well-structured health care system but the annual gross domestic product per capita was less than 7,000 US dollars during more than 10 years of the study follow-up period. Evidence that is available mostly from observational studies in other populations shows that children and adults who were breastfed had lower levels of total blood cholesterol, lower risk of type-2 diabetes and marginally lower levels of adiposity and blood pressure compared to those who were formula-fed. However, no evidence that longer duration of breastfeeding is protective against adult hypertension, diabetes or overweight/adiposity was found in studies limited to low-/middle-income populations. In contrast, the later introduction of complementary foods demonstrated protective effects against adult adiposity, a known correlate of cardiometabolic risk. Body mass index (BMI) and waist circumference decreased significantly by 0.19 kg/m² and by 0.45 cm, respectively, per each 3-month increase in age at introduction of complementary foods. Unfortunately, no information on age of introduction and type of complementary foods was provided in the paper by Martin et al.
Addressing the growing obesity epidemic is likely to be a major factor in improving the cardiometabolic profiles of US children and adolescents.

In the study population at 11.5 years of age the prevalence of obesity (defined as BMI values at or above the 95th percentile of the Centers for Disease Control and Prevention (CDC) sex-specific BMI growth charts)\textsuperscript{12} was about 5.0\% (5.4\% and 4.7\% for intervention and control group, respectively)\textsuperscript{13} which is about 3.5 times lower than the prevalence of obesity among the US children aged 6-11 years reported in 2009-2010.\textsuperscript{14} The prevalence of obesity in the US children and adolescents aged 2-19 has increased dramatically from 5.0\% in the early 1970s to 16.9\% in 2009-2010.\textsuperscript{15,14} According to the most recent CDC report, although the rates of childhood obesity leveled off during 1999-2010 among girls, they continue to increase among boys.\textsuperscript{14} Currently numerous studies carried out among children and adolescents confirm that the same cardiovascular risk factors associated with obesity, such as type 2 diabetes, hypertension, and abnormal lipid profile have substantially higher prevalence in obese children compared to normal weight children.\textsuperscript{16} Consistent adverse associations between obesity and CVD risk factors were reported in a systematic review and meta-analysis of 63 studies of almost 50,000 children aged 5 to 15 years. In obese children compared with normal weight children, systolic BP was higher by 7.49 mm Hg. An increase of 1.0 mg/dL in total cholesterol and 1.4 mg/dL in LDL cholesterol for each body mass index point increase was reported in these analyses. Obesity also adversely affected concentrations of fasting insulin, insulin resistance, and size of left ventricular. The PROBIT researchers reported no difference in the prevalence of obesity between intervention and control group.\textsuperscript{13} This may be another reason why no differences in cardiometabolic profiles were found between intervention and control groups in the study by Martin et al.
What is the current evidence on effectiveness of weight-related interventions to improve cardiometabolic profiles of children and adolescence?

Reducing the risk of obesity is one of the most plausible mechanisms underlying the positive effects of breastfeeding on cardiometabolic profile in children. Several meta-analyses of observational studies examined anti-obesogenic effects of breastfeeding. The results of two of them showed a 4% reduction in overweight for each month of breastfeeding and a 15% decrease in the risk of obesity for exclusive breastfeeding compared to formula feeding in later life. However, the reported magnitude of associations in the studies included in the reviews was modest and varied among the studies due to possible factors that were not taken into account in the studies.

It is speculative to predict what strength and direction of associations between breastfeeding and cardiometabolic profile would be if the study took place in the US. Nevertheless, the interventions limited to promotion of breastfeeding are unlikely to have a significant impact on the cardiometabolic profile of children and adolescence given a high prevalence of childhood obesity in the US. Most of the currently available studies that examined the effectiveness of the interventions to reduce cardiometabolic risks in pediatric population were weight-related studies. In a systematic review and meta-analysis of 8 randomized trials among obese 6 to 12 years old children educational interventions with follow-up 6 months or longer when compared to usual care or no intervention resulted in a significant reduction in waist circumference by 3.2 cm (3 studies) and BMI by 0.9 kg/m² (5 studies). Interventions in these studies were carried in the school and/or family settings “through classroom lessons; orientations to increase the intake of fruits and vegetables, increase physical activity; or modification of physical education classes; and/or family-based programs”. The effect of intervention on blood
pressure among these studies was assessed in only 2 studies with significant 3.7 mmHg reductions observed for diastolic BP in one study. However, in this review no differences in outcomes were found in 18 studies that investigated the effectiveness of obesity prevention interventions. In another systematic review of 15 randomized controlled trials among overweight and obese children aged 18 years or younger, the addition of exercise to dietary intervention compared with the diet-only intervention resulted in significantly larger improvements in levels of HDL cholesterol (3.9 mg/dL), fasting glucose (2.2 mg/dL), and fasting insulin (-2.8 μIU/mL) at 6 month follow-up in.21 Parent involvement seems to play an important role in child weight-reduction interventions. The results of 36 randomized controlled studies showed that child and adolescent participants of weight-related interventions that required parent participation gained BMIs about 1.2 kg/cm² less than the respective control groups' participants.21 In addition, in this analysis, compared to shorter interventions with parent participation, longer interventions with parent participation appeared to be more successful. Only eight of 36 these studies examined the effects of weight reduction on cardiometabolic indicators. Significantly larger improvements in systolic blood pressure (4 studies), fasting insulin (1 study), C-reactive protein (1 study), and lipid levels (3 studies) were reported in the parent involvement group.

Although multiple studies demonstrated that school-based interventions focused on weight loss or healthy weight maintenance, improved diet, and/or increased physical activity, only twelve of them examine the effects of these interventions on cardiometabolic profile in children. The results of systematic review of school-based interventions aimed at reducing BMI or weight in children ≤ 18 years showed that interventions targeted at overweight/obese children reduced their BMI by 0.35 kg/m² while those delivered to all children reduced it by 0.16 kg/m². Physical activity used in isolation (11 studies) or combined with improved nutrition (29 studies)
reduced BMI by 0.13 kg/m² and 0.17 kg/m², respectively.²² In twelve of 41 studies that reported cardiometabolic measurements, children in the intervention group had a significantly larger decrease in blood pressure (7 studies), lipid including total cholesterol, low density lipoprotein cholesterol, or triglyceride (6 studies), fasting insulin (1 study), or fasting glucose levels (1 study). School-based physical activity interventions were effective in increasing duration of physical activity from five to 45 min more per day, reducing time spent watching television from five to 60 min less per day, and physical fitness level of an individual in a systematic review of 44 studies.²³ It should be noted, however, that the effects of physical activity on blood pressure and BMI in this review were inconsistent across studies and the strength and direction of associations were dependent on type of intervention and study duration. Only four and three of the 16 studies demonstrated statistically significant decreasing effects on mean systolic and diastolic blood pressure, respectively. Significant changes in BMI were reported in some of these significant association studies (one of 4 and two out of 3 of systolic and diastolic blood pressure studies, respectively). Given that physical activity seldom alters total cholesterol and LDL cholesterol unless it is accompanied by reduction in dietary fat intake and body weight loss in adults²⁴, it is not surprising that only one of the 10 studies reported a statistically significant positive effect on mean blood cholesterol level. Error! Bookmark not defined.

Conclusions

The study Martin et al. is a unique and valuable contribution to a better understanding of the cardiometabolic effects of breastfeeding in childhood and adolescence. The absence of significant differences in cardiometabolic profiles between the intervention and control groups does not question the importance to promote breastfeeding as it as many other benefits for infant health. Unfortunately, today virtually every specialty of medical practice is already facing, or
will be facing in the near future, the adverse cardiometabolic consequence of the childhood obesity epidemic. It is hard to imagine improving cardiovascular health of the US children and adolescents without recognizing the urgency of addressing the childhood obesity problem. This challenging goal can not be achieved without identifying interventions supported by rigorous evidence from studies with sophisticated design, adequate sample size, and sufficient duration of follow-up.

**Conflict of Interest Disclosures:** None. The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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