Nutrient enrichment of human milk with human and bovine milk–based fortifiers for infants born weighing <1250 g: a randomized clinical trial

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ABSTRACT

Background: Human milk-based fortifiers (HMBFs) are being adopted in neonatal care to enrich the nutrients in human milk for very low birth weight (VLBW) infants despite being costly and there being limited efficacy data. No randomized clinical trial has evaluated the use of HMBF compared with bovine milk–based fortifiers (BMBFs) in the absence of formula feeding.

Objective: We determined if HMBF compared with BMBF for routine nutrient enrichment of human milk improves feeding tolerance, reduces morbidity, reduces fecal calprotectin (a measure of gut inflammation), and supports the growth of infants <1250 g.

Design: In this blinded randomized clinical trial, infants born weighing <1250 g were recruited from neonatal units in Ontario, Canada between August 2014 and November 2015. The infants were fed mother's milk and donor milk as required. Fortification commenced at 100 mL/kg per day of HMBF (0.81 kcal/mL) or BMBF (0.72 kcal/mL) and advanced at 140 mL/kg per day to 0.88 and 0.78 kcal/mL, respectively. The primary outcome was percentage of infants with a feeding interruption for ≥12 h or a >50% reduction in feeding volume. Secondary outcomes included a dichotomous mortality and morbidity index (i.e., affirmative for any one of death, late-onset sepsis, necrotizing enterocolitis, chronic lung disease, or severe retinopathy of prematurity), fecal calprotectin, and growth.

Results: Of 232 eligible infants, 127 (54.7%) were randomized ($n = 64$ HMBF, $n = 63$ BMBF). Mean ± SD birth weight and gestational age of infants were 888 ± 201 g and 27.7 ± 2.5 wk, respectively. No statistically significant differences were identified in feeding interruptions [17/64 HMBF, 20/61 BMBF; unadjusted risk difference: −6.2% (95% CI: −22.2%, 9.8%)]. There was no statistically significant difference in the mortality and morbidity index (35.9% HMBF, 49.2% BMBF, adjusted $P = 0.07$), changes in fecal calprotectin, or growth z scores.

Conclusions: Among infants born weighing <1250 g and exclusively fed human milk, the use of HMBF did not improve feeding tolerance or reduce mortality and morbidity compared with BMBF. This trial was registered at clinicaltrials.gov as NCT02137473. *Am J Clin Nutr* 2018;108:108–116.

Keywords: nutrient fortification, human milk, preterm infants, very low birth weight

INTRODUCTION

Mother's milk is the optimal source of nutrition for all infants (1). Among very low birth weight (VLBW) infants, mother's milk supplemented with donor human milk, instead of formula, when there is insufficient volume improves enteral feeding tolerance and reduces the risk of necrotizing enterocolitis (NEC), a life-threatening gastrointestinal condition (2, 3).

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Supplemental Tables 1–3 and Supplemental Figures 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BMBF, bovine milk–based fortifier; CNN, Canadian Neonatal Network; HMBF, human milk–based fortifier; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PN, parenteral nutrition; RCT, randomized clinical trial; ROP, retinopathy of prematurity; SickKids, The Hospital for Sick Children; VLBW, very low birth weight.

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Bioactive components in human milk, including immunoglobulins, cytokines, growth factors, and oligosaccharides, play a role in gastrointestinal development and modulation of the immune function (1, 4). It is proposed that feeding bovine protein may negatively impact gut permeability, influence gut epithelial cell cytotoxicity, and promote dysbiotic colonization of the gastrointestinal tract (5–7).

To meet the nutritional requirements of VLBW infants, bovine milk–based fortifiers (BMBFs) are routinely added to human milk (8). Human milk–based fortifiers (HMBFs) are now available; however, they are costly, and there are limited efficacy data supporting their use. Ghandehari et al. (9) and Sullivan et al. (10) reported that VLBW infants randomized to a diet of mother's milk, supplemental donor milk, and HMBF had a reduction in the probability of requiring parenteral nutrition (PN) and lower rates of NEC (6% compared with 16%, $P = 0.02$) compared with infants fed mother's milk with BMBF and supplemental formula. While promising, this trial does not reflect the current standard of care, which includes use of mother's milk with supplemental donor milk (11, 12). Further, the trial was not completely blinded and the NEC incidence in the bovine arm was considerably higher than that experienced in Canada for infants of the same size fed mother's milk fortified with BMBF and supplemental formula (13). Given these limitations, additional research was warranted prior to the routine adoption of HMBF into clinical care. Given the absence of a randomized clinical trial (RCT) comparing HMBF and BMBF as supplements together with donor milk, and with the sample size required, it would be challenging to secure funding for a blinded RCT with NEC as the primary outcome. At the 2010 national incidence rate (7.44%), a sample size of 1194 infants born weighing <1250 g would be required to observe a 50% reduction in NEC with 80% power at an α level of 0.05 (13). The aim of this study, therefore, was to determine whether, in the absence of formula, the addition of an HMBF to mother's milk with supplemental donor milk would reduce the percentage of infants, born weighing <1250 g, who had a major feeding interruption more or less than the addition of a BMBF. Although the etiology of NEC is multifactorial, feeding intolerance may be an early sign of future feeding interruption, which not only affects the provision of nutrition and growth, but also places the infant at higher risk for NEC (14–16). Secondary outcomes include other measures of feeding tolerance (e.g., days on PN), a dichotomous mortality and morbidity index, fecal calprotectin (e.g., gut inflammation), and growth.

METHODS

In this multicenter, triple-blind RCT, infants were enrolled from 2 tertiary neonatal intensive care units (NICUs) located at the Sinai Health System and The Hospital for Sick Children (SickKids) in Toronto, Canada between August 2014 and November 2015. Infants were eligible to participate if they had a birth weight <1250 g and if their parents consented to supplemental donor milk. Exclusion criteria included receipt of formula or BMBF prior to randomization and if enteral feeding had not commenced within 14 d of birth. Additionally, infants were excluded if a chromosomal or congenital anomaly affecting growth was identified prior to enrollment, if they were participating in another study affecting their nutritional management, or if there was a reasonable likelihood of transfer to an NICU where human research ethics approval had not been secured.

Study day 1 was defined as the day nutrient fortification of enteral feeds commenced. The feeding intervention continued until infants were 84 d of age, discharge, or when they consumed ≥2 complete oral feeds daily over 3 d, whichever came first. Importantly, the feeding intervention and data collection continued after infants were transferred to community hospitals ($n = 16$ level II NICUs) in the Greater Toronto Area for convalescence to meet the aforementioned criteria. The trial was completed in March 2016. The Human Research Ethics Board at each hospital approved the study protocol. An independent data and safety monitoring committee reviewed the safety data after the first 61 infants had completed the intervention.

Infants were randomly assigned to either the HMBF or BMBF group through an online third-party service. Randomization occurred in blocks of 4, stratified by birth weight (<1000, 1000–1249 g) and recruitment center. Enteral feeds were prepared daily with the assigned fortifier in accordance with physician orders (volume and nutrient density) under laminar flow in milk preparation rooms located at recruitment centers. For infants at community hospitals, milk was couriered daily to and from SickKids with the use of coolers containing ice packs and a thermometer.

Feeding intervention

Mother's milk was always provided first. Pasteurized donor human milk (Holder, 30 min at 62.5°C), provided as a supplement, was from the Rogers Hixon Ontario Human Milk Bank, with back-up from the NorthernStar Mothers Milk Bank. A weight-based enteral feeding protocol was developed for this study (**Supplemental Table 1**) and daily feeding goals were posted at each infant's bedside. Once a feeding order reached ≥100 mL/kg per day, nutrient fortification of milk commenced. The goal was to discontinue PN at 120 mL/kg per day, with full enteral feeding defined as 160 mL/kg per day. Enteral feeds were further concentrated if, after full enteral feeds were achieved, weekly weight gain was <15 g/kg per day. At the end of the feeding intervention, infants were weaned from the study feeds over 3 d. At the time of the trial, recruiting tertiary hospitals used donor milk routinely as a supplement to mother's milk. The use of donor milk as a supplement and the length of time for which it was provided varied in level II NICUs. Enteral feeding protocols varied across centers, but feeds were advanced at a rate of 10–25 mL/kg per day to >140–200 mL/kg per day (the goal in tertiary NICUs was 160 mL/kg per day). Nutrient fortification commenced at ≥120 mL/kg per day and central lines were removed once feeding tolerance was observed. None of the participating hospitals prescribed probiotics or were using HMBF.

To ensure that the feeding assignments were masked, amber-coloured syringes were used for tube feeds and coloured wrapping was used for bottles. There was no indication of the treatment group (e.g., "a" or "b") on the feeding labels. Further, standardized multivitamin drops were provided in both arms of the study during the intervention and contained 375 IU of vitamin A, 200 IU of vitamin D, and 17.5 mg of vitamin C daily, with an additional 200 IU of vitamin D until the infant weighed 2 kg. Daily dosing of iron followed the local hospital protocol (2–3 mg elemental iron/kg per day). Except for the diet

technicians preparing the feeds and one research dietitian assigned to supervise the milk preparation areas, all other members of the research and clinical teams, including the nurses assessing feeding tolerance and the staff abstracting data from the medical records, remained blinded to the feeding assignments.

To mimic the current standard of care with minimal disruption of clinical routines, the feeding supplies (e.g., brands) in use at the participating NICUs, including donor human milk, BMBF, protein modular, and multivitamin drops, were used where appropriate. Supplies unique to the study, including amber feeding syringes and donor human milk, outside the eligibility criteria for any individual hospital were purchased. The HMBF was provided by the manufacturer at cost.

The baseline characteristics of the infants were collected from their medical records. To evaluate the generalizability of the sample, mothers were asked to report their age, education, income, and ethnicity from fixed multiple-choice lists with the option for alternative answers.

Human milk–based fortifier group

In the HMBF arm (intervention), Prolact + 4, Prolact + 6 and Prolact + 8 (Prolacta Bioscience) were mixed with human milk according to the manufacturer's instructions, in the ratios 1:4, 3:7, and 2:3, respectively (**Supplemental Table 2**). These human milk–based products are manufactured according to a patented process involving ultrafiltration and pasteurization of donor milk. Fortification began at 0.81 kcal/mL (24 kcal/oz), and when the infant had reached 140 mL/kg per day it was increased to 0.88 kcal/mL (26 kcal/oz). As HMBF is not used in Toronto, we adopted the Baylor College of Medicine/Texas Children's Hospital's approach of concentrating feeds to 0.88 kcal/mL routinely, rather than in response to poor growth (17, 18). No bovine–based products (e.g., protein modular or powdered formula) were used to concentrate enteral feeding in this arm of the study.

Bovine milk–based fortifier group

In the BMBF group (standard of care), human milk was nutrient-enriched with Similac Human Milk Fortifier Powder (Abbott Nutrition) to 0.72 kcal/mL (22 kcal/oz) and 0.78 kcal/mL (24 kcal/oz), and with the addition of powdered formula (Similac Neosure, Abbott Nutrition) to further concentrate feeds to 0.88 kcal/mL (26 kcal/oz). The BMBF available in Canada at the time of the study contained intact, nonhydrolyzed bovine proteins. At 0.72, 0.78, and 0.88 kcal/mL, nutrient additions displaced 100 mL of human milk by 1.4, 2.8, and 4.5 mL, respectively. Fortification began at 0.72 kcal/mL (2 packages/100 mL human milk), and when the infant reached 140 mL/kg per day it was increased to 0.78 kcal/mL (4 packages/100 mL human milk). To mimic the average mother's milk protein concentration of 1.2 g/dL, an intact-protein powder modular (Beneprotein, Nestle) was routinely added to donor milk (0.4 g/100 mL) after nutrient fortification had reached 0.78 kcal/mL.

Study outcomes

The primary outcome was percentage of infants with an interruption in enteral feeding, unrelated to a clinical procedure, that lasted for ≥12 h or a >50% reduction in volume over the same time frame. Secondary outcomes included other measures of feeding tolerance (e.g., days of PN), a dichotomous mortality and morbidity index, fecal calprotectin, and growth. Measures of feeding tolerance and other outcomes were collected from medical records daily in tertiary care centers and weekly from community hospitals by research staff. If it was not clear why a feed was missed or not recorded, this was discussed with the health care providers.

Incidence of NEC Stage ≥II, late-onset sepsis, chronic lung disease, and severe retinopathy of prematurity (ROP) have been associated with enteral feeding type (2, 3, 19, 20). As we have done previously, owing to the low prevalence of individual morbidities, a dichotomous mortality and morbidity index was used as a secondary outcome, where an affirmative response indicated that the infant had died or developed any one of the aforementioned morbidities (2). Exploratory analyses of individual morbidities were also preplanned, but the study was not designed to detect differences between feeding groups. Infants were classified as having NEC of "any stage" if clinical symptoms according to Bell's criteria were demonstrated and ≥7 d of treatment had been received (e.g., antibiotics and suspension of enteral feeds) (14). Infants with evidence of associated septic shock, pneumatosis, bowel perforation, or histologic evidence of bowel ischemia consistent with NEC on bowel resection were classified as Bell Stage ≥II. Two neonatologists and one radiologist, unaware of feeding assignments, reviewed all the potential NEC cases. Late-onset sepsis was defined as a positive culture in blood, cerebrospinal fluid, or suprapubic or catheter urine ≥5 d, and chronic lung disease was classified as oxygen support at 36 wk (13). Severe ROP was defined as ROP requiring treatment with laser or intraocular antivascular injection or international criteria stage 4/5 (21).

Stools were collected weekly for 8 wk and stored at −80°C. Fecal calprotectin concentrations, a noninvasive marker of gut inflammation, were determined in stools collected within 7 d prior to commencing fortification and 14 d thereafter with the use of an ELISA kit (Calprest, Eurospital) (22–25).

Daily weights were extracted from the medical record, and weekly lengths and head circumference measurements were assessed with the use of length boards and nonstretchable tape measures. Absolute measures were converted to z scores (26).

Statistical analysis

Statistical analyses were conducted with the use of SAS Version 9.4 (SAS Institute). All tests of hypothesis were 2-tailed, and $P < 0.05$ was considered statistically significant. There was no imputation for missing data. A sample size of 62 infants per group was estimated to be sufficient to observe a reduction in feeding interruptions from the local baseline of ∼30% (for exclusively mother's milk–fed VLBW infants with BMBF) to 10% (with HMBF) (2), with 80% power and an α level of 0.05. This effect size was agreed a priori to be clinically meaningful and is in the range observed by Assad et al. (27), as their NICU transitioned from the use of bovine milk–based formulas and fortifiers to human milk–based products.

Baseline continuous and categoric variables were analyzed through t tests and chi-square tests, respectively. Categoric outcome variables (e.g., infants with feeding intolerance, affirmative for the dichotomous mortality and morbidity index,

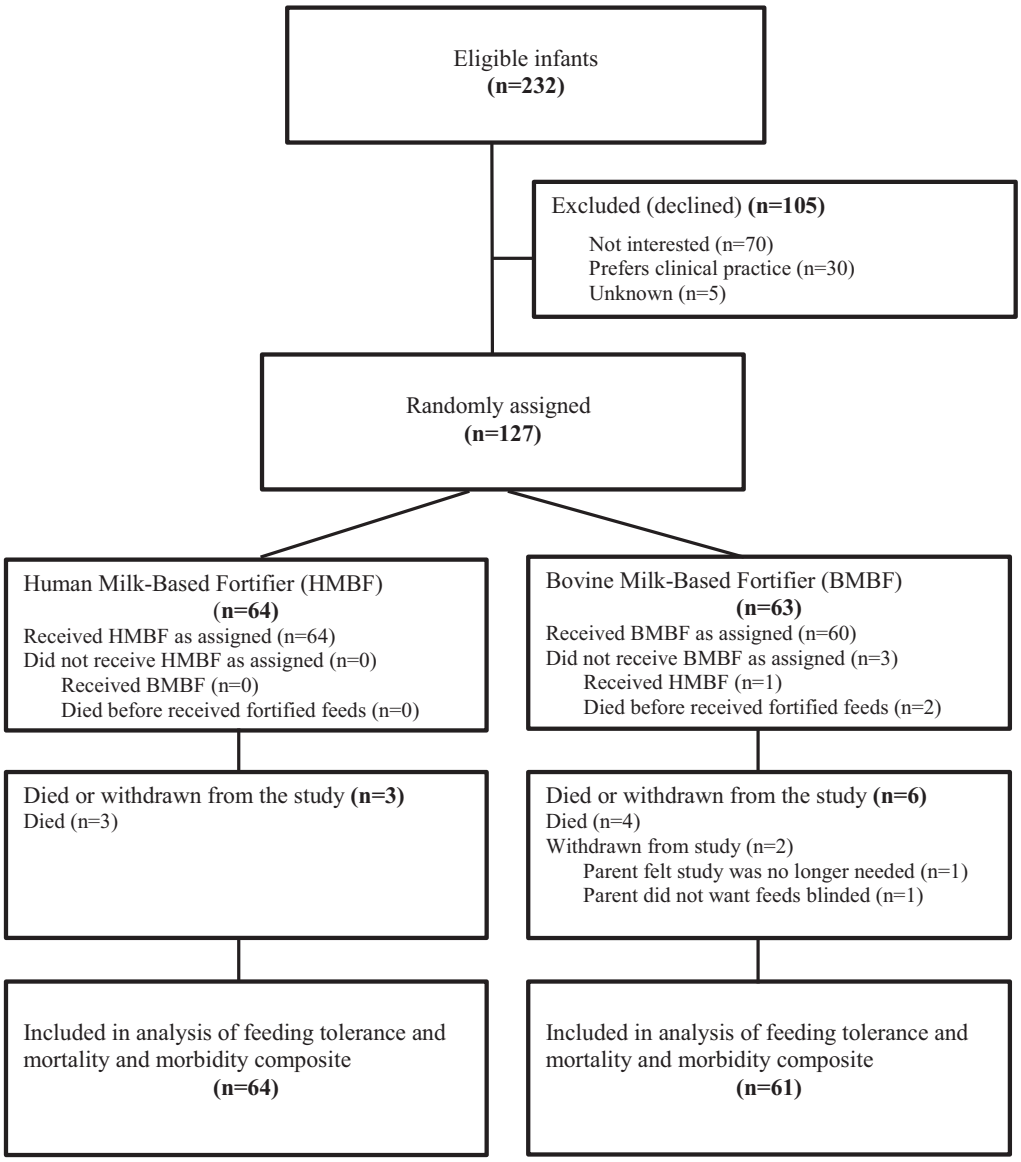

FIGURE 1 Flow diagram of infants through a randomized trial comparing HMBF and BMBF for nutrient-enriching mother's milk and supplemental donor milk. BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier.

individual morbidities such as late-onset sepsis or NEC) were analyzed between groups through the use of logistic regression, both unadjusted and then as sample size permitted, adjusted for birth weight group (<1000 and 1000–1249 g). Continuous outcomes for feeding metrics (e.g., days of PN, days in the feeding intervention, percentage of donor milk consumed) were analyzed through the use of linear regression models adjusted for birth weight group or Wilcoxon rank-sum tests where data were not and could not be transformed to produce a normal distribution. Given the small number of patients recruited at SickKids, a surgical referral center, sensitivity analyses were performed on measures of feeding tolerance excluding these infants.

Data collected at multiple time points (e.g., growth, log transformed fecal calprotectin) were analyzed through the use of linear repeated-measures regression models (PROC MIXED), with treatment, birth weight group, and time as the main effects and the interaction terms of treatment × time and treatment × birth weight group. In addition, for growth, sex and the interaction term of treatment × sex were included. In all models, if interaction terms were not statistically significant, they were removed from the model and the analyses were rerun.

RESULTS

Study infants

The families of 127 of 232 (54.7%) eligible infants agreed to participate, and these infants were randomly assigned to receive HMBF ($n = 64$) or BMBF ($n = 63$) (**Figure 1**). One infant randomly assigned to the BMBF group was incorrectly assigned and received HMBF throughout the intervention. Data from this infant were analyzed as randomized. Two infants randomly assigned to the BMBF group died prior to receiving fortifier and were not included in the analyses of the outcomes. The baseline characteristics of the infants and

TABLE 1
Baseline characteristics of study infants and their families[1]

Characteristics	HMBF ($n = 64$)	BMBF ($n = 63$)
Birth characteristics		
Sex, *n* (%)		
Female	39 (60.9)	34 (54.0)
Male	25 (39.1)	29 (46.0)
Weight, g	887 ± 208[2]	889 ± 196
Gestational age,[3] wk	27.9 ± 2.7	27.5 ± 2.3
Multiple birth status, *n* (%)		
Singleton	42 (65.6)	39 (61.9)
Multiple	22 (34.4)	24 (38.1)
Small for gestational age, *n* (%)	13 (20.3)	16 (25.4)
Received antenatal steroids, *n* (%)	56 (87.5)	56 (88.9)
SNAP-II score[4]	13.3 ± 11.2	14.2 ± 10.9
Apgar score at 5 min	7.4 ± 2.1 ($n = 62$)	7.3 ± 2.3
Mother's age, y	32.9 ± 4.7	33.7 ± 5.8
Mother's education, *n* (%)		
High school or less	9 (14.5)	10 (16.1)
College or vocational diploma	23 (37.1)	23 (37.1)
Baccalaureate	22 (35.5)	20 (32.3)
Postbaccalaureate	8 (12.9)	9 (14.5)
Mother's ethnicity, *n* (%)		
European	25 (40.3)	18 (29.0)
South Asian	22 (35.5)	34 (54.8)
East Asian	7 (11.3)	3 (4.8)
Mixed or other	8 (12.9)	7 (11.3)
Maternal parity, *n* (%)		
1	43 (67.2)	38 (60.3)
>1	21 (32.8)	25 (39.7)
Family living below poverty line,[5] *n* (%)	14 (22.6) ($n = 62$)	16 (25.8) ($n = 62$)
Study day 1 characteristics[6]		
Weight, g	1032 ± 208	1002 ± 237
Length, cm	36.0 ± 3.0	35.9 ± 2.7 ($n = 62$)
Head circumference, cm	25.0 ± 2.0	25.0 ± 1.8 ($n = 62$)
Postnatal day	16.8 ± 10.1	15.6 ± 8.6
Days on enteral nutrition[7]	14.5 ± 7.9	13.4 ± 6.8
Days on parenteral nutrition[7]	16.3 ± 10.2	15.3 ± 8.6

[1]Continuous baseline variables were analyzed by *t* tests and categoric variables by chi-square tests. No statistically significant differences were found between treatment groups. BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier.
[2]Mean ± SD (all such values).
[3]Gestational age determined by maternal estimates of her last menstrual period. If early ultrasound prediction differed by ≥2 wk, the gestational age estimate derived from early ultrasound was used.
[4]Score for Neonatal Acute Physiology II. Higher values indicate greater neonatal risk and newborn illness.
[5]Based on 2012 Statistics Canada family size–adjusted cut-off values. For example, a family of 4 with a household income less than CAN$37,052 would be living below the poverty line. In 2012, this would equal the same amount in U.S. dollars and in 2015, US$29,816.
[6]The day nutrient fortification of human milk commenced.
[7]Birth to study day 1.

mothers were comparable between the groups, and showed diversity of ethnicity, education, and income (**Table 1**). The mean ± SD birth weight and gestational age of the infants were 888 ± 201 g and 27.7 ± 2.5 wk, respectively. Study day 1 occurred on mean postnatal day 16 ± 9.

Feeding intervention

Infants in the HMBF and BMBF groups remained in the feeding intervention for a median of 48 d (IQR: 30, 61 d) and 51 d (IQR: 39, 62 d), respectively ($P = 0.43$). No infant's feeding assignment was unblinded either proactively or, to the best of our knowledge, inadvertently. No infant in either arm of the study received supplemental formula instead of donor milk prior to the 3-d weaning period at the end of the feeding intervention. Seven infants died during the intervention and 2 infants were withdrawn from the study with no further data collection (Figure 1). Sixteen infants discontinued the feeding intervention early, but collection of their data continued. This subset of infants remained in the feeding intervention for a median of 34 d (IQR: 18, 48 d). Nine (14.1%) infants in the HMBF group discontinued the intervention early because of feeding intolerance ($n = 5$) or poor growth ($n = 4$), whereas 3 (4.9%) infants in the BMBF group discontinued the intervention early because of poor growth ($P = 0.13$). No infant in the BMBF group discontinued the feeding intervention early because of feeding intolerance. Other reasons for early discontinuation of the feeding intervention included transfer to a nonparticipating NICU ($n = 2$, BMBF), palliative care ($n = 1$, HMBF), and thickening of feeds ($n = 1$, HMBF).

Twenty-eight (43.8%) infants in the HMBF group and 35 (57.4%) in the BMBF group required supplemental donor milk during the intervention ($P = 0.13$). As expected because of differential displacement of the 2 fortifiers on mother's milk, a smaller percentage of supplemental donor milk was fed to the infants in the HMBF group [29.4% (IQR: 5.1%, 83.2%)] compared with the BMBF group [66.1% (IQR: 24.7%, 96.8%)] ($P = 0.04$). The enteral feeds of 45 (70.3%) infants in the HMBF group and 40 (65.6%) in the BMBF group were nutrient-enriched above the target of 0.88 and 0.78 kcal/mL, respectively ($P = 0.70$).

Study outcomes

All infants in the HMBF group and 61 of 63 (96.8%) in the BMBF group had their feeding tolerance assessed. As mentioned above, 2 infants in the BMBF group died prior to receiving the feeding intervention. No statistically significant difference was identified in the percentage of infants with a feeding interruption (primary outcome, **Table 2**). The unadjusted risk difference was −6.2% (95% CI: −22.2%, 9.8%; $P = 0.45$). No other measures of feeding tolerance differed between groups; however, the 95% CIs were wide. These findings remained unchanged in sensitivity analyses that excluded infants enrolled at SickKids (**Supplemental Table 3**). Among the infants who experienced a feeding interruption, the median (IQR) days with the feeding interruption did not differ between the HMBF [2 d (IQR: 1, 3 d)] and BMBF [2 d (IQR: 1, 6 d)] groups ($P = 0.75$).

Of the infants randomly assigned to the HMBF and BMBF groups, 36% and 49%, respectively, scored affirmatively on the mortality and morbidity index (**Table 3**). The unadjusted risk difference was −13.4%, with a wide 95% CI of −30.4% to 4.0% ($P = 0.13$). In a preplanned exploratory analysis, fewer infants in the HMBF group had severe ROP (1.6%) than in the BMBF group (10.2%) [risk difference: −8.6% (95% CI: −16.9%, −0.02%); $P = 0.04$]. No other statistically significant differences in individual morbidities, including NEC, were observed between the groups.

TABLE 2
Percentage of infants with feeding intolerance during the feeding intervention[1]

	HMBF ($n = 64$)[2]	BMBF ($n = 61$)[2]	Unadjusted risk difference[3]	*P* value	Adjusted risk difference[3]	*P* value
Feeding interruption[4]	17 (26.6)	20 (32.8)	−6.2 (−22.2, 9.8)	0.45	−7.2 (−21.8, 7.4)	0.34
Enteral nutrition terminated and parenteral nutrition restarted	3 (4.7)	1 (1.6)	3.1 (−3.0, 9.1)	0.33	—	
Feedings withheld for a complete day						
Any cause	9 (14.1)	14 (23.0)	−8.9 (−22.5, 4.7)	0.20	−11.4 (−28.5, 5.7)	0.19
Not because of a clinical procedure/breastfeeding	7 (10.9)	10 (16.4)	−5.5 (−17.5, 6.6)	0.37	−7.6 (−23.4, 8.2)	0.34
Gastric residuals[5]	26 (40.6)	25 (41.0)	−0.4 (−17.6, 16.9)	0.97	−5.4 (−19.6, 8.9)	0.46
Abdominal distension[6]	51 (79.7)	52 (85.2)	−5.6 (−18.4, 7.7)	0.41	−6.4 (−19.4, 6.6)	0.33

[1]BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier.
[2]Values are *n* (%).
[3]Values are percentages (95% CIs). Differences between feeding groups were analyzed by logistic regression analyses with and without adjustment for birth weight stratum (<1000, 1000–1249 g). Adjusted analyses were not performed for "Enteral nutrition terminated and parenteral nutrition restarted" because of insufficient sample size.
[4]A major feeding interruption was defined as feedings held for ≥12 h or feeds reduced by >50% (mL/kg per day) not because of a clinical procedure, or transitioning to the breast.
[5]Defined as >50% of the prefeed volume for bolus or >50% of the hourly volume for slow bolus and continuous feeds.
[6]Defined as a measurement on any day >2 cm from the average measurement on the previous day.

No statistically significant differences were observed in fecal calprotectin concentrations between the HMBF [115.8 μg/g (IQR: 46.7, 277.5 μg/g)] and BMBF [66.5 μg/g (IQR: 17.0, 179.0 μg/g)] groups during the week prior to study day 1 (**Supplemental Figure 1**). Likewise, no statistically significant differences were observed between the HMBF [114.7 μg/g (IQR: 63.4, 197.1 μg/g)] and BMBF [119.6 μg/g (IQR: 71.3, 158.7 μg/g)] groups 1 wk after study day 1 or between the HMBF [115.1 μg/g (IQR: 49.6, 202.8 μg/g)] and BMBF [143.7 μg/g (IQR: 66.1, 213.9 μg/g)] groups 2 wk thereafter.

Anthropometric measures were comparable between the fortifier groups at study day 1 and at the end of the feeding intervention, whether expressed as absolute measures or *z* scores (**Table 4**). Infants in the BMBF group had more rapid weight gain during the intervention than infants in the HMBF group ($P = 0.04$, **Supplemental Figure 2**). However, neither length ($P = 0.20$) nor head circumference ($P = 0.10$) gains differed over time. No statistically significant treatment differences over time were found between the groups when anthropometric measures were converted to *z* scores (**Supplemental Figure 3**).

TABLE 3
Mortality and major morbidity diagnosed on or after study day 1 to hospital discharge[1]

	HMBF[2]	BMBF[2]	Unadjusted risk difference[3]	*P* value	Adjusted risk difference[3]	*P* value
Mortality and morbidity index[4]	23/64 (35.9)	30/61 (49.2)	−13.4 (−30.4, 4.0)	0.13	−14.5 (−29.9, 1.0)	0.07
Death	3/64 (4.7)	4/61 (6.6)	−1.9 (−10.0, 6.2)	0.65	—	
Late-onset sepsis	8/64 (12.5)	14/61 (23.0)	−10.5 (−23.8, 2.9)	0.12	−11.7 (−24.7, 1.3)	0.07
Necrotizing enterocolitis						
All stages	3/64 (4.7)	6/61 (9.8)	−5.2 (−14.2, 3.9)	0.27	—	
Stage ≥II	3/64 (4.7)	3/61 (4.9)	−0.2 (−7.7, 7.3)	0.95	—	
Oxygen support at 36 wk postconception	16/64 (25.0)	18/61 (29.5)	−4.5 (−20.1, 11.1)	0.57	−2.0 (−13.3, 9.3)	0.73
Severe retinopathy of prematurity	1/62 (1.6)	6/59 (10.2)	−8.6 (−16.9, −0.02)	0.04	—	
Severe brain injury[5]	11/64 (17.2)	8/61 (13.1)	4.1 (−8.5, 16.6)	0.52	—	

[1]The median duration of time between study day 1 (first day of nutrient fortification) and hospital discharge was 64 d (IQR: 43, 83 d) for infants in the HMBF group and 63 d (IQR: 49, 90 d) for infants in the BMBF group. BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier; ROP, retinopathy of prematurity.
[2]Values are *n*/total (%).
[3]Values are percentages (95% CIs). Differences between feeding groups were analyzed by logistic regression analyses with and without adjustment for birth weight stratum (<1000, 1000–1249 g). Adjusted analyses were not performed on all outcomes because of insufficient sample size.
[4]The mortality and major morbidity index is a dichotomous variable that is affirmative if death or any one of the following occurred: confirmed late-onset sepsis (confirmed by positive culture in blood, cerebrospinal fluid, or suprapubic urine ≥5 d), necrotizing enterocolitis (Bell Stage ≥ II), chronic lung disease (oxygen support at 36 wk), or ROP (international stage 4/5, laser or intraocular antivascular injection).
[5]Defined as echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, or ventriculomegaly with or without intraventricular hemorrhage.

TABLE 4
Anthropometric data of infants who survived initial hospitalization[1]

	Unadjusted means (95% CI)		Change during intervention-adjusted effect[2] (95% CI)	
Measure	HMBF ($n = 61$)	BMBF ($n = 57$)	HMBF ($n = 61$)	BMBF ($n = 57$)
Weight, g				
Study day 1	1013 (960, 1065)	998 (935, 1061)	1124 (990, 1258)	1303 (1150, 1456)
End of intervention	2136 (2008, 2264)	2300 (2158, 2443)	—	—
Length, cm				
Study day 1	35.9 (35.1, 36.7)	36.0 (35.3, 36.7)	7.3 (6.3, 8.3)	8.1 (7.1, 9.2)
End of intervention	43.2 (42.5, 44.0)	44.2 (43.3, 45.1)	—	—
Head circumference, cm				
Study day 1	25.0 (24.5, 25.5)	25.0 (24.5, 25.5)	6.2 (5.5, 6.8)	6.8 (6.1, 7.4)
End of intervention	31.2 (30.7, 31.7)	31.8 (31.2, 32.4)	—	—
Weight-for-age z score				
Study day 1	−1.2 (−1.5, −1.0)	−1.1 (−1.3, −0.9)	−0.4 (−0.8, 0.0)	−0.2 (−0.5, 0.2)
End of intervention	−1.7 (−2.0, −1.3)	−1.3 (−1.6, −1.0)	—	—
Length-for-age z score				
Study day 1	−1.4 (−1.7, −1.0)	−1.0 (−1.3, −0.8)	−0.5 (−1.0, 0.0)	−0.6 (−1.0, −0.1)
End of intervention	−1.8 (−2.2, −1.5)	−1.6 (−1.9, −1.2)	—	—
Head circumference-for-age z score				
Study day 1	−1.8 (−2.1, −1.5)	−1.5 (−1.7, −1.2)	0.5 (0.2, 0.9)	0.5 (0.2, 0.9)
End of intervention	−1.3 (−1.5, −1.0)	−0.9 (−1.2, −0.6)	—	—

[1]Data were analyzed through the use of linear repeated-measures regression models with the main effects of treatment, time (as a categoric variable), birth weight group (<1000, 1000–1249 g), and sex, and the interactions of treatment × time, treatment × birth weight group, and treatment × sex. The treatment × birth weight group and treatment × sex interaction terms were removed as not statistically significant; analyses were rerun without these interaction terms. A statistically significant effect of time was observed for all other anthropometric measures ($P < 0.05$). No statistically significant interactions of treatment × time were observed. The median (IQR) duration of the intervention for infants who survived initial hospitalization in the HMBF group was 49 d(33, 61 d), and in the BMBF group it was 51 d(39, 62 d). BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier.

[2]Adjusted for sex and birth weight group (<1000, 1000–1249 g).

DISCUSSION

Results from this RCT indicate that when mother's milk, with donor milk as a supplement, is nutrient-enriched with an HMBF, there is no difference in feeding tolerance among infants born weighing <1250 g than when it is nutrient-enriched with a BMBF. Specifically, no statistically significant differences were found in the percentage of infants with a feeding interruption and, among infants who experienced a feeding interruption, there was no difference in the number of days on which this occurred. In addition, no statistically significant differences were identified between groups for days of PN, days to full enteral feeding, and percent of infants who had their enteral feeds discontinued with resumption of PN. Finally, whereas 5 of 64 (8%) infants in the HMBF group discontinued the feeding intervention early because of feeding intolerance, no infants in the BMBF group did so.

Similarly, in the present study, no statistically significant differences were observed between infants in the HMBF (23/64, 35.9%) and BMBF (30/61, 49.2%) groups for a dichotomous mortality and morbidity index which included preselected serious morbidities that have been reported in the literature to be inversely related to the provision of human milk (2, 3, 19, 20). Important in relation to the generalizability of the findings from this study, the incidence of serious morbidity was similar to that reported by the Canadian Neonatal Network (CNN) over the 2014 and 2015 time frame during which the RCT was conducted (13). The CNN captures key clinical outcomes on most infants born weighing <1250 g in Canada. Specifically, components of the morbidity index, including rates of late-onset sepsis [CNN compared with present study: 14.5 (2014), 14.8 (2015) compared with 17.6], chronic lung disease (26.6, 25.7 compared with 27.2), NEC (7.6, 6.4 compared with 7.2), and ROP requiring treatment (7.0, 7.5 compared with 5.8) in the current study are quite comparable to those reported by CNN. In preplanned exploratory analyses, no statistically significant differences were observed between treatments in the individual components of this composite except severe ROP.

This is the first published RCT to compare the efficacy of HMBF and BMBF in the absence of formula, which is the recommended standard of care in North America (11, 12); hence, comparison of our study findings with those of others needs to be approached with caution. Two published RCTs have examined the efficacy of HMBF; however, they used supplemental formula feeding in the BMBF arm of their studies, which is not the current standard of care (9, 10, 28). In the first, infants born weighing ≤1250 g and fed mother's milk, supplemental donor milk, and HMBF ($n = 138$) had a reduction in the probability of PN on any given day and lower rates of NEC (6% compared with 16%, $P = 0.02$) compared with those fed mother's milk with BMBF and supplemental formula ($n = 69$). Of note, the incidence of NEC in the intervention arm of this trial is similar to that of the current study and the Canadian national incidence for infants born weighing <1250 g (13). In the second trial, infants born weighing ≤1250 g whose mothers did not intend to provide milk were randomized to receive donor milk and HMBF ($n = 29$) or formula ($n = 24$) (28). A

statistically significant reduction in the days of PN and surgical NEC were observed in the donor milk with HMBF group (27 d PN, 0 case surgical NEC) compared with the formula group (36 d PN, 4 cases surgical NEC). In a retrospective review, Assad et al. (27) reported that, as their NICU transitioned from bovine milk–based formulas and fortifiers to human milk–based products, the percentage of infants who had enteral feeds withheld differed: formula only, 34%; mother's milk, supplemental formula, and BMBF, 63%; mother's milk, supplemental donor milk, and BMBF, 34%; and exclusively human milk, 6%. Reductions in days of PN and days to full feeds with the exclusive human milk diet were also observed during the transition. The contribution to these findings of unmeasured factors, such as the caregiver's perception of tolerance or the increase in mother's milk provision observed nationally over the course of the study, is unclear (29).

Despite differences in the feeding protocols and estimated nutrient compositions of the feeds, infants in both arms of our study grew at similar rates. Given that both the caloric value and protein density of the enteral feedings in the HMBF arm of the study were greater than those in the BMBF arm at each stage of the feeding protocol, one might have anticipated greater growth in the HMBF group. Although discussion surrounding the use of HMBF and BMBF to date has focused on their protein source, there are marked differences in their other ingredients, their micronutrient composition, and how the fortifiers are processed and heat-treated, many of which could impact the availability of energy and protein to an infant (Supplemental Table 2) (30, 31). It is known that infant growth differs by enteral feeding type (mother's milk, donor milk, formula), and may additionally be affected by the fortifier used if a standard feeding protocol is used without regard to the composition of the feeding (17, 18, 28, 32).

It is tempting to speculate that differences in the nutrient composition of the fortifiers used herein could account for the reduction in severe ROP in the HMBF group. A recent systematic review concluded that supplemental vitamin A, vitamin E, or inositol showed evidence, at least in observational studies, of being associated with a reduction in all stages of, or severe, ROP (33). However, BMBF contributed more vitamin A and E than HMBF, and whereas there is a small amount of inositol in BMBF, there is none in HMBF.

One strength of this study is that donor milk was used exclusively as a supplement to mother's milk, as is recommended (11, 12). Furthermore, the blinding of feeding assignments minimized the possibility of investigator or caregiver bias about tolerance to the fortifiers. Biases leading to group differences in the reporting of study outcomes in unblinded feeding studies are well known (34). We acknowledge that this study, like the published RCTs that used formula as a supplement, was not designed to detect differences in individual morbidities, including NEC Stage ≥II. As described earlier, given the required sample size, cost, and absence of clinical data that reflected current clinical practice, it would have been challenging to conduct an RCT with NEC as the primary endpoint. Further, although no statistically significant differences between groups were found in the percentage of infants with a feeding interruption (primary outcome) or those affirmative for the mortality and morbidity index (secondary outcome), the 95% CIs around these estimates were wide. In the present study, the percentage risk difference in feeding interruptions between treatments was less than the predefined minimally clinically important difference of 20%. Future blinded RCTs with a larger sample size would be necessary to detect the smaller effect size reported herein (−6.2%). A larger sample size would also allow for investigation of whether different subgroups of infants born weighing <1250 g differentially respond to fortifier type. An additional limitation of the study is that it does not address whether differences in feeding tolerance would be observed if nutrient fortification of human milk commenced after an enteral feeding volume of 40 mL/kg per day was achieved (e.g., the first fortified feed was given at 60 mL/kg per day), which is current clinical practice using HMBF in some neonatal units. Assuming no issues with feeding tolerance and hence advancement of enteral feeds, fortification of human milk with the 60 mL/kg per day enteral feed would allow fortification of milk ∼2 d earlier.

In conclusion, among infants born weighing <1250 g, there was no difference in feeding tolerance between neonates who received HMBF and those who received BMBF. In a high mother's milk use setting where donor milk is used as a supplement, the results of this trial suggest that routine use of HMBF over BMBF to improve feeding tolerance should not be considered a treatment goal.

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The authors' responsibilities were as follows—DLO, AK, CT, PSS, and SU: designed the research; DLO and AK: analyzed the data; DLO and SU: have primary responsibility for the final content; and all authors: conducted the research, participated in writing and critical revision of the manuscript for important intellectual content, and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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Corrigendum to O'Connor et al. Nutrient enrichment of human milk with human and bovine milk–based fortifiers for infants born weighing < 1250 g: a randomized clinical trial. Am J Clin Nutr 2018;108:108–16.

In Table 3, some of the values in the row for "Mortality and morbidity index" were incorrect. In the original Table 3, each infant was classified as being affirmative for the "mortality and morbidity index" if chronic lung disease was present using either National Institutes of Health criteria (e.g., oxygen support for ≥28 days) or oxygen support at 36 weeks (1,2). As indicated in the methods, the authors intended to only use oxygen support at 36 weeks. A corrected version of Table 3 is provided below. The overall conclusions of the article are unaffected by these changes. The authors regret any inconvenience caused by this error.

TABLE 3 Mortality and major morbidity diagnosed on or after study day 1 to hospital discharge[1]

	HMBF[2]	BMBF[2]	Unadjusted risk difference[3]	*P* value	Adjusted risk difference[3]	*P* value
Mortality and morbidity index[4]	23/64 (35.9)	30/61 (49.2)	–13.4 (–30.4, 4.0)	0.13	–14.5 (–29.9, 1.0)	0.07
Death	3/64 (4.7)	4/61 (6.6)	–1.9 (–10.0, 6.2)	0.65	—	
Late-onset sepsis	8/64 (12.5)	14/61 (23.0)	–10.5 (–23.8, 2.9)	0.12	–11.7 (–24.7, 1.3)	0.07
Necrotizing enterocolitis						
All stages	3/64 (4.7)	6/61 (9.8)	–5.2 (–14.2, 3.9)	0.27	—	
Stage ≥ II	3/64 (4.7)	3/61 (4.9)	–0.2 (–7.7, 7.3)	0.95	—	
Oxygen support at 36 wk postconception	16/64 (25.0)	18/61 (29.5)	–4.5 (–20.1, 11.1)	0.57	–2.0 (–13.3, 9.3)	0.73
Severe retinopathy of prematurity	1/62 (1.6)	6/59 (10.2)	–8.6 (–16.9, –0.02)	0.04	—	
Severe brain injury[5]	11/64 (17.2)	8/61 (13.1)	4.1 (–8.5, 16.6)	0.52	—	

[1]The median duration of time between study day 1 (first day of nutrient fortification) and hospital discharge was 64 d (IQR: 43, 83 d) for infants in the HMBF group and 63 d (IQR: 49, 90 d) for infants in the BMBF group. BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier; ROP, retinopathy of prematurity.

[2]Values are *n*/total (%).

[3]Values are percentages (95% CIs). Differences between feeding groups were analyzed by logistic regression analyses with and without adjustment for birth weight stratum (<1000, 1000–1249 g). Adjusted analyses were not performed on all outcomes because of insufficient sample size.

[4]The mortality and major morbidity index is a dichotomous variable that is affirmative if death or any one of the following occurred: confirmed late-onset sepsis (confirmed by positive culture in blood, cerebrospinal fluid, or suprapubic urine ≥5 d), necrotizing enterocolitis (Bell Stage ≥ II), chronic lung disease (oxygen support at 36 wk), or ROP (international stage 4/5, laser or intraocular antivascular injection).

[5]Defined as echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, or ventriculomegaly with or without intraventricular hemorrhage.

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Corrigendum for O'Connor et al. Nutrient enrichment of human milk with human and bovine milk—based fortifiers for infants born weighing < 1250 g: a randomized clinical trial. Am J Clin Nutr 2018;108:108–16.

A corrigendum was published for Table 3 of this paper (Volume 110, Issue 2, Page 529, August 2019). The authors assumed, incorrectly, that the corrigendum link would be displayed adjacent to the abstract in PubMed as it is on the Oxford site where readers access the on-line version of the manuscript. Changes to the text below reflect the earlier corrigendum for Table 3 and will facilitate dissemination of a revised abstract through PubMed and other platforms and revision of the on-line version of the manuscript. We apologize for any confusion this error has caused.

In the Abstract results section (last sentence), the values in the brackets should read, "35.9% HMBF, 49.2% BMBF, adjusted $P = 0.07$."

In the Results (page 112, last paragraph, 1st sentence), the number "48%" should be changed to "36%"

In the Results (page 112, last paragraph), the second sentence should be revised to read, "The unadjusted risk difference was − 13.4%, with a wide 95% CI of − 30.4% to 4.0% ($P = 0.13$)."

In the Discussion (page 114, second paragraph, 1st sentence), the phrase, "HMBF (31/64, 48.4%)" should read, "HMBF (23/64, 35.9%)."

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Erratum for Mandaviya et al. Reply to P-A Dugué et al., Am J Clin Nutr 2020;111:230–31.

The first sentence of the letter-reply should refer to "Dugué et al" and point to the letter to the editor published in the January 2020 issue of the journal [Dugué et al. Overall lack of replication of associations between dietary intake of folate and vitamin B-12 and DNA methylation in peripheral blood, Am J Clin Nutr 2020;111:228–30, https://doi.org/10.1093/ajcn/nqz253].

doi: https://doi.org/10.1093/ajcn/nqaa059

Corrigendum to Long et al. Circulating folate concentrations and risk of coronary artery disease: a prospective cohort study in Chinese adults and a Mendelian randomization analysis. Am J Clin Nutr 2020;111:635–43.

Some of the values in **Table 4** were incorrect. The corrected tables appear below. Many values have changed, but the overall conclusions of the article are unaffected by these changes. The authors apologize for the error and for any confusion it may have caused.

Abstracts-Results

In the MR analysis, the OR of CAD per SD increase in genetically predicted serum folate was 1.00 (0.88, 1.14) and 0.88 (0.59, 1.32) for European and Chinese populations, respectively.

Results- MR analysis

Table 4 shows the characteristics of the folate-associated SNPs and their associations with folate concentrations and CAD risk. There was no evidence of possible association between genetically predicted folate concentrations and CAD risk: the OR for CAD per SD unit increment in the genetically predicted folate status was 1.00 (95% CI: 0.88, 1.14; $P = 0.95$). The association was not statistically significant in the sensitivity analyses using the weighted median method (OR: 1.00; 95% CI: 0.84, 1.19; $P = 0.99$), and MR-Egger method (OR: 0.22; 95% CI: 0.02, 2.10; $P = 0.19$). The MR-Egger approach did not detect directional pleiotropy (MR-

