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What are the causal effects of breastfeeding on IQ, obesity and blood pressure? Evidence from comparing high-income with middle-income cohorts

Marie-Jo A Brion,[1,2]* Debbie A Lawlor,[1,2] Alicia Matijasevich,[3] Bernardo Horta,[3] Luciana Anselmi,[3] Cora L Araújo,[3] Ana Maria B Menezes,[3] Cesar G Victora[3] and George Davey Smith[1,2]

[1]MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Bristol, UK, [2]School of Social and Community Medicine, University of Bristol, Bristol, UK and [3]Postgraduate Programme in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

*Corresponding author. MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK. E-mail: Marie-Jo.Brion@bristol.ac.uk

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Background A novel approach is explored for improving causal inference in observational studies by comparing cohorts from high-income with low- or middle-income countries (LMIC), where confounding structures differ. This is applied to assessing causal effects of breastfeeding on child blood pressure (BP), body mass index (BMI) and intelligence quotient (IQ).

Methods Standardized approaches for assessing the confounding structure of breastfeeding by socio-economic position were applied to the British Avon Longitudinal Study of Parents and Children (ALSPAC) ($N \simeq 5000$) and Brazilian Pelotas 1993 cohorts ($N \simeq 1000$). This was used to improve causal inference regarding associations of breastfeeding with child BP, BMI and IQ. Analyses were extended to include results from a meta-analysis of five LMICs ($N \simeq 10\,000$) and compared with a randomized trial of breastfeeding promotion.

Findings Although higher socio-economic position was strongly associated with breastfeeding in ALSPAC, there was little such patterning in Pelotas. In ALSPAC, breastfeeding was associated with lower BP, lower BMI and higher IQ, adjusted for confounders, but in the directions expected if due to socioeconomic patterning. In contrast, in Pelotas, breastfeeding was not strongly associated with BP or BMI but was associated with higher IQ. Differences in associations observed between ALSPAC and the LMIC meta-analysis were in line with those observed between ALSPAC and Pelotas, but with robust evidence of heterogeneity detected between ALSPAC and the LMIC meta-analysis associations. Trial data supported the conclusions inferred by the cross-cohort comparisons, which provided evidence for causal effects on IQ but not for BP or BMI.

Conclusion While reported associations of breastfeeding with child BP and BMI are likely to reflect residual confounding, breastfeeding may have causal effects on IQ. Comparing associations between populations with differing confounding structures can be used to improve causal inference in observational studies.

Keywords ALSPAC, breastfeeding, causation, cognition, cohort, Pelotas

Introduction

Determining causal effects on health and disease from observational epidemiology studies is often limited by problems with confounding. Even large studies with detailed confounder adjustment may still be affected by residual confounding.[1] Although randomized controlled trials (RCTs) are the 'gold standard' for causal inference in public health research, for many modifiable risk factors with potential causal effects, RCTs are not feasible or ethical. Furthermore, in disease prevention trials, there may be such a long lead-time between intervention and outcome that the very large and long-term follow-up studies that would be needed can only occasionally be carried out. Because of the ethical issues of 'experimenting' on participants and the costs of RCTs, one would also always want to conduct trials on interventions with the strongest prior evidence of having a likely causal effect. Therefore, leveraging the most robust causal inference possible from observational epidemiology is important.

Various methods for improving causal inference have been discussed previously.[2,3] These include maternal–paternal comparisons as tests of intrauterine effects,[2] comparing outcomes betweens siblings discordant for an exposure (e.g. mothers diabetic for one pregnancy but not the other or where mothers breastfed one sibling but not the other);[4,5] and a range of genetically informative approaches (including twin studies,[6–8] that can additionally explore confounding by genetic factors, assisted conception studies[9] and Mendelian randomization, which uses genetic information as instrumental variables for modifiable exposures[10]). The application of several different approaches to any particular research question, building upon standard conventional methods potentially improves the reliability of causal inferences.

This article explores an additional method of exploring residual confounding and improving causal inference, by comparing observational associations in a cohort from a high-income country (HIC) with those from low- or middle-income countries (LMIC), where confounding structures are known to differ.[11] This approach is based on the idea that if an observed association is causal, the association should be present in both cohorts, regardless of differing confounding structures. Associations that are not replicated in cohorts with differing confounding structures are likely to reflect residual confounding in the cohort reporting an association, particularly if the direction of the association is consistent with plausible sources of residual confounding. This has been suggested previously in several studies of non-Western populations where associations of breastfeeding and lower obesity, previously observed in high-income and Western cohorts, were not replicated.[12–14]

We develop this concept further by, first, directly comparing two cohorts [one from an HIC, the British Avon Longitudinal Study of Parents and Children (ALSPAC) and the other from a middle-income country, the Brazilian 1993 Pelotas cohort] with individual-level data, using a standardized approach for analyses between cohorts. Using this approach, we compare the confounding structure of breastfeeding between the two settings and explore associations of breastfeeding in relation to three child outcomes that have been reported in the literature: body mass index (BMI), blood pressure (BP) and cognitive function (IQ; Intelligence Quotient). Secondly, we extend this comparison to a recently published meta-analysis of breastfeeding in five LMIC cohorts.[15] Finally, inferences made from these cross-cohort comparisons will be compared with the results from a randomized trial of breastfeeding promotion[16,17] since, as highlighted, RCTs are the 'gold standard' for assessing causality in health research.

Methods

ALSPAC

Participants

ALSPAC is a geographically based prospective cohort study investigating the health and development of children.[18] Pregnant women residing in three health districts in the south west of England with an expected date of delivery between 1 April 1991 and 31 December 1992 were eligible to enrol. A total of 14 541 pregnant women were recruited and 13 678 had a live-born, singleton child. For this study, we excluded parents and children of multiple births. Ethical approval of the ALSPAC study was obtained from the ALSPAC Law and Ethics Committee and three Local Research Ethics Committees. From annual clinics that the whole cohort were invited to attend, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed at 7 years, BMI at 9 years and IQ at 4 years. Indicators of socioeconomic position included in this study were family income, maternal education, paternal education and family occupational social class. A full description of all variables is provided as Supplementary Data at *IJE* online. Data on breastfeeding in infancy are available for 10 665 children. Data on BP, BMI and IQ are available for 7430, 6868 and 6851 children, respectively. The main analyses exploring breastfeeding and child outcomes were carried out in 5193 (SBP/DBP), 4852 (BMI) and 4891 (IQ) children with data on breastfeeding, outcome and potential confounding factors.

Pelotas

Participants

Pelotas is situated in the extreme south of Brazil, near the Uruguayan border, with a population of approximately 320 000 urban inhabitants, where >99% of all births occur in a hospital. In 1993, the five maternity hospitals in the city were visited daily and 5249 live newborns were enrolled; only 16 mothers could not be interviewed. This cohort is described in detail elsewhere.[19] At 1 and 3 months, a systematic sample of 13% of the subjects was assessed. At 6 months, 1 year and 4 years, all low birth-weight infants plus a systematic sample of 20% of the remaining—including those visited at 1 and 3 months—were targeted for follow-up. Breastfeeding data were collected at these follow-ups and are available for 1419 children. At 11 years, the whole cohort was followed up at a home visit, where BMI ($N = 4442$) and BP ($N = 4434$) measurements were taken. Data on IQ are available in a subsample of children at 4 years ($n = 614$) who were invited to take part in detailed psychological assessments.[20] Indicators of socio-economic position included in this study were the same as those included in ALSPAC, that is, family income, maternal education, paternal education and family occupational social class. A full description of all variables is provided as Supplementary Data at *IJE* online. The main analyses were carried out on 1083 children for SBP and DBP, 1085 children for BMI and 506 children for IQ, with complete data on breastfeeding, outcome and potential confounding factors. Only singleton children were included in analyses.

Statistical analysis

Breastfeeding was analysed in grouped months and with never breastfed and breastfed for <1 month combined into a single category. This is because the number of infants never breastfed in Pelotas was extremely low (3%) and because there is substantial misclassification between the two categories.[21] We aimed to compare associations of socio-economic position and breastfeeding/child outcomes between ALSPAC and Pelotas. Since we were not able to transform the indicators of socio-economic position in each cohorts into variables with categories of equal sizes (such that they could be compared easily between the cohorts), we used indices of inequality [slope index of inequality (SII) for continuous outcomes; relative index of inequality (RII) for binary outcomes].[22] These indices (SII/RII) relate health outcomes to a measure of socio-economic position that takes into account the different proportions in each category. Each indicator of socio-economic position is converted into a variable represented by scores from 0 to 1, with each category corresponding to a score calculated as the mid-point for the proportion of participants in that category based on the cumulative distribution. Where 0 is the lowest socio-economic level and 1 is the highest level, the scores reflect the relative social position of individuals in that category; that is, the proportion of individuals with a lower socio-economic position. For example, if 10% of the participants from one cohort fall in the lowest category for income, participants in this group would be allocated a score of 0.05 (0.1/2). If 25% of the participants fall in the second category, participants in this category would be allocated a score of 0.225 ($0.1 + 0.25/2$), and so on. The SII/RII is then obtained by regressing each outcome measure on these 0 to 1 scores.[22] For continuous outcomes, linear regression was used giving the mean difference in the outcome measure in the highest level (1) compared with the lowest level (0) of the socio-economic variable. For binary outcomes, logistic regression was used giving the odds of the outcome in the highest socio-economic level (1) compared with the lowest (0). For the main analysis, associations of breastfeeding duration with child BP, BMI and IQ were explored using multiple linear regression, both unadjusted and then adjusted for child sex and indicators of socio-economic position (family income, maternal education, paternal education, occupational social class). All analyses involving BP were also adjusted for child height; however, as height may be a potential mediator of an association between breastfeeding and child BP, main associations were also repeated without this adjustment. To explore potential effects of missing data from loss to follow-up, associations of breastfeeding with indicators of socio-economic positions were analysed comparing both the restricted sample (with complete data on breastfeeding, all confounders and at least one outcome) with the maximal sample available. All Pelotas analyses were weighted to account for the over-sampling of low birth-weight infants. To compare associations in ALSPAC and Pelotas, we generated a summary association (per breastfeeding category difference, reflecting the linear trend from one category to the next) and then used a *Q*-test (obtained from the Stata metan command) to test for heterogeneity between these associations. These tests for heterogeneity were also carried out for comparisons between ALSPAC and the meta-analyses from five LMIC cohorts. Analyses were carried out using Stata 10 (Stata Corp, College Station, TX).

Results

Prevalence for durations of breastfeeding are displayed in Table 1, showing greater prevalence for each category of breastfeeding duration over 1 month in Pelotas compared with ALSPAC. In addition, there was a higher prevalence of any breastfeeding (96.8 vs 84.3%) and exclusive breastfeeding at 2

Table 1 Distribution of infants according to duration of any breastfeeding

Breastfeeding duration (months)	Prevalence (%)	
	Pelotas	ALSPAC
0 to <1	15.6	36.8
1 to <3	25.4	15.6
3 to <6	23.6	13.7
⩾6	35.3	33.9

For analyses, the categories of never breastfed and breastfed <1 month were merged as the prevalence of never breastfed in Pelotas was extremely low and there is substantial misclassification between these categories.[21]

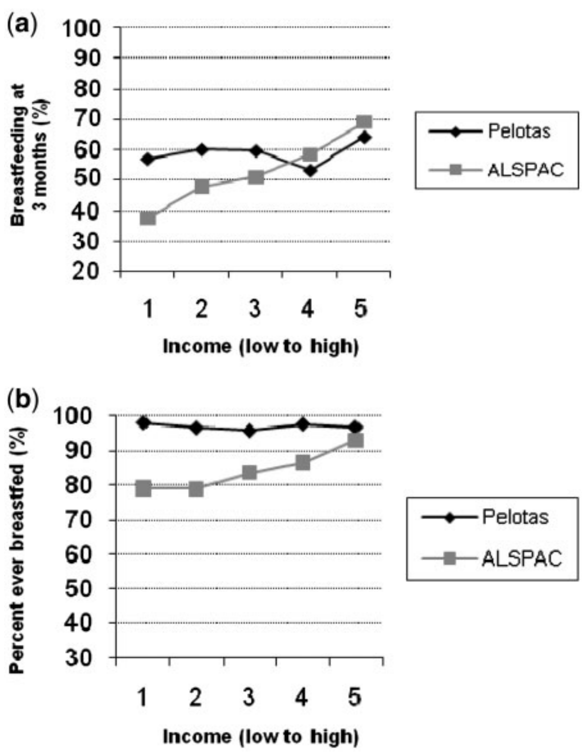

Figure 1 (**a**) Prevalence of breastfeeding (exclusive or non-exclusive) at 3 months by family income group and (**b**) prevalence of ever breastfed by family income

months (65.7 vs 38.3%) in Pelotas compared with ALSPAC.

Figure 1a and b shows the prevalence of breastfeeding at 3 months and of ever breastfed according to family income (a key indicator of socio-economic position). There was no association between family income and breastfeeding in Pelotas and a strong positive association in ALSPAC, with higher rates of breastfeeding observed in the higher income groups.

To compare between cohorts, the magnitude of the associations of socio-economic variables with breastfeeding at 3 months and child outcomes, RIIs and SIIs are presented in Table 2. For each of the indicators of socio-economic position, there was strong inequality in breastfeeding prevalences between the highest and lowest levels of socio-economic position in ALSPAC, which was not observed in Pelotas. RIIs for breastfeeding were between ∼3.5 and ∼8.5 times greater in ALSPAC compared with Pelotas. SIIs for child outcomes were similar between ALSPAC and Pelotas. In both cohorts, more favourable socio-economic position was associated with lower SBP and DBP and higher IQ. However, more favourable socio-economic position was associated with lower BMI in ALSPAC but 'higher' BMI in Pelotas. RIIs for breastfeeding were re-assessed using the maximum sample available (Supplementary Table S1 available as supplementary data at *IJE* online). These were compared with those presented here that are based on restricted samples (i.e. only included individuals with complete data on breastfeeding, all confounders and at least one outcome). Associations in the maximal sample were similar to those observed in the restricted sample, but with even greater differences between the ALSPAC and Pelotas samples (RIIs were between ∼4.5 and ∼10.5 times greater in ALSPAC compared with Pelotas).

Associations of breastfeeding with child BP, BMI and IQ are presented in Table 3. In ALSPAC, longer duration of breastfeeding was associated with lower SBP and DBP in children, in unadjusted analyses. However, in Pelotas, child SBP and DBP were not strongly associated with duration of breastfeeding. Similar findings were observed when associations are adjusted for indicators of socio-economic position. For BMI in ALSPAC, longer duration of breastfeeding was associated with lower child BMI; however, in Pelotas there was weaker evidence for associations of breastfeeding with child BMI, with a trend towards breastfeeding being associated with higher BMI. These findings also remained the same after adjusting for indicators of socio-economic position. For IQ, in both ALSPAC and Pelotas, longer duration of breastfeeding was associated with higher child IQ, with similar magnitudes of association between the two cohorts. These associations persisted in both cohorts after adjustment for indicators of socio-economic position. All Pelotas analyses were weighted to account for the oversampling of low-birth-weight infants: however, to ensure that there was no effect modification by low birth weight, main associations were stratified by low birth weight. Associations were consistent in low birth weight and normal birth weight children (P-values for interaction between birth weight and breastfeeding duration for SBP = 0.6, DBP = 0.8 and IQ = 0.96; see Supplementary Table S2 available as supplementary data at *IJE* online). For associations of breastfeeding with SBP and DBP, analyses were also repeated without adjustment for child height; results were not substantially altered (data not shown).

Table 2 Associations of indicators of socio-economic position with breastfeeding and child outcomes in ALSPAC and Pelotas 1993

		Index of inequality in health outcome by socio-economic position					
		ALSPAC			Pelotas		
Health outcome Breastfeeding[a]	**Indicator of socio-economic position**	*N*	OR (95% CI)	*P*	*N*	OR (95% CI)	*P*
Breastfeeding at 3 months	Income	5831	4.21 (3.43 to 5.16)	<0.001	1087	1.15 (0.72 to 1.82)	0.6
	Social class	5831	7.49 (6.12 to 9.18)	<0.001	1087	1.55 (0.96 to 2.51)	0.08
	Maternal education	5831	12.96 (10.50 to 16.00)	<0.001	1087	1.49 (0.91 to 2.45)	0.1
	Paternal education	5831	7.31 (6.00 to 8.89)	<0.001	1087	1.49 (0.91 to 2.43)	0.1
Child outcome[b]		***N***	**Difference in outcome (95% CI)**	***P***	***N***	**Difference in outcome (95% CI)**	***P***
Systolic BP (mmHg)	Income	5218	−2.04 (−2.90 to −1.17)	<0.001	1083	−4.02 (−6.72 to −1.32)	0.004
	Social class	5218	−2.41 (−3.29 to −1.53)	<0.001	1083	−2.42 (−5.24 to 0.40)	0.1
	Maternal education	5218	−3.09 (−3.95 to −2.23)	<0.001	1083	−3.60 (−6.55 to −0.65)	0.02
	Paternal education	5218	−2.50 (−3.36 to −1.65)	<0.001	1083	−2.73 (−5.70 to 0.24)	0.07
Diastolic BP (mmHg)	Income	5218	−1.41 (−2.05 to −0.76)	<0.001	1083	−2.70 (−4.82 to −0.58)	0.01
	Social class	5218	−1.08 (−1.74 to −0.42)	0.001	1083	−1.86 (−4.02 to 0.31)	0.1
	Maternal education	5218	−1.76 (−2.41 to −1.11)	<0.001	1083	−1.87 (−4.28 to 0.53)	0.1
	Paternal education	5218	−1.40 (−2.13 to −0.85)	<0.001	1083	−2.21 (−4.54 to 0.12)	0.06
BMI (kg/m^2)	Income	4867	−0.53 (−0.81 to −0.24)	<0.001	1085	1.52 (0.75 to 2.28)	<0.001
	Social class	4867	−0.58 (−0.87 to −0.28)	<0.001	1085	0.83 (0.00 to 1.66)	0.05
	Maternal education	4867	−0.84 (−1.13 to −0.56)	<0.001	1085	1.25 (0.39 to 2.11)	0.004
	Paternal education	4867	−0.90 (−1.18 to −0.62)	<0.001	1085	1.59 (0.76 to 2.42)	<0.001
IQ	Income	4904	14.49 (12.89 to 16.08)	<0.001	507	13.17 (8.52 to 17.83)	<0.001
	Social class	4904	16.78 (15.15 to 18.40)	<0.001	507	16.86 (11.94 to 21.78)	<0.001
	Maternal education	4904	21.23 (19.70 to 22.77)	<0.001	507	20.86 (16.05 to 25.67)	<0.001
	Paternal education	4904	20.28 (18.75 to 21.81)	<0.001	507	12.41 (7.30 to 17.52)	<0.001

[a]For breastfeeding as an outcome (binary), indices of inequality were assessed using logistic regression; associations reflect odds ratios for still breastfeeding at 3 months in the highest socioeconomic position (SEP) level vs the lowest level.

[b]For child outcomes (continuous variables), indices of inequality were assessed using linear regression; associations reflect mean difference in outcome in the highest SEP level vs the lowest. SBP and DBP are adjusted for height at measurement.

OR, odds ratio; CI, confidence interval.

Table 3 Associations of breastfeeding with child BP, BMI and IQ in the ALSPAC and Pelotas cohorts

					Mean difference in outcome by breastfeeding duration category				
Outcome	**Cohort (age at measure)**	***N***	**Breastfeeding duration**	**Unadjusted mean**	Unadjusted[a] β (95% CI)	*P* trend	Adjusted[b] β (95% CI)	***P* trend**
SBP (mmHg)	ALSPAC (7 years)	5193	0 to <1 month	99.5	Reference	<0.001	Reference	0.001
			1 to <3 months	98.7	−0.89 (−1.63 to −0.15)		−0.69 (−1.44 to 0.05)	
			3 to <6 months	99.2	−0.52 (−1.28 to 0.24)		−0.05 (−0.83 to 0.73)	
			⩾6 months	97.9	−1.78 (−2.35 to −1.21)		−1.16 (−1.78 to −0.54)	
	Pelotas (11 years)	1083	0 to <1 month	102.4	Reference	0.5	Reference	0.7
			1 to <3 months	101.7	−0.70 (−3.04 to 1.64)		−0.81 (−3.15 to 1.53)	
			3 to <6 months	100.0	−2.02 (−4.48 to 0.40)		−1.99 (−4.46 to 0.47)	
			⩾6 months	102.1	−0.68 (−3.00 to 1.63)		−0.50 (−2.82 to 1.83)	
DBP (mmHg)	ALSPAC (7 years)	5193	0 to <1 month	56.8	Reference	<0.001	Reference	0.04
			1 to <3 months	56.2	−0.66 (−1.21 to −0.10)		−0.57 (−1.12 to −0.13)	
			3 to <6 months	56.5	−0.38 (−0.94 to 0.19)		−0.10 (−0.68 to 0.48)	
			⩾6 months	56.0	−0.90 (−1.33 to −0.47)		−0.57 (−1.03 to −0.10)	
	Pelotas (11 years)	1083	0 to <1 month	64.2	Reference	0.99	Reference	0.9
			1 to <3 months	62.9	−1.31 (−3.19 to 0.57)		−1.39 (−3.26 to 0.48)	
			3 to <6 months	62.3	−1.68 (−3.64 to 0.28)		−1.68 (−3.64 to 0.28)	
			⩾6 months	64.0	−0.42 (−2.25 to 1.41)		−0.29 (−2.12 to 1.54)	
BMI (kg/m^2)	ALSPAC (9 years)	4852	0 to <1 month	17.95	Reference	<0.001	Reference	<0.001
			1 to <3 months	17.77	−0.17 (−0.42 to 0.07)		−0.13 (−0.38 to 0.11)	
			3 to <6 months	17.52	−0.42 (−0.67 to −0.18)		−0.35 (−0.60 to −0.10)	
			⩾6 months	17.37	−0.58 (−0.77 to −0.39)		−0.46 (−0.66 to −0.26)	
	Pelotas (11 years)	1085	0 to <1 month	18.5	Reference	0.1	Reference	0.2
			1 to <3 months	18.3	−0.18 (−0.90 to 0.54)		−0.12 (−0.84 to 0.59)	
			3 to <6 months	18.0	−0.44 (−1.16 to 0.27)		−0.42 (−1.14 to 0.29)	
			⩾6 months	18.9	0.46 (−0.24 to 1.16)		0.40 (−0.30 to 1.10)	
IQ	ALSPAC (8 years)	4891	0 to <1 month	101.1	Reference	<0.001	Reference	<0.001
			1 to <3 months	104.0	2.82 (1.45 to 4.18)		1.09 (−0.19 to 2.37)	
			3 to <6 months	107.0	5.87 (4.46 to 7.28)		2.13 (0.79 to 3.47)	
			⩾6 months	109.5	8.40 (7.33 to 9.47)		2.90 (1.82 to 3.98)	
	Pelotas (4 years)	506	0 to <1 month	89.1	Reference	<0.001	Reference	<0.001
			1 to <3 months	91.0	1.88 (−2.36 to 6.10)		1.74 (−2.01 to 5.48)	
			3 to <6 months	95.4	6.31 (1.73 to 10.90)		5.74 (1.62 to 9.85)	
			⩾6 months	95.8	6.71 (2.64 to 10.77)		5.65 (2.02, 9.27)	

[a]SBP and DBP adjusted for height at measurement.
[b]Adjusted models include child sex, family income, maternal education, paternal education, family occupational social class and (for SBP and DBP) height at measurement.
CI, confidence interval.

Figure 2a and b displays comparisons of breastfeeding associations between ALSPAC and Pelotas, and between ALSPAC and the large LMIC consortium (COHORTS) meta-analyses ($N > 10\,000$).[15] The latter comparison supported the trends observed in the smaller ALSPAC–Pelotas comparison, i.e. that associations of breastfeeding with SBP, DBP and BMI are not observed in LMIC cohorts. Although tests for heterogeneity between ALSPAC–Pelotas breastfeeding associations suggest differences were robust for BMI (P heterogeneity = 0.009) this was not the case for SBP (P heterogeneity = 0.6) and DBP (P heterogeneity = 0.5). However, with the larger sample from the COHORTS consortium, differences between ALSPAC and the LMIC meta-analyses were detected for associations with SBP (P heterogeneity <0.001), DBP (P heterogeneity = 0.005) and BMI (P heterogeneity <0.001). For IQ, associations with breastfeeding were consistent between ALSPAC and Pelotas (P-values for heterogeneity = 0.5 and 0.09 for unadjusted and adjusted associations, respectively). IQ was not reported in the COHORTS consortium meta-analysis.

As associations may be different for prolonged breastfeeding, analyses were repeated exploring associations of breastfeeding for >1 year with each outcome. Crude and adjusted associations are presented in Supplementary Table S2 (available as supplementary data at *IJE* online). In ALSPAC, associations of breastfeeding for >1 year were generally more strongly associated with child outcomes than breastfeeding ⩽1 year (both versus no breastfeeding), but were in the same direction as that reported above for breastfeeding duration using categories up to 6 months. In Pelotas, stronger associations were observed for breastfeeding ⩽1 year compared with ⩾1 year with directions consistent with those observed in ALSPAC.

In Table 4, the results of ALSPAC and Pelotas comparisons for breastfeeding associations with BP, BMI and IQ, are compared with results from a breastfeeding promotion RCT, in which randomization to breastfeeding promotion resulted in much longer duration of any and exclusive breastfeeding compared with the control group.[16] The results from this RCT can be considered the gold-standard test of the true causal effects of breastfeeding on the outcomes that we have assessed here. Consistent with our cohort comparisons, the trial found that breastfeeding increased childhood intelligence[17] but did not influence BP or BMI.[16]

Discussion

In this study, we aimed to determine if greater duration of breastfeeding has causal effects on child BP, BMI and IQ by making comparisons between HIC and LMIC cohorts. We first used individual-level data and standardized approaches to analyse differences between the UK ALSPAC cohort and the Brazilian Pelotas 1993 cohort. The advantage of comparing associations of breastfeeding with child health between ALSPAC and Pelotas is that marked differences in the socio-economic patterning of breastfeeding were found to exist between the two cohorts. Since a major unresolved issue among epidemiological studies of breastfeeding associations with later outcomes is residual confounding by socio-economic position, comparisons between cohorts where the socio-economic patterning of breastfeeding is found to differ can potentially improve causal inference with respect to effects of breastfeeding on child health.

In ALSPAC, as is generally the case in HICs,[23] breastfeeding was more common among women from higher socio-economic groups, whereas in Pelotas socio-economic position was not strongly associated with breastfeeding.

In ALSPAC, breastfeeding was associated with all outcomes, specifically with lower SBP, DBP and BMI, and with higher IQ, even in models adjusting for socio-economic position. If these associations are not explained by residual confounding due to socio-economic position (or other characteristics that are socio-economically patterned), then we would expect similar magnitudes of association in the Pelotas cohort, where socio-economic position could not be a confounder since it is unrelated to the exposure. What we found in Pelotas was that breastfeeding was not strongly associated with SBP, DBP or BMI, but was associated with higher IQ, suggesting that associations with the former in ALSPAC, and other Western population cohorts, are likely to be explained by residual confounding, whereas the association with IQ is likely to be causal. However, despite observing differences between ALSPAC and Pelotas in terms of the effect sizes of breastfeeding associations with BP and BMI, formal tests for heterogeneity indicated that there was little evidence that the associations differed statistically between the cohorts. This is likely to be due to the smaller sample size of Pelotas and, indeed, when ALSPAC associations were compared with a larger sample from a LMIC consortium, there was evidence of systematic differences between ALSPAC and the LMIC cohorts with respect to the associations of breastfeeding with SBP, DBP and BMI.

As a further validation of this cohort comparison method, we compared our results with those of an RCT[16,17] and found that it also supported the suggestion that breastfeeding did not protect against greater BMI or BP but did increase IQ. These conclusions are further validated by several recent systematic reviews and meta-analyses of observational studies relating breastfeeding to BMI, BP and cognitive function, which also suggest that with BMI[24] and BP[25,26] associations may be importantly influenced by residual confounding, whereas associations with cognitive function appear robust and less likely to be due to confounding.[27]

Although we found evidence of causal effects of breastfeeding for child IQ, the crude association was

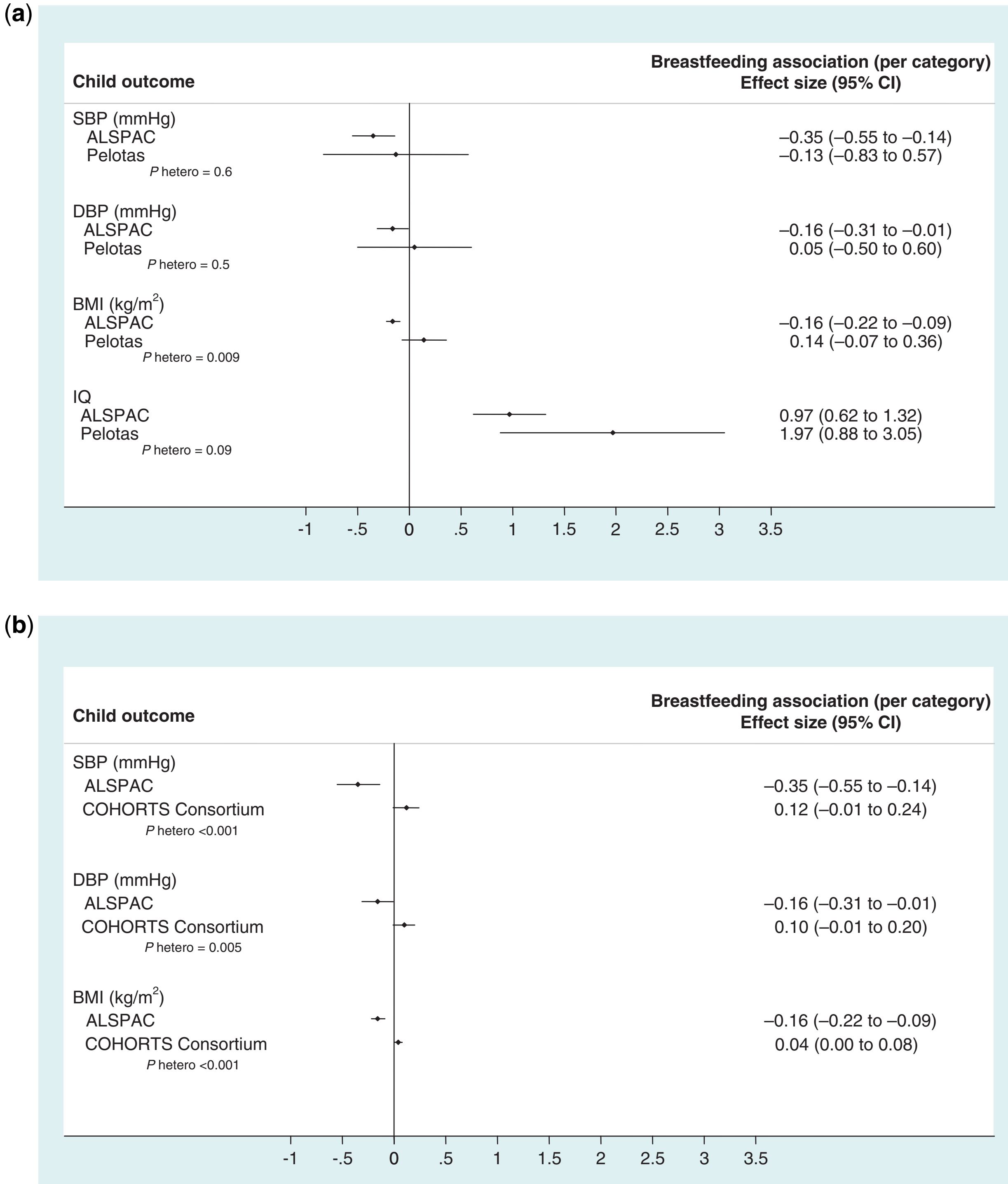

Figure 2 (**a**) Comparison of breastfeeding associations with child outcomes between ALSPAC and Pelotas and (**b**) comparison of breastfeeding associations with child outcomes between ALSPAC and published meta-analyses[15] from the COHORTS Consortium based on five LMIC cohorts. Effect sizes reflect the difference in child outcomes per increasing category of grouped breastfeeding duration. (ALSPAC/Pelotas: 0 to <1 m, 1 to <3 m, 3 to <6 m, 6 months or more; COHORTS: **None, ⩽1 m, ⩽3 m, ⩽6 m, ⩽9 m, ⩽12 m, ⩽18 m, ⩽24 m, >24 months**). CI, confidence interval

Table 4 Summary of results from the cross-cohort comparison and validation using a randomized trial

	Comparison method						Validation	
	Association with any breastfeeding (per category)[a]						Effect of breastfeeding intervention	
	ALSPAC			Pelotas			Belarus	
	Strong socio-economic patterning in breastfeeding			Weak socio-economic patterning in breastfeeding			Randomized trial	
Outcome	β	95% CI	*P*	β	95% CI	*P*	Difference in outcome[b]	95% CI
SBP (mmHg)	−0.35	−0.55 to −0.14	0.001	−0.13	−0.83 to 0.57	0.7	0.2	−2.9 to 3.3
DBP (mmHg)	−0.16	−0.31 to −0.01	0.04	0.05	−0.50 to 0.60	0.9	0.2	−1.8 to 2.2
BMI (kg/m^2)	−0.16	−0.22 to −0.09	<0.001	0.14	−0.07 to 0.36	0.2	0.1	−0.2 to 0.3
IQ	0.97	0.62 to 1.32	<0.001	1.97	0.88 to 3.05	<0.001	5.9	−1.0 to 12.8

[a]None/<1 month; 1 to <3 months; 3 to <6 months; ⩾6 months; fully adjusted models.
[b]Intervention vs control. Results extracted from publications from the Belarus PROBIT trial.[16,17]
CI, confidence interval.

found to attenuate substantially following adjustment for confounders. It may be argued that a large attenuation of effects following confounder adjustment suggests a high likelihood of any remaining associations being due to residual confounding. Some of the adjustment factors, such as maternal and paternal education, are strongly related to parental IQ, which has a direct link to offspring IQ. Thus, it is possible that residual confounding may be a persisting factor in the association of breastfeeding with IQ. Indeed, it has been found that maternal IQ may be the primary driver of the associations between breastfeeding and child IQ in HICs.[5] However, in a previous study in the Philippines, breastfeeding was also found to be positively associated with child cognition,[28] despite an inverse association between breastfeeding and socio-economic position and the RCT evidence also suggests a causal effect,[17] which is consistent with our cohort comparisons.

Strengths and limitations

The main strength of this article is in exploring causal inference when confounding patterns show marked differences between the cohorts being compared. A further strength is that in both cohorts we were able to adjust for a range of socio-economic markers (income, occupational social class and parental education), unlike other cohorts where fewer indicators are available. Consistent with prospective cohort studies, and in particular birth cohorts, there was attrition over the follow-up period. However, when we examined the associations of socio-economic position with breastfeeding in the both the maximal number in each cohort (i.e. not restricting analyses to only those with follow-up outcome data and all co-variables) and the samples restricted to complete data, the direction and magnitude of these associations were similar in both cohorts. This suggests that those who were followed up in relation to child outcomes and analysed here are not a select group with respect to the association of socio-economic position and breastfeeding. In addition, as mentioned above, the comparisons between ALSPAC and Pelotas may have been underpowered to detect some cross-cohort differences in breastfeeding associations due to the smaller sample size in the Pelotas cohort ($N \simeq 1000$ in Pelotas vs ~5000 in ALSPAC). Thus, we included an additional comparison of ALSPAC with a large published meta-analysis of breastfeeding associations in five LMICs ($N > 10\,000$)[15] and this provided robust evidence for systematic differences between the HIC and LMIC cohorts with respect to breastfeeding associations with SBP, DBP and BMI, which were consistent with the trends observed in the ALSPAC–Pelotas comparison. Finally, the interpretation of our findings is based on the underlying assumption of this method that the differences between the two cohorts are explained by the different confounding structures (in particular the relationship of socio-economic position to breastfeeding) in the two countries. Another possible explanation for the discrepant findings between them is that the effect of breastfeeding is being modified by an unmeasured factor that is only frequent in one of the cohorts. For example, breast milk substitutes used in the two cohorts might differ. However, for this to be a plausible explanation for the observed results, the modifying factor (i.e. breast milk substitute) would have to be one that only has an impact on the association of breastfeeding with BMI and BP but not with its association with cognitive function. Furthermore, the consistency of our cohort comparison results with the findings from a large RCT of breastfeeding promotion does not support this.

Conclusions

We have demonstrated how comparing associations between populations with differing confounding structures can be used to explore the likelihood of residual confounding and improve causal inference. Based on this method, we find that previously reported associations of breastfeeding with child BMI and BP are likely to reflect residual confounding; however, we find evidence of a causal relationship between breastfeeding and child IQ. This method could be extended to other epidemiological associations where the confounding structure of the exposure or outcome varies between different populations and where large enough sample sizes are available to facilitate reliable comparisons. Different confounding structures may be considered to exist where associations with exposure and outcome are present in one population, and hence could confound the association, and absent in another for either exposure or outcome (or both) as presented here or where the association of the potential confounder with either exposure or outcome exists in opposite directions between populations[12,28] or where the strength of the associations with exposure or outcome differs between populations.[29] Further studies with large sample sizes characterizing such exposures that differ in their confounding structure among populations will be required.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: None declared.

KEY MESSAGES

- Residual confounding remains an unresolved problem in observational epidemiology studies.
- Comparing associations between populations with different confounding structures can be used to improve causal inference.
- This approach is applied here to cross-cohort comparisons of breastfeeding associations in HICs and LMICs where the socio-economic patterning of breastfeeding is known to differ.
- There was evidence to suggest that although associations of breastfeeding with lower child BP and BMI are likely to be due to residual confounding, associations with greater child IQ may be causal.

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