The Association of Breastfeeding Duration and Early Childhood Cardiometabolic Risk

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Objective To evaluate the association between breastfeeding duration and early childhood cardiometabolic risk.

Study design A cross-sectional study of 1539 healthy children, 3-6 years of age, recruited through The Applied Research Group for Kids! practice-based research network between October 2009 and August 2015. Adjusted multivariable linear regression was used to examine the association between breastfeeding duration and cardiometabolic risk z score and individual cardiometabolic risk factors of waist circumference, systolic blood pressure, glucose, high-density lipoprotein cholesterol, and triglycerides.

Results The mean breastfeeding duration was 12.5 months (SD = 8.4). Breastfeeding duration was associated with lower cardiometabolic risk z score (beta = –0.03; 95% CI –0.05, –0.01). In analysis of cardiometabolic risk factors, each additional 3 months of breastfeeding was associated with a 0.13 cm (95% CI –0.20, –0.05) lower waist circumference and 0.16 mm Hg (95% CI –0.30, –0.02) lower systolic blood pressure. Compared with children who breastfed for 6-12 months, those who breastfed for 12-24 months had a lower systolic blood pressure of 1.07 mm Hg (95% CI –2.04, –0.10). There was no association between breastfeeding duration and cardiometabolic risk for those who breastfed beyond 24 months.

Conclusions Breastfeeding duration is associated with lower cardiometabolic risk, although the magnitude of association is small. Causation cannot be inferred. Breastfeeding beyond 24 months may not have an added benefit for cardiometabolic health. *(J Pediatr 2018;192:80-5).*

Nutrition during critical windows in early life can influence and program later cardiometabolic health.[1,2] Breastfeeding is the best source of nutrition for infants to optimize growth and development.[3] The World Health Organization recommends exclusive breastfeeding for the first 6 months of life, introduction of complementary foods at 6 months of age, and continued breastfeeding up to 2 years of age and beyond.[4] The American Academy of Pediatrics recommends continued breastfeeding until at least 12 months of age and continued for as long as mutually desired by mother and baby.[3] Similar recommendations have been endorsed by Health Canada[5] and worldwide.[6,7]

The relationship between cardiometabolic risk factors and breastfeeding duration is unclear. However, cross-sectional studies have linked cardiometabolic risk factors to breastfeeding in childhood.[8-11] A longitudinal cohort study in the United Kingdom found that early breastfeeding was associated with lower blood pressure at a median age 7.5 years follow-up; the association was greater among those who had been breastfed for at least 6 months.[9]

We hypothesized that longer breastfeeding duration may have a protective effect on cardiometabolic risk in childhood. The primary objective of our study was to examine the association between breastfeeding duration and a summary measure of cardiometabolic risk factors in children 3-6 years of age. For the secondary objectives, first, we examined the association between breastfeeding duration and individual cardiometabolic risk factors including waist circumference (WC), systolic blood pressure (SBP), glucose, high-density lipoprotein (HDL) cholesterol, and triglycerides. Second, we modeled breastfeeding duration as a categorical variable to assess the effects of lower and upper ranges of breastfeeding duration on cardiometabolic risk.

Methods

This was a cross-sectional study of healthy urban children between October 2009 and August 2015. Participants were children aged 3-6 years who attended scheduled

HDL	High-density lipoprotein
SBP	Systolic blood pressure
TARGetKids!	The Applied Research Group for Kids
WC	Waist circumference

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healthcare visits at pediatric and family practices affiliated with The Applied Research Group for Kids (TARGetKids!) in Toronto, Canada. TARGetKids! is a primary care practice-based research network that recruits and follows children through scheduled well-child healthcare visits.[12]

Research personnel embedded in 9 participating pediatric and family medicine practices recruited study participants. Sociodemographic, lifestyle, and dietary information were collected using a standardized parent-completed survey instrument based on the Canadian Community Health Survey.[13] Nonfasting blood samples and physical measures were collected at study visits. MediData Rave (MediData Solutions, New York, New York) was used as the secure electronic data capture system and data repository for all TARGetKids! data.[12] Children were excluded if they had chronic conditions except asthma, severe developmental delay, failure to thrive, and gestational age of less than 32 weeks. In addition, families who were not fluent in English were excluded. Excluded children were less than 10% of the population. Children with missing data on exposure or outcome variables were also excluded.

Consent was obtained from parents. Research ethics approval was granted through the Research Ethics Boards at The Hospital for Sick Children and St. Michael's Hospital, Toronto, Canada.

The primary exposure variable was breastfeeding duration which was determined from response to the questions (1) "Has your child ever been breastfed?"; (2) "Is your child currently breastfeeding?"; and (3) "At what age did you stop breastfeeding?" Maternal recall of breastfeeding duration estimate has been found to be valid and reliable, especially after a short period of ≤3 years.[14] Participants who had never breastfed were classified as having a breastfeeding duration of 0 months and those previously breastfed were assigned the duration at the age breastfeeding stopped. Those currently breastfeeding were classified as having duration equal to the child's current age. Breastfeeding duration was a continuous variable in the primary analysis. In the secondary analysis, breastfeeding duration was modeled as a categorical variable, defined as 0-6, >6-12, >12-23, and ≥24 months, to assess the effects of lower and upper ranges on cardiometabolic risk . Categories were determined from the mean breastfeeding duration and consistent with previously published studies that assessed breastfeeding duration and cardiometabolic risk.[8,15,16]

Trained research assistants measured child and parent height, weight, and WC using standardized anthropometric protocols. Child height was measured using a stadiometer (SECA) and weight was measured using a precision digital scale (SECA, Hamburg, Germany). Without established WC standards for young children, standardized WC was calculated within our study population by age (in years) and sex. Within each age and sex group, a mean and SD were computed for WC. Our standardized WC was similar to a large US sample of comparable age range from the National Health and Nutritional Examination Survey.[17]

Children >3 years old had their blood pressure measured during their scheduled healthcare visit as recommended by the National High Blood Pressure Education Program guidelines and using National Health and Nutritional Examination Survey cut-off points.[18] Systolic blood pressure was measured by auscultation using a standard clinical sphygmomanometer and recommended size blood pressure cuff bladder. Nonfasted blood samples were collected by research assistants who are trained pediatric phlebotomists and transported to Mount Sinai Services for laboratory analysis. Glucose was measured using enzymatic reference method with hexokinase; and lipid (triglycerides and HDL cholesterol) measurements using enzymatic colorimetric on the Roche Modular platform. Standardization was based on existing values for children.[19] Our group and others have shown that fasting status has small and likely unimportant differences on glucose and lipid measurements.[20,21]

The primary outcome was a continuous cardiometabolic risk z score that was calculated for each subject as follows: cardiometabolic risk z score = (z WC + z triglycerides + z SBP + z-glucose + [-z HDL cholesterol]) divided by the square root of 5. Because higher HDL cholesterol is indicative of a healthier metabolic profile the inverse of HDL cholesterol was used. A lower cardiometabolic risk z score indicates lower cardiometabolic risk. Although there is no consistent definition of the metabolic syndrome in young children, prior research has used similar cardiometabolic risk scores.[22-26] Continuous cardiometabolic risk score has construct validity in children[27] and may predict later cardiometabolic risk in children and adolescents.[26] For secondary outcomes, we examined continuous cardiometabolic risk factors including WC, SBP, glucose, HDL cholesterol, and triglycerides.

All potential confounders were selected a priori based on the literature and data collected using a parent-completed, standardized questionnaire.[12] Potential confounders included birth weight, maternal age, maternal ethnicity, maternal education, family income, household smoke exposure, and paternal or maternal history of cardiovascular disease or diabetes. Maternal ethnicity was categorized into European, East Asian, South Asian/Southeast Asian, and other. Other included Arab, African, Latin American, mixed ethnicity, and North American aboriginal. A positive paternal or maternal history of cardiovascular disease or diabetes was dichotomized to "any" or "none" if the child's parent reported being diagnosed with any of the following conditions: heart disease, hypertension, high cholesterol, diabetes, depression. Family history of cardiovascular disease, diabetes, or depression,[28] and overweight/obesity has been associated with cardiometabolic risk in children.[29-31] Outcomes were standardized for child age and sex and, therefore, age and sex were not included as potential confounders in the model.

Statistical Analyses

Descriptive analyses of primary predictor, outcomes, and potential confounders were examined. For the primary analysis, multivariable linear regression was performed to examine the association between breastfeeding duration and cardiometabolic risk z score. Similarly, in secondary analysis, individual cardiometabolic risk factors including WC, SBP, glucose, HDL cholesterol, and triglycerides were examined. In addition, breastfeeding duration was modeled as a categorical

variable to assess possible nonlinear associations with cardiometabolic risk. Breastfeeding for 6-12 months was defined as the reference group.

All potential confounders were thought to be clinically important and were included in the final models regardless of associated *P* values to prevent biased regression coefficients and falsely inflated R^2 values from data-driven variable selection techniques.[32] Potential confounders had <15% missing values, except for family income (<20%), with the majority of potential confounders missing <10%. Multiple imputation was performed for missing data using chained equations.[33] Complete cases analysis was consistent with imputed results (not shown). The variance inflation factor was computed for each covariate to test for multicollinearity. All statistical tests were 2-sided, and a priori a significance level of less than 0.05 was specified. Statistical analysis was conducted using R version 3.3.1 (The R Foundation, Vienna, Austria) (http://www.R-project.org/).

Results

Between October 2009 and August 2015, 1547 children aged 3-6 years had a TARGetKids! healthcare visit with complete data on breastfeeding duration and the cardiometabolic risk factors including SBP, WC, and lipid measurements. Only 8 subjects were excluded because of implausible values, thus, our final analysis included 1539 subjects.

The mean breastfeeding duration was 12.5 months (SD = 8.4), mean infant age was 52.5 months (SD = 10.2), and 47% of children were female (**Table I**). At outcome assessment, children who breastfed longer tended to be older, have a higher birth weight, and be shorter in height. Mothers of children who breastfed longer tended to be older, have a higher body mass index, be of European ethnicity, have a college education, and have a higher family income. Children who breastfed longer had lower cardiometabolic risk z score, WC, and SBP.

In the primary adjusted analysis, each additional 3 months of breastfeeding duration was associated with a decrease in cardiometabolic risk z score by 0.03 (95% CI −0.05, −0.01; *P* = .02) (**Table II**). Adjustment was made for birth weight, child z height, child age, child sex, maternal age, maternal ethnicity, maternal education, family income, household smoke exposure, and maternal or paternal history of cardiovascular disease or diabetes.

In the secondary adjusted analysis of cardiometabolic risk factors, each additional 3 months of breastfeeding duration was associated with a decrease in WC by 0.13 cm (95% CI

Table I. Subject characteristics

		Breastfeeding duration				
	Level	0 mo	1-6 mo	>6-12 mo	12-23 mo	24+ mo
N		34	362	525	444	174
Age, mo, mean (SD)		54.85 (9.33)	52.80 (9.95)	52.74 (10.16)	51.03 (10.35)	54.33 (10.18)
Breastfeeding duration, mo, mean (SD)		0.00 (0.00)	4.05 (1.88)	10.10 (1.68)	16.21 (2.83)	30.08 (7.12)
Birth weight, kg, mean (SD)		2.95 (0.68)	3.17 (0.76)	3.34 (0.94)	3.35 (0.62)	3.30 (0.72)
Child sex, n (%)	Female	17 (50.00)	167 (46.13)	246 (46.86)	204 (45.95)	89 (51.15)
	Male	17 (50.00)	195 (53.87)	279 (53.14)	240 (54.05)	85 (48.85)
z Height, mean (SD)		0.23 (1.20)	0.16 (1.04)	0.16 (1.04)	−0.02 (1.62)	−0.15 (0.96)
Maternal age, y, mean (SD)		30.73 (5.78)	33.23 (5.09)	33.73 (3.90)	33.76 (4.15)	34.80 (5.04)
Maternal BMI, mean (SD)		25.44 (4.65)	26.09 (5.97)	24.45 (4.72)	24.06 (4.56)	25.01 (4.55)
Maternal ethnicity, n (%)	European	13 (46.43)	211 (63.17)	342 (70.08)	287 (69.16)	98 (61.64)
	East Asian	3 (10.71)	19 (5.69)	42 (8.61)	26 (6.27)	10 (6.29)
	South Asian	5 (17.86)	19 (5.69)	32 (6.56)	25 (6.02)	15 (9.43)
	Southeast Asian	2 (7.14)	20 (5.99)	17 (3.48)	3 (0.72)	10 (6.29)
	Other*	5 (17.86)	65 (19.46)	55 (11.27)	74 (17.83)	26 (16.35)
Maternal education, n (%)	No college	4 (12.90)	53 (15.01)	32 (6.20)	21 (4.77)	16 (9.36)
	College	27 (87.10)	300 (84.99)	484 (93.80)	419 (95.23)	155 (90.64)
Household smoke exposure (%)	No	29 (85.29)	300 (87.98)	454 (89.19)	393 (91.61)	143 (85.12)
	Yes	5 (14.71)	41 (12.02)	55 (10.81)	36 (8.39)	25 (14.88)
Family income (Canadian $), n (%)	0-59 999	9 (29.03)	49 (16.96)	44 (10.58)	42 (11.35)	28 (20.00)
	60 000-99 999	9 (29.03)	43 (14.88)	59 (14.18)	59 (15.95)	36 (25.71)
	100 000-149 999	6 (19.35)	53 (18.34)	81 (19.47)	87 (23.51)	31 (22.14)
	Over 150 000	7 (22.58)	144 (49.83)	232 (55.77)	182 (49.19)	45 (32.14)
Paternal history of CVD/diabetes, no, n (%)	No	17 (70.83)	280 (86.42)	402 (88.35)	335 (88.39)	124 (83.22)
	Yes	7 (29.17)	44 (13.58)	53 (11.65)	44 (11.61)	25 (16.78)
Maternal history of CVD/diabetes, no, n (%)	No	17 (80.95)	298 (93.42)	430 (95.98)	355 (92.93)	138 (91.39)
	Yes	4 (19.05)	21 (6.58)	18 (4.02)	27 (7.07)	13 (8.61)
Cardiometabolic risk z score,† mean (SD)		0.17 (1.07)	0.12 (1.11)	0.01 (1.11)	−0.09 (1.09)	−0.08 (1.11)
Waist circumference, cm, mean (SD)		54.46 (5.32)	53.39 (4.87)	52.96 (4.26)	52.82 (4.76)	52.28 (4.29)
Systolic blood pressure, mm Hg, mean (SD)		89.06 (6.12)	88.96 (7.87)	88.13 (7.50)	86.64 (7.93)	88.21 (7.95)
HDL cholesterol, mg/dL, mean (SD)		1.34 (0.33)	1.39 (0.34)	1.37 (0.33)	1.38 (0.34)	1.39 (0.31)
Triglycerides, mg/dL, mean (SD)		1.11 (0.53)	1.15 (0.66)	1.11 (0.64)	1.12 (0.63)	1.06 (0.60)
Glucose, mg/dL, mean (SD)		4.55 (0.60)	4.65 (0.69)	4.59 (0.73)	4.57 (0.71)	4.66 (0.75)

BMI, body mass index; *CVD*, cardiovascular disease

*Other includes Arab, African, Latin American, mixed ethnicity, and North American aboriginal.

†Cardiometabolic risk score derived from the sum of 5 sex- and cohort-specific z-scores for waist circumference, triglycerides, glucose, HDL cholesterol, and systolic blood pressure divided by the square root of 5.

Table II. Association of (3-month interval) breastfeeding duration and cardiometabolic risk z score – fully adjusted model

Characteristics	Estimate	95% CI Lower	95% CI Upper	*P* value
Total breastfeeding duration, mo	−0.03	−0.05	0.01	.01
Birth weight, kg	−0.04	−0.12	0.04	.29
Child z height	0.11	0.07	0.17	<.001
Maternal age, y	−0.01	−0.03	0.00	.09
Maternal ethnicity – East Asian (vs European)	0.25	0.03	0.47	.03
Maternal ethnicity – South Asian (vs European)	0.05	−0.27	0.37	.75
Maternal ethnicity – Southeast Asian (vs European)	0.20	−0.17	0.57	.30
Maternal ethnicity – other* (vs European)	−0.07	−0.32	0.20	.63
Maternal education, college	0.17	−0.05	0.39	.14
Family income (Canadian $)				
0-59 999 vs over 150 000	−0.02	−0.24	0.20	.83
60 000-99 999 vs over 150 000	0.06	−0.12	0.25	.51
100 000-149 999 vs over 150 000	0.00	−0.16	0.16	.98
Household smoke exposure	−0.06	−0.25	0.13	.54
Paternal history of CVD/diabetes (vs none)	0.16	−0.02	0.33	.08
Maternal history of CVD/diabetes (vs none)	−0.07	−0.32	0.19	.61

Child age and sex were removed from model as cardiometabolic risk factors were z score adjusted.
Cardiometabolic risk z score derived from the sum of 5 sex- and cohort-specific z scores for WC, triglycerides, glucose, HDL cholesterol, and SBP divided by the square root of 5.
Fully adjusted model includes birth weight, child z height, child age, child sex, maternal age, maternal ethnicity, maternal education, family income, household smoke exposure, and maternal or paternal history of cardiovascular disease or diabetes.
*Other includes Arab, African, Latin American, mixed ethnicity, and North American aboriginal.

−0.20, −0.05; $P = .00$), and a decrease in SBP by 0.16 mm Hg (95% CI −0.30, −0.02; $P = .02$) (Table III). In the categorical analysis, children who breastfed >12-23 months had lower SBP compared with children who breastfed 6-12 months (beta = −1.07; 95% CI −2.04, −0.10; $P = .03$). Children who breastfed 0-6 months had a difference in cardiometabolic risk z score compared with children who breastfed 6-12 months (beta = −0.14; 95% CI −0.01, 0.28; $P = .06$). Further, for cardiometabolic risk factors, children who breastfed 0-6 months had a difference in WC compared with children who breastfed 6-12 months (beta = −0.55; 95% CI −0.02, 1.12; $P = .06$). Breastfeeding duration beyond 24 months was not associated with cardiometabolic risk (Table IV).

Table III. Breastfeeding duration (3-month interval) and cardiometabolic risk z score and factors – fully adjusted model

	Estimates	95% CI Lower	95% CI Upper	*P* value	Model R^2
Cardiometabolic risk z score*	−0.03	−0.05	−0.01	.01	0.04
WC, cm*	−0.13	−0.20	−0.05	.00	0.16
SBP, mm Hg*	−0.16	−0.30	−0.02	.02	0.07
HDL cholesterol, mg/dL	0.00	−0.01	0.01	.92	0.06
Triglycerides, mg/dL	−0.01	−0.02	0.00	.16	0.03
Glucose, mg/dL	0.00	−0.01	0.01	.95	0.02

Breastfeeding duration estimates for 3-month breastfeeding duration intervals.
Cardiometabolic risk z score derived from the sum of 5 sex- and cohort-specific z scores for WC, triglycerides, glucose, HDL cholesterol, and SBP divided by the square root of 5.
Fully adjusted model includes birth weight, child z height, child age, child sex, maternal age, maternal ethnicity, maternal education, family income, household smoke exposure, and maternal or paternal history of cardiovascular disease or diabetes.
*Statistically different at $P < .05$.

Discussion

Our study suggests that in healthy 3- to 6-year-old children, those who breastfed longer have lower cardiometabolic risk. Waist circumference and blood pressure may be the influential factors. Although the magnitude of the association is small, our findings support the American Academy of Pediatrics recommendations[3] that infants should breastfeed until at least 12 months of age. Continuation of breastfeeding beyond 24 months may not have added protection against cardiometabolic risk.

Observational studies supported the role of early nutrition during critical windows to program long-term cardiovascular disease.[34] Early studies established breastfeeding to offer a protective effect on cardiometabolic risk factors such as lipid measurements[35] and blood pressure.[16,36] However, studies were subject to varying breastfeeding definitions, long periods of maternal recall, and residual confounding. Because the optimal period of breastfeeding remains unclear, our study explored breastfeeding duration as continuous and categorical variables.

Table IV. Categorical breastfeeding duration and cardiometabolic risk z-score and factors – fully adjusted model

	Breastfeeding 0-6 mo vs 6-12 mo				Breastfeeding >12-23 mo vs 6-12 mo				Breastfeeding ≥24 mo vs 6-12 mo			
	Beta	95% CI Lower	95% CI Upper	*P* value	Beta	95% CI Lower	95% CI Upper	*P* value	Beta	95% CI Lower	95% CI Upper	*P* value
Cardiometabolic risk z score	0.14	−0.01	0.28	.06	−0.08	−0.22	0.06	.27	−0.02	−0.21	0.17	.86
WC, cm	0.55	−0.02	1.12	.06	0.07	−0.47	0.62	.80	−0.46	−1.21	0.29	.23
SBP, mm Hg	0.80	−0.21	1.80	.12	−1.07	−2.04	−0.10	.03	−0.02	−1.35	1.31	.98
HDL cholesterol, mg/dL	0.01	−0.04	0.05	.72	0.02	−0.03	0.06	.44	−0.01	−0.06	0.05	.82
Triglycerides, mg/dL	0.06	−0.02	0.15	.15	0.01	−0.08	0.09	.90	−0.04	−0.15	0.08	.52
Glucose, mg/dL	0.06	−0.04	0.15	.25	−0.01	−0.10	0.08	.84	0.08	−0.04	0.21	.19

Cardiometabolic risk z score derived from the sum of 5 sex- and cohort-specific z scores for WC, triglycerides, glucose, HDL cholesterol, and SBP divided by the square root of 5.
Fully adjusted model includes birth weight, child z height, child age, child sex, maternal age, maternal ethnicity, maternal education, family income, household smoke exposure, and maternal or paternal history of cardiovascular disease or diabetes.

Distinctly, our study had many participants with longer breastfeeding duration, a short maternal recall period, and adjustment for numerous potential confounding variables, including child height, family income, and parental history of cardiovascular disease.

Previous studies have reported higher total cholesterol levels in breastfed infants compared with those who were formula-fed, but the associations were not consistent in later childhood.[35] A recent meta-analysis suggested that breastfeeding had a small but protective effect on development of poor outcomes for individual cardiometabolic risk factors,[37] and may lead to lower levels of cholesterol and triglycerides in later life.[38] In contrast, a randomized controlled trial to assess an intervention to improve breastfeeding duration did not influence individual cardiometabolic risk factors in children at 11.5 years of age.[39] Likewise, a meta-analysis on long-term consequences of breastfeeding on total cholesterol and blood pressures found no association.[40] Although uncertainty exists about consequences of breastfeeding on lipid measurements, our study and others[39,40] found no association. We postulate that the effect may not be present or be too small to detect in early childhood.

Studies focused on the associations of breastfeeding duration and combined cardiometabolic risk factors have showed inconsistent results.[41,42] A population-based cohort study found that breastfeeding duration was not consistently associated with cardiometabolic risk factors at 6 years of age. Researchers examined breastfeeding duration categories less than 6 months vs ≥6 months. They reported that shorter breastfeeding duration was associated with increased cardiometabolic risk factors, however, the association did not remain significant after adjustment for potential confounders.[15] We had a unique opportunity to study longer breastfeeding duration as our study had a relatively large proportion of infants who had breastfed beyond 12 months of age (mean 12.5 months, SD = 8.4).

Plausible explanatory mechanisms for the effect of breastfeeding on cardiometabolic risk in early childhood may be related to specific growth factors or hormones in human milk that are not present in infant formula. Notably, slower early growth patterns of breastfed compared with formula-fed infants may be protective for cardiometabolic risk.[34] Consistent with the growth acceleration hypothesis that rapid early growth can affect infant nutrition, epigenetic "marking,", or set-points of hormonal axes that influence appetite, satiety, and growth.[41]

Our study has limitations. The cross-sectional analysis cannot determine causality. Children were recruited from primary care practices in a large Canadian city and may not be generalizable to children of other urban or nonurban areas. Although, our sample had a high self-reported income, the maternal and infant characteristics of longer breastfeeding duration were similar to other Canadian studies.[43] Further, we were not able to adjust for unmeasured potential confounders, such as infant feeding patterns or early introduction of complementary foods. Lastly, our early childhood cardiometabolic risk score equally weighed each component, which may not be a biological representation and may not serve as the most useful proxy marker for later cardiometabolic disease.

Breastfeeding duration is associated with lower cardiometabolic risk. The magnitude of association is small at an individual level but may have meaningful impact at the population level. Breastfeeding beyond 24 months may not have an added benefit to cardiometabolic health. ■

*We thank all of the participating families for their time and involvement in TARGet Kids! and are grateful to all practitioners who are currently involved in the TARGet Kids! practice-based research network (**Appendix**).*

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Appendix

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