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Association of breastfeeding status with risk of autism spectrum disorder: A systematic review, dose-response analysis and meta-analysis

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ABSTRACT

Current evidence indicates that nutritional status in newborns, especially the duration of breastfeeding, plays a key role in the pathogenesis of autism spectrum disorder. We aimed to systematically review and meta-analyze relevant studies with findings of an association between autism spectrum disorder and breastfeeding patterns, and undertook an extensive dose-response analysis to interpret the results more accurately. Ten electronic databases and manual search of reference lists were used to identify relevant studies in September 2018. Dose-response and conventional meta-analysis were conducted by the random-effects model. The study protocol was registered in PROSPERO with CRD42016043128. Seven case-control studies were found in which the association between ever breastfeeding and risk of autism spectrum disorder was investigated. We found a 58 % decrease in the risk of autism spectrum disorder with ever breastfeeding and a 76 % decrease in the risk with exclusive breastfeeding. According to our dose-response meta-analysis, breastfeeding for 6 months was associated with a 54 % reduction in the risk. In the conventional meta-analysis, breastfeeding for 12–24 months was associated with the most significant reduction in the risk of autism spectrum disorder. Our results highlight the importance of breastfeeding to decrease the risk of autism spectrum disorder.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interaction, and restricted, repetitive patterns of behaviors, interests or activities. It affects psychosocial competence and functions in infants and children (Flores-Mireles et al., 2015). Several red flags in child developmental milestones can raise concerns regarding the existence of neurodevelopmental disorders starting as early as 2–6 months, when infants may demonstrate abnormal eye contact (Clifford and Dissanayake, 2008; Emond et al., 2010; Jones and Klin, 2013; Landa, 2007). By the age of 10 months, changes in joint attention, feeding behaviors, reciprocal

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vocalizations and mutual gaze can be observed (Clifford and Dissanayake, 2008; Emond et al., 2010; Jones and Klin, 2013; Landa, 2007). Many children with delayed or abnormal social interactions during the first year of life are later diagnosed with ASD (Clifford and Dissanayake, 2008; Ozonoff et al., 2010).

The global prevalence of ASD highlights the gaps in autism research; for example, in the USA one out of 68 children has been diagnosed with ASD (Klauck, 2006). Despite being a global concern for pediatric care, its etiology and risk factors remain elusive. In several studies, correlations have been reported between ASD and major risk factors; however, the underlying mechanism remains unclear (Ozonoff et al., 2010). In this context there is evidence from previous studies of a high albeit incomplete concordance between monozygotic twins compared to fraternal twins, indicating a polygenetic and epistatic etiology, and also exemplifying the importance of environmental factors that may interact with genetic mutations (Bailey et al., 1995; Klauck, 2006; Newschaffer et al., 2002; Santangelo and Tsatsanis, 2005).

The importance of breastfeeding (BF) in neurodevelopmental disorders among newborns is well recognized (Victora et al., 2016). BF is a natural means to provide newborns and young infants with essential nutrients required for healthy growth and immune system development. According to the World Health Organization (WHO), colostrum – the sticky, yellowish human milk produced at the end of pregnancy – is highly recommended within the first hour after birth (World Health Organization, 2018). Exclusive BF is defined as feeding only with human milk. No other liquids or solids are given – not even water – with the exception of oral rehydration solutions, vitamins, minerals or medicines in the form of drops or syrups (e-Library of Evidence for Nutrition Actions (eLENA), 2018). Exclusive BF should be continued for the first six months after birth, according to WHO recommendations.

According to one major randomized controlled trial and a few observational studies, BF, especially during the first six months of life, significantly favors neurocognitive development (Anderson et al., 1999; Christensen et al., 2016; Gardener et al., 2011; Newschaffer et al., 2002; Santangelo and Tsatsanis, 2005; Sayehmiri et al., 2015). This effect may be a result of the nutritional or hormonal content of human milk, or the skin-to-skin contact and bonding between mother and child during nursing (Drane and Logemann, 2000; Sayehmiri et al., 2015). The positive influence BF on neurocognitive development has been corroborated in most recent studies, in which evidence was reported in support of the association between the duration of BF and children's cognitive functions independently of parental and socioenvironmental factors (American Academy of Pediatrics, 2012; Drane and Logemann, 2000; Kramer et al., 2008; Robinson and Fall, 2012).

The impact of confounding factors such as maternal intelligence quotient (IQ), parental education, and socioeconomic factors on the relationship between BF and ASD has also been assessed in different studies, with conflicting evidence. Several observational studies reported that the cognitive advantage of BF persists even after adjustment for the above-mentioned covariates (Anderson et al., 1999; Christensen et al., 2016; Gardener et al., 2011; Sayehmiri et al., 2015). However, according to Brion et al., the association between BF and neural development in children can be affected by confounding factors, including parental education and socioeconomic factors (Brion et al., 2011). Discrepancies between the evidence reported to date can be attributed to differences in the methods used to assess children's intelligence, as well as in the duration and intensity of BF (Belfort et al., 2013; Julvez et al., 2014). Existing meta-analyses have only considered the confounding effect of parental IQ, leaving a gap in efforts to address the impact of other confounders and thus achieve a more accurate interpretation of the body of literature. These findings highlight the need for more strictly controlled studies (Jain et al., 2002; Quigley et al., 2012). For example, Al Farsi et al. and Shafai et al. suggested that BF might lower the risk of ASD in children (Al-Farsi et al., 2012; Shafai et al., 2014). This evidence, however, remains inconclusive because it contradicts the findings of other studies by Burd et al. and Husk et al. (Burd et al., 1988; Husk and Keim, 2015).

Therefore, the present systematic review and meta-analysis was designed to explore the qualitative and quantitative nature of the association between BF and risk of ASD, considering the inconclusive evidence from different study designs. An additional aim of this study was to evaluate the dose-dependence of the impact of BF on ASD.

2. Methods

2.1. Design

We performed our study according to the recommendations of the updated Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement (Table S1) (Liberati et al., 2009). Our protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with identification number CRD42016043128.

2.2. Setting

In September 2018 we searched these ten electronic databases: PubMed, Scopus, Web of Science (WoS), WHO Global Health Library (GHL), Virtual Health Library (VHL), Google Scholar, POPLINE, New York Academy of Medicine Grey Literature Report (NYAM), System for Information on Grey Literature in Europe (SIGLE) and PsychINFO via PsychNET. A manual search of the references cited in studies identified in the initial search was also conducted to retrieve relevant articles with PubMed and Google Scholar (Vassar et al., 2016). In addition, unpublished literature was sought by contacting the American Academy of Child and Adolescent Psychiatry Autism and Intellectual Disability Committee. Moreover, an updated search has been conducted prior to finalizing the study to include any new relevant studies.

2.3. Sample

Three reviewers independently screened titles and abstracts to select potential full-text articles for further scrutiny according to our inclusion and exclusion criteria. The inclusion criteria were BF or a history of BF, children (< 18 years old) with a clinical diagnosis of ASD or screened for ASD based on a questionnaire, or at risk for ASD based on sibling status or developmental or behavioral risk factors raising suspicion of ASD.

All original articles were included without restrictions for study design. No restrictions on language, publication date, country, socioeconomic status or time period were used. Our exclusion criteria were as follows: unreliably extracted data, overlapping datasets, books, conference papers, theses, case reports, reviews and articles for which the full text was not available (e.g. conference presentations, editorials, and author responses). Non-original articles (reviews and analyses), *in vitro* studies and nonhuman trials were also excluded. Any disagreement was resolved through discussion and arbitration in conjunction with the senior authors. The procedure for study selection and analysis is summarized in the PRISMA flow diagram (Fig. 1).

2.4. Data collection

Data were extracted independently by three reviewers with standard data extraction forms, and any disagreement was resolved through discussion and consensus among reviewers and senior researchers. For studies reported in more than one publication, all publications were compared and the ones with a complete data set were selected. We also noted any discrepancies between different versions of any publication. Data were extracted in several matrices including characteristics of the publication, study design, characteristics of the study population, country where participants were recruited, and ASD diagnostic criteria. We also extracted data that provided information about sample size,

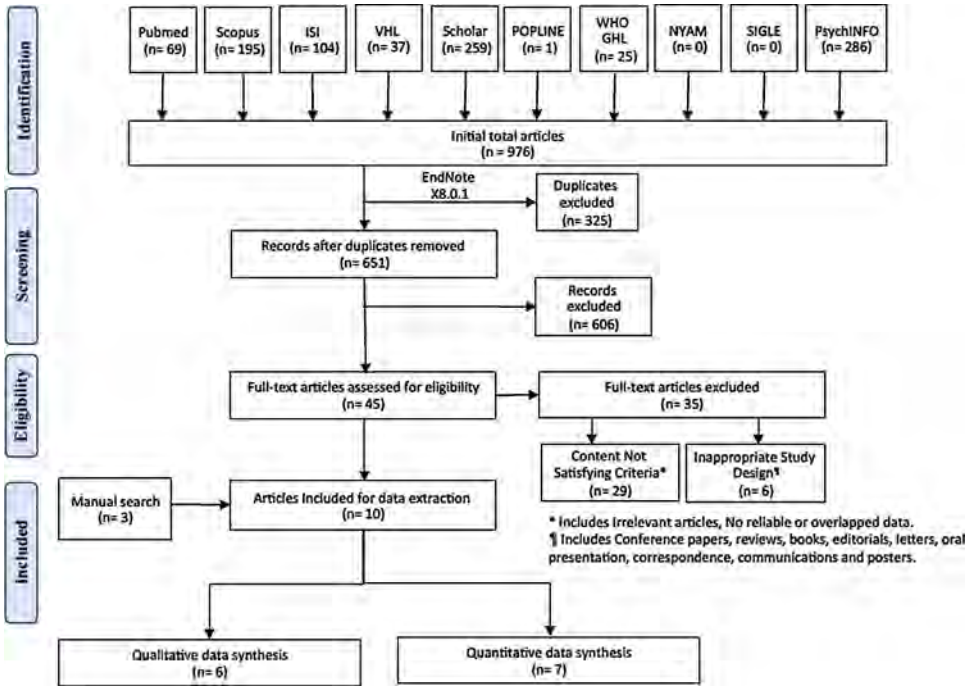

Fig. 1. PRISMA flow diagram of the research and review process.

study design, the definition of BF and BF types, follow-up, and individual characteristics of the participants. Confounders, patterns of BF and effect sizes that quantified the association between BF and the risk of ASD were also extracted.

Three authors independently assessed the quality of all studies included. Discrepancies were resolved by discussion in conjunction with the senior authors. In accordance with our study design, we used NIH-Quality Assessment Tools, e.g. either the Observational Cohort and Cross-Sectional tool or the Case-Control tool, to assess the quality of the studies (National Heart Lung and Blood Institute, 2019). Study quality was classified as follows: a score of 10–14 was good, 5–9 was fair, and studies scoring below 4 were considered of poor quality.

2.5. Data analysis

The association between BF and ASD was measured as the adjusted odds ratio (OR) of each study. Among the different follow-up time points, we considered never BF as the reference time point. Two outcomes were investigated: the association between either ever BF or ever exclusive BF and ASD. For studies that did not report the ever BF or ever exclusive BF as a reference, we used the effective count method described by Hamling et al. to recalculate relative risk (RR) (Hamling et al., 2008).

Because of the limited number of studies in which the outcomes of exclusive BF were reported, we investigated the dose-response association only for the outcome of ever BF. For this analysis, we used the duration if specified. For studies in which the duration was reported as a range, we used the midpoint between the upper and lower bound as the average duration. If the lower bound was unknown, we considered it as zero. If the upper bound was unknown, we assumed the last time point to indicate the duration. After including only studies with variance estimates for ≥ 3 known quantitative exposure categories, we then used the method proposed by Greenland et al. (Greenland and Longnecker, 1992) and Orsini et al. (Orsini et al., 2012), who proposed the use of ln RR and 95 % confidence intervals (CIs) for the different durations of BF to calculate linear trends or study-specific slopes. The log-linear association was also investigated; this value was then relaxed by using regression cubic splines by considering 4 knots at the 5th, 35th, 65th, and 95th percentiles of the aggregated exposure distribution with the dosresmeta R package (Crippa and Orsini, 2016).

A random-effects model was applied according to the method proposed by DerSimonian and Laird (DerSimonian & Laird, 1986) to yield more conservative results. A sensitivity analysis was also conducted to evaluate the accuracy of the results of the present meta-analysis. All analyses were done with R version 3.2.5 (R Foundation for Statistical Computing). All p values were 2-tailed, and p-values less than 0.05 were considered statistically significant.

3. Results

3.1. Study characteristics

With our search strategy, we located 976 publication titles and abstracts eligible for screening. Out of the 13 articles included, six studies were selected for the qualitative synthesis and seven studies were included in the quantitative synthesis (Fig. 1). The sample sizes in these studies ranged from 42 to 129,733. The characteristics of included articles, i.e. sample size, study design, diagnostic methods and definitions of BF types, are summarized in Table 1. In most studies, the Diagnostic and Statistical Manual of Mental Disorders DSM-IV criteria (n = 5) (Al-Farsi et al., 2012; Bawono et al., 2012; Field, 2014; Husk and Keim, 2015; Say et al., 2016) and DSM-III criteria (n = 2) (Burd et al., 1988; Tanoue and Oda, 1989) were used to diagnose ASD. In one study the Childhood Autism Rating Scale (CARS) was used (George et al., 2014), and in another study, the ICD-9 and ICD-10 codes were used (Dodds et al., 2011). In the remaining studies, no information was reported about the clinical criteria used to diagnose ASD in the study samples (Brown et al., 2014; Schultz et al., 2006; Shafai et al., 2014; Shamberger, 2011) (Table 1).

According to WHO 2008, exclusive BF is defined as BF for a period of 6 months after birth without other foods or liquids (including water). However, infants can receive oral rehydration solution, drops, and syrups (vitamins, minerals, and medicines) (e-Library of Evidence for Nutrition Actions (eLENA), 2018). Ever BF has been defined as BF in any period and for any duration. In all nine case-control studies included in the present study (Al-Farsi et al., 2012; Bawono et al., 2012;

Table 1
Characteristics of the included studies.

Author, year, country	Study Design	Study Group	Mean Age or Age Range	Sample Size	Diagnostic Method of ASD	BF Categories	Odds Ratio /Relative Risk (95 % CI)	Matched/Adjusted Factors if Present	Quality
Brown, 2014, Australia (Brown et al., 2014)	Case Control	Children with ASD Children without ASD	ND	19 23	ND	Compares ever exclusive BF with never BF	0.26 (0.07-0.89)	Child gender and fatty acid deficiency score	Fair
Dodds, 2011, Canada (Dodds et al., 2011)	Retrospective longitudinal cohort study	Children with ASD Children without ASD	1-17 years old	924 128,809	ICD-9 code 299 or ICD 10 code F84	Compares ever BF with never BF	1.15 (1.01–1.31)	Birth year and genetic susceptibility (defined as having a sibling with autism or a mother with an underlying psychiatric or neurologic illness)	Fair
Bawono, 2012, Indonesia (Bawono et al., 2012)	Case Control	Children with ASD Children without ASD	5.3 ± 1.4 years old	52 104	DSM IV-TR	Compares ≥ 6 months BF with never BF Compares never exclusive BF, 0–6 months and 6 - < 12 months with ≥ 12 months	2.01 (1.02–3.96) 5.75 (1.4–23.49) 2.17 (0.73–6.46) 1.59 (0.54–4.62)	Child gender, age, and residence	Good
George, 2014, India (George et al., 2014)	Case Control	Children with ASD Children without ASD	42.01 months 41.58 months	143 200	CARS with a cut-off score of > 30	Compares never BF with ≥ 6 months	3.4 (1.28–8.99)	Child age, immunization statue	Fair
Tanoue, 1989, Japan (Tanoue and Oda, 1989)	Case Control	Infantile ASD Non ASD	3 years old	145 224	DSM III	Compares never BF with < 1 week, 1 week - 1 month, 1–2 months, 2–3 months, 3–6 months, 6–12 months, and ≥ 12 months	0.43 (0.16–1.15), 0.24 (0.11-0.52), 0.23 (0.10-0.51), and 0.27 (0.12-0.57)	Child age	Good
Al-Farsi, 2012, Oman (Al-Farsi et al., 2012)	Case Control	Children with ASD Children without ASD	6.8 ± 2.9 years old 6.4 ± 3.3 years old	102 102	DSM-IV TR	Compares never BF, < 1 month, 1–6 months, 7–12 months and 13–18 months with 19–24 months Compares exclusive BF, < 3 months, ≤ 3 months, ≤ 4 months, ≤ 5 months and ≤ 6 months	6.6 (1.9–22.3), 3.79 (1.5–9.5), 3.52 (1.42–8.8), 2.14 (0.9–5.1) 3.3 (0.29–38), 2.97 (1.62–5.5), 0.99 (0.33–2.99), and 0.41 (0.04–3.87)	Maternal age, maternal education, family income, and antenatal and perinatal complications	Good
Say, 2015, Turkey (Say et al., 2016)	Case Control	Children with ASD Children with ADHD Children without ASD	8.73 ± 3.86 years old 8.80 ± 1.98 years old 8.45 ± 4.61 years old	98 96 79	DSM-IV	Compares never BF with 1 month, 3 months, 6 months, 12 months and ≥ 24 months	0.23 (0.02–2.06), 0.22 (0.02–1.92), 0.2 (0.02–1.76), 0.21 (0.02–1.98) and 0.53 (0.04–6.65)	Age and gender-matched children	Fair
Schultz, 2006, USA (Schultz et al., 2006)	Case Control	Children with ASD Children without ASD	7.8 ± 3.9 7.4 ± 4.5	861 123	Self-reported	Compares never BF with < 2 months, 2–6 months, and ≥ 6 months	0.69 (0.32–1.48), 0.51 (0.24–1.1), and 0.4 (0.23-0.71)	Age-matched children	Poor
Husk, 2015, USA (Husk and Keim, 2015)	Case Control	Children with ASD Children without ASD	2-5 years old	37,901	DSM-IV	Compares never exclusive BF with 3 months and 6 months ≤ 3 months ≤ 6 months Compares never exclusive BF with 3 months and 6 months Compares exclusive BF with never BF	0.7 (0.4–1.5) and 0.7 (0.3–1.7) 0.6 (0.3–1.3), and 0.7 (0.4–1.2) 0.7 (0.4–1.3)	Child gender, age, race, birth order, parental education, mother's age, family income, and whether the child had a personal doctor or nurse	Good
Shamberger, 2013, USA (Shamberger, 2011)	Ecological study	ASD group Non-ASD group	3–21 years old	ND	ND	Compares benefits of ever BF, at 3 months, 6 months, and 12 months	–		Poor

(*continued on next page*)

Table 1 (*continued*)

Author, year, country	Study Design	Study Group	Mean Age or Age Range	Sample Size	Diagnostic Method of ASD	BF Categories	Odds Ratio /Relative Risk (95 % CI)	Matched/Adjusted Factors if Present	Quality
Field, 2014, USA (Field, 2014)	Case Control	Children with ASD and ADHD Children without ASD	ND	31 81 612	DSM-IV TR	Compares benefits of BF < 4 months and ≥ 4 months	–	Age/sex-matched controls	Fair
Shafai, 2014, USA (Shafai et al., 2014)	Cross Sectional	Children with ASD Children without ASD	ND	60 85	Survey	Assess benefits of BF < 2 months, 2–4 months, 4–6 months, 6–9 months, 9–12 months, 12–15 months, 15–18 months, 18–24 months, and ≥ 24 months	–		Poor
Burd, 1988, USA (Burd et al., 1988)	Case Control	Children with PDD Children without PDD	9.0 ± 4.6 years old 8.8 ± 4.7 years old	50 50	DSM-III	ND	–		Fair

Note. Abbreviations: CARS, C-childhood Autism Rating Scale; ND, not described; ASD, autism spectrum disorder; PDD, pervasive developmental disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; BF, breastfeeding; ADHD, attention deficit hyperactivity disorder.

Dodds et al., 2011; George et al., 2014; Husk and Keim, 2015; Say et al., 2016; Schultz et al., 2006; Shafai et al., 2014; Tanoue and Oda, 1989) ever BF was investigated, and in six of these studies, exclusive BF was reported (Al-Farsi et al., 2012; Bawono et al., 2012; Brown et al., 2014; Husk and Keim, 2015; Schultz et al., 2006; Shamberger, 2011).

3.2. Quality assessment

Among all studies included in the present analysis, four were rated as good quality (Al-Farsi et al., 2012; Bawono et al., 2012; Husk and Keim, 2015; Tanoue and Oda, 1989), six as fair quality (Brown et al., 2014; Burd et al., 1988; Dodds et al., 2011; Field, 2014; George et al., 2014; Say et al., 2016) and three as poor quality (Schultz et al., 2006; Shafai et al., 2014; Shamberger, 2011). According to the quality assessment criteria, most of the case-control studies were deficient in design and reporting aspects, e.g. sample size justification (n = 5), blinding of assessors to case or control status (n = 9), use of concurrent controls (n = 7), and adjustment for confounders in the statistical analyses (n = 5). Similarly, among observational studies, poor quality was due in most cases to inadequate assessor blinding (n = 4), loss to follow-up > 20 % (n = 3), and inadequate assessment of exposure prior to outcome measurement (n = 3) (Table 1).

3.3. Qualitative synthesis

Six studies were included in the qualitative synthesis (Burd et al., 1988; Dodds et al., 2011; Field, 2014; Husk and Keim, 2015; Shafai et al., 2014; Shamberger, 2011). In the study by Husk et al., the age of the studied children was limited to 2–5 years. However, ASD disorders may well be diagnosed in older children, especially in low-income families (Husk and Keim, 2015). In the study by Dodds et al., there was no adjustment for multiple comparisons, raising the possibility of type-I error (Dodds et al., 2011).

Shamberger et al. concluded that mothers who use BF exclusively should also continue their prenatal vitamins or their equivalent, and make better dietary choices. Moreover, they suggested that ASD might be nutritionally related to a possible deficiency in riboflavin or cognitive function-related vitamins, e.g. thiamine or vitamin D (Shamberger, 2011). Shafai et al. performed a survey study of parents of children with ASD and reported a lower rate of ASD diagnosis associated with a longer duration of BF. Children fed with human milk for more than 12 months were 6.53 times less likely to have ASD compared to children with BF for less than 12 months (Shafai et al., 2014).

In addition, Field et al. reported a significant correlation between parental age and risk of ASD or attention deficit hyperactivity disorder (ADHD) in females but not males. They hypothesized that adequate BF might countermand maternal age and protect the offspring (Field, 2014). Also, Burd et al. investigated the broader category of pervasive developmental disorder (PDD) and BF. They found that the BF rates in patients with PDD (26 %) and a control group (22 %) were significantly lower than the expected rates for the PDD (45.2 %) and control groups (45.5 %). The difference between the PDD and control groups was not clinically significant, and the authors suggested that children with PDD do not have a lower rate of expected and actual BF compared to children with normal development in their control group (Burd et al., 1988).

3.4. Risk of ASD and ever BF

Seven case-control studies (Al-Farsi et al., 2012; Bawono et al., 2012; George et al., 2014; Say et al., 2016; Schultz et al., 2006; Shafai et al., 2014; Tanoue and Oda, 1989) explored the association between ever BF and risk of ASD. The summary OR for ASD risk was 0.42 (95 % CI: 0.30 – 0.57), which indicated a significantly lower risk of developing ASD compared to never BF with 0 % heterogeneity (Q = 2.87, p = 0.82, I^2 = 0 %) (Table 1 and Fig. 2).

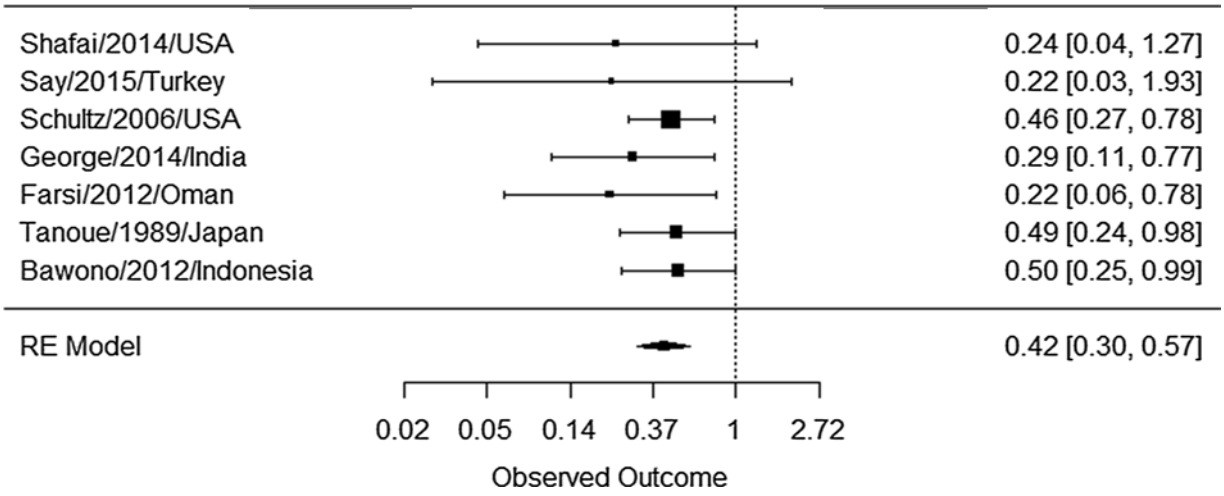

Fig. 2. Random-effects model of the effect of ever BF on the risk of developing ASD. Squares indicate study-specific RRs (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95 % CIs; the diamond indicates the summary RR estimate with its 95 % CI.

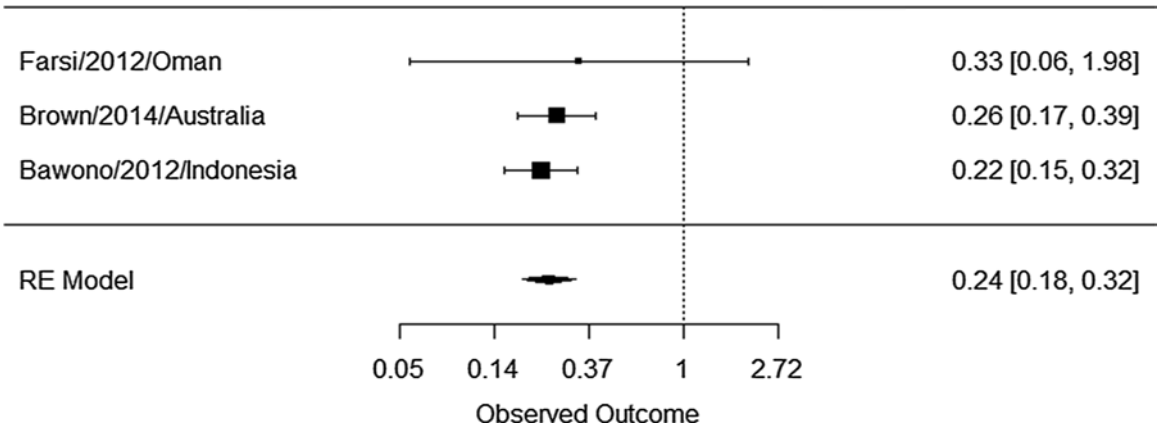

Fig. 3. Random-effects model of the effect of exclusive BF on the risk of developing ASD. Squares indicate study-specific RRs (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95 % CIs; the diamond indicates the summary RR estimate with its 95 % CI.

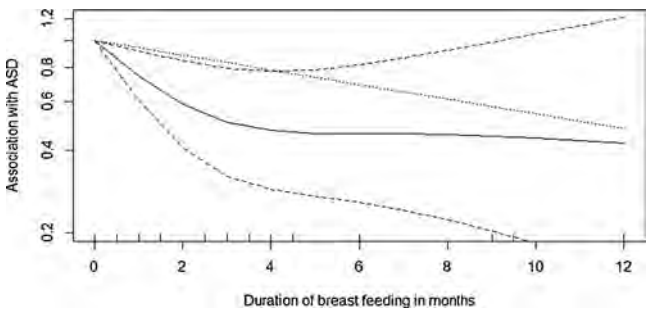

Fig. 4. Pooled dose-response relation between BF and risk of ASD (solid line).

3.5. Risk of ASD and exclusive BF

In the same context, three case-control studies (Al-Farsi et al., 2012; Bawono et al., 2012; Brown et al., 2014) investigated the association between risk of ASD and exclusive BF. According to the present results, there was a significant association between exclusive BF and a significant reduction in the risk of developing ASD, with an OR of 0.24 (95 % CI: 0.18 – 0.32) and zero heterogeneity (Q = 0.46, p = 0.79, I^2 = 0 %) (Table 1 and Fig. 3).

3.6. Dose-response analysis of total duration of BF

Four case-control studies (Al-Farsi et al., 2012; Husk and Keim, 2015; Say et al., 2016; Schultz et al., 2006; Tanoue and Oda, 1989) were included in the dose-response analysis. We found that BF during the first 6 months after birth was associated with a significantly lower risk (31.82 % less compared to never BF) of developing ASD (95 % CI: 0.49 – 0.98), and it became 54.04 % risk reduction (95 % CI: 0.49 – 0.98), after applying the restricted cubic spline model with no significant heterogeneity (Q = 15.47, p = 0.08, I^2 = 41.8 %) (Fig. 4).

3.7. Subgroup analysis

We undertook a subgroup analysis of the seven case-control studies (Al-Farsi et al., 2012; Bawono et al., 2012; George et al., 2014; Husk and Keim, 2015; Say et al., 2016; Schultz et al., 2006; Tanoue and Oda, 1989) that reported the risk of ASD at multiple time points. These studies were also included in our conventional meta-analysis to evaluate the association between BF and the development of ASD. The summary OR was 0.35 (95 % CI: 0.17 – 0.73) at 1 month, 0.30 (95 % CI: 0.13 – 0.69) at 1–3 months, 0.38 (95 % CI: 0.20 – 0.69) at 3–6 months, 0.36 (95 % CI: 0.26 – 0.48) at 6–12 months, and 0.23 (95 % CI: 0.14 – 0.36) at 12–24 months (Fig. 5).

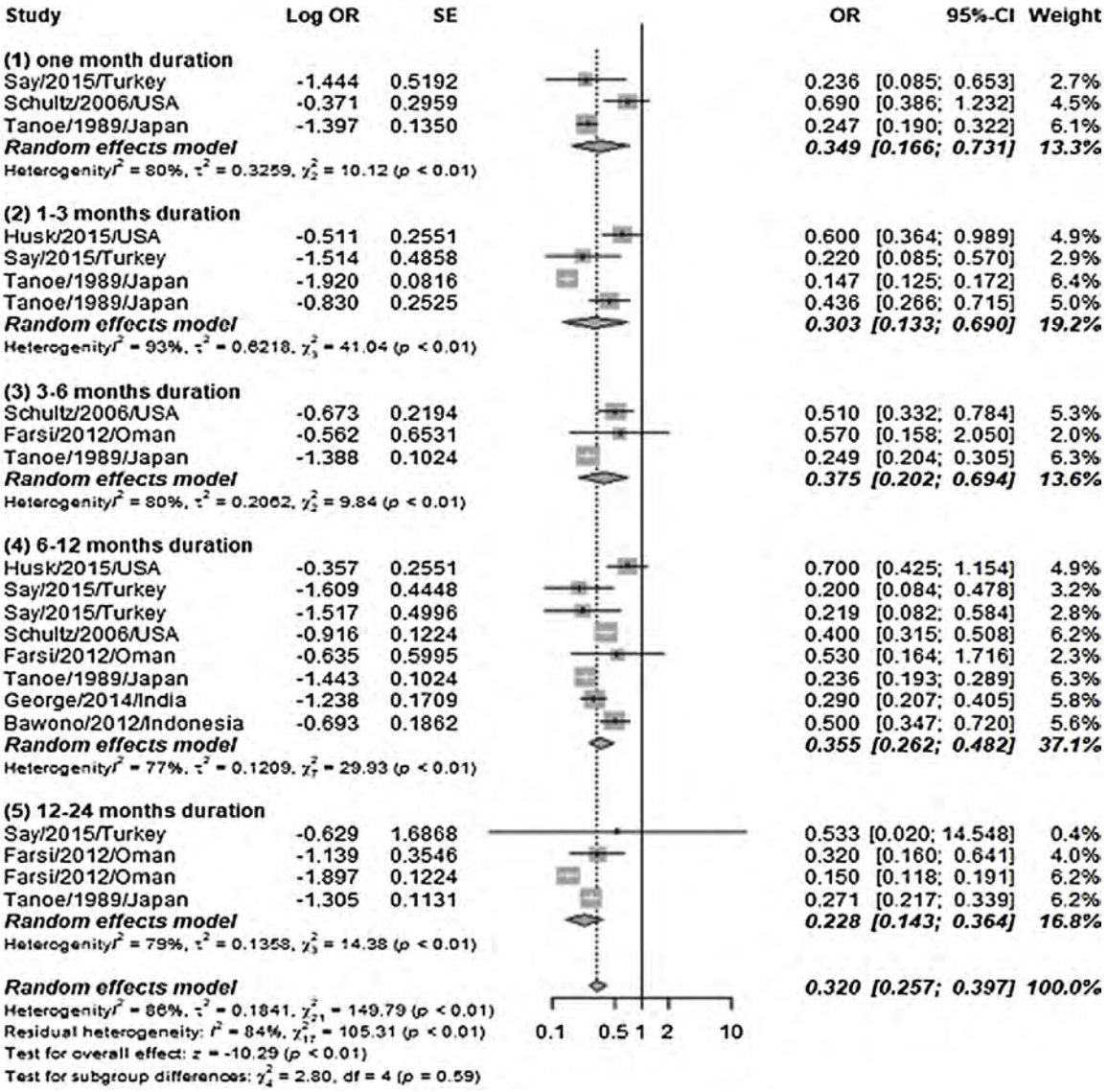

Fig. 5. Forest plot (random-effects model) of BF duration at multiple time points and risk of ASD. Squares indicate study-specific RRs (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95 % CIs; the diamond indicates the summary RR estimate with its 95 % CI.

4. Discussion

According to our results, BF was indeed related to the risk of developing ASD. We found that ever BF was associated with a 58 % lower risk of developing ASD, and that exclusive BF was associated with a 76 % lower risk. According to our dose-response meta-analysis, a 54 % risk reduction was associated with every 6 months of BF. In a second conventional meta-analysis, 12–24 months of BF was associated with the most significant reduction in the risk of ASD [0.23 (95 % CI: 0.14 – 0.36)]. This inverse relationship signifies the importance of BF and is also considered to be biologically reasonable.

The etiology of ASD is poorly understood and may be attributable to the complex interplay between genetic and environmental factors. The authors of one recent study redefined the role of both genetic and environmental factors in the development of ASD (Sandin et al., 2014) on the basis of their examination of the health records for all individuals born between 1982 and 2006 in Sweden (Sandin et al., 2014). The investigators were able to identify 14,516 individuals with a diagnosis of ASD (Sandin et al., 2014). They also suggested that genetic and environmental factors contributed equally to the pathogenesis of ASD – a conclusion that was consistent across the study's 24-year span (Sandin et al., 2014). This has overturned the previous notion of ASD being caused by genetic factors only.

The association between BF and ASD is still controversial, with conflicting evidence from different studies. In the present study, the main sources of this confusion were two particular studies (Dodds et al., 2011; Husk and Keim, 2015). Both of them had limitations and methodological flaws that may have caused this problem. First, Dodds and colleagues were not able to classify persons with autism according to IQ or severity because data for these factors were not available. Moreover, they used the ICD-9 code, which does not distinguish between autism and Asperger syndrome, so these two entities could not be separated during data synthesis (Dodds et al., 2011). Regarding the study by Husk et al., their data synthesis was restricted to children less than 6 years old; hence it was likely that some diagnoses were missed in families of low socioeconomic status. In addition, they overlooked covariates such as preterm status, which may have altered the validity of their results. Although they tried to adjust their results for non-response bias, this factor may also have affected their results (Husk and Keim, 2015).

The findings of the National Survey of Children's Health are consistent with the results of our systematic review and meta-analysis. This survey examined the association between BF and the subsequent

development of ASD (Husk and Keim, 2015). After confounding factors were controlled for, no association was observed between BF and a diagnosis of ASD (Husk and Keim, 2015). Similar findings were observed in another study of preterm infants (Johnson et al., 2010). On the other hand, several studies have reported a moderate to strong inverse relationship between BF and ASD, in contrast with the present results (Boucher et al., 2017; Der et al., 2006; Field, 2014; Johnson et al., 2010; Schultz et al., 2006; Shafai et al., 2014). However, these studies were limited by the confounding effects of genetic factors, family history, and demographic factors. Moreover, these studies were adjusted for age only.

In another related study, the authors investigated the broader category of PDD and BF (Burd et al., 1988). These authors found no significant difference in BF rates between 50 children with PDD and 50 control children, although in both groups the rate of BF was significantly lower than the national average. Further, BF rates in the normal siblings of children with PDD were almost identical to the national average. Other studies were limited by recall bias, smaller sample size, and the use of screening tools for the diagnosis of ASD (Boucher et al., 2017; Der et al., 2006; Field, 2014; Johnson et al., 2010; Schultz et al., 2006; Shafai et al., 2014).

BF has been recognized as a protective factor against the development of ASD. Previous advances in our understanding of cognitive-developmental pathways and the etiology of ASD have led many scientists to hypothesize a relationship between poor BF practices and ASD. These hypotheses tend to be multidimensional, implicating poor BF as a cause of nutritional, hormonal and humoral deficiencies in children, thus putting them at a greater risk of ASD (Husk and Keim, 2015). Suboptimal BF practices also lead to poor bonding between the mother and child, resulting in poor sensory stimulation in the child (Al-Farsi et al., 2012). All of these factors might act as epigenetic factors through DNA methylation and acetylation, and thereby contribute to the pathogenesis of ASD (Eshraghi et al., 2018).

Because nutritional and humoral deficiencies have been recognized in persons with ASD, the link between poor BF practices and the risk of ASD has been investigated in earlier research. Breast milk is a rich source of long-chain polyunsaturated omega 3 and omega 6 fatty acids, which are considered important in cognitive, social and language development in children aged 6 months to 3.5 years (Sauerwald et al., 2001). Deficiencies in these fatty acids have been reported in persons with ASD, supporting the inference of causation for BF. Breast milk is also a rich source of vitamin A, IgA, peptide b-casomorphin 7, insulin-like growth factors I and II, basic fibroblast growth factor, epidermal growth factor, and antioxidants including glutathione (Schams, 1994; Warner and Warner, 2005). Poor BF practices lead to deficiencies in these nutrients and factors, resulting in disruption of the gut lining and increased vulnerability to environmental toxins and infections (Andersson et al., 2009). Similar hypotheses revolving around gastrointestinal and autoimmune dysfunction have been proposed in the development of ASD (Wozniak et al., 2017). Lastly, BF promotes maternal bonding with the child, providing the sensory stimulation necessary for cognitive development. It also promotes a rich sensory environment, a state of calmness and love, and feelings of affection between the mother and child (Shafai et al., 2014).

Our meta-analysis included 13 studies, and this limited information may explain the inconclusive results regarding the association between BF and ASD. In addition, the studies included in this meta-analysis varied widely in terms of population size, setting, and methodology. Most studies in the present analysis had a small sample size, possible publication bias, and low statistical power, and were based on parental surveys for the diagnosis of ASD. Also, approach differences in the utilization of varying definitions of ASD among the included studies; should be taken into consideration while interpreting the current findings (Sritharan and Koola, 2019). The use of parental surveys may have led to over-diagnosis or under-diagnosis in these studies; especially in the light of issues related to parental guilt and stigma (Liao et al., 2019). The authors recommend that future studies use larger sample sizes to reach more robust conclusions.

5. Conclusions

Our systematic review and meta-analysis provide support for the protective effects of BF against the risk of ASD. We also found evidence that this protective effect acts in a dose-dependent manner. Due to the variability and heterogeneity of the studies, further large-scale observational studies with different types and durations of BF are needed. The underlying mechanisms of the association between BF and ASD remain an important area for further research.

Author contributions

NTH was responsible for the idea and supervision. Screening and extraction were done by all authors under the supervision of NTH. Data analysis and its interpretation were done by AHZ and SG. Tables and figures were done by AHZ, LT, and SG. All authors contributed to the manuscript writing and revision. All authors gave approval of the final version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ajp.2019.101916.

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