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Introduction of complementary feeding before 4 months of age increases the risk of childhood overweight or obesity: a meta-analysis of prospective cohort studies

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ABSTRACT

The association between the age at introduction of complementary feeding and the risk of overweight or obesity during childhood has been hotly debated, but the result remains uncertain. This meta-analysis of prospective cohort studies attempted to evaluate this association, as well as provide evidence for infant feeding recommendations. The PubMed, Embase, and Cochrane databases were systematically searched for relevant original articles published prior to March 1, 2015 that met predefined inclusion criteria. The pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated using fix-effect or random-effect models, which were chosen based on heterogeneity among studies. Ten articles consisting of 13 studies, where 8 measured being overweight as an outcome and 5 measured being obese, were included in this meta-analysis. There were a total of 63,605 participants and 11,900 incident cases in the overweight studies, and 56,136 individuals and 3246 incident cases in the obese studies. The pooled results revealed that introducing complementary foods before 4 months of age compared to at 4 to 6 months was associated with an increased risk of being overweight (RR, 1.18; 95% CI, 1.06-1.31) or obese (RR, 1.33; 95% CI, 1.07-1.64) during childhood. No significant relationship was observed between delaying introduction of complementary foods after 6 months of age, and being overweight (RR, 1.01;

Abbreviations: RR, relative risk; CI, confidence interval; WHO, World Health Organization; BMI, body mass index; IOTF, International Obesity Task Force; SD, standard deviation; SE, standard error.

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95% CI, 0.90-1.13) or obese (RR, 1.02; 95% CI, 0.91-1.14) during childhood. The results of this study suggest that the introduction of complementary foods to infants before 4 months of age should be avoided to protect against childhood obesity.

1. Introduction

Children overweight and obesity are recognized as a major public health problem worldwide [1]. According to the World Health Organization (WHO) data covering 144 countries, the worldwide prevalence of overweight and obesity in preschool children aged 0 to 5 years old increased from 4.2% in 1990 to 6.7% in 2010 [2] and is projected to reach 9.1% (about 60 million) by 2020 [2]. An estimated 31.8% of 2- to 19-year-old Americans in 2011 to 2012 and 20% of school-aged children in the European Union in 2010 to 2011 were overweight or obese [3,4]. In China, the prevalence of general obesity (including overweight) increased significantly from 6.1% in 1993 to 13.1% in 2009 among children and adolescents aged 6 to 17 years old [5]. Being overweight and/or obese during childhood tends to be accompanied by metabolic syndromes, hypertension or dyslipidemia, and predicts the risk of diabetes mellitus, stroke, coronary artery disease and several cancers later in life [6–8]. Thus, it is important to assess the potential risk factors for being overweight and obese as a child.

In recent years, evidence has accumulated suggesting that early complementary feeding may be one risk factor for childhood overweight and obesity [9–18]. Complementary feeding is defined as giving infants food and liquid in addition to formula and/or breast milk, when breast milk and/or formula alone no longer meet the nutritional requirements of the infant [19,20]. The age recommended to start complementary feeding varies based on country, although WHO issued a global recommendation in 2001 that infants should be exclusively breastfed for the first 6 months of life and then complementary foods should be introduced at this time [21]. Several observational studies reported that early introduction of complementary feeding increased the risk of childhood overweight or obesity [9–18]. However, the association was not observed in other related studies [22–24]. Recently, 2 systematic literature reviews were published focusing on this possible association [25,26]. However, these reviews failed to find a clear association between these parameters. This was likely due to heterogeneity from the differences in study design, age when outcomes were measured, and types of outcome (body mass index [BMI], body weight, body composition, overweight or obesity) determined in the studies included in the analyses. In the present study, we hypothesize that early introduction of complementary feeding increases the risk of childhood overweight or obesity and late introduction decreases the risk. To test this hypothesis, a meta-analysis of published studies was performed using inclusion criteria that differed from the aforementioned systematic reviews and, thus, included data from prospective cohort studies that provided RRs with 95% CIs and reported the outcome as overweight or obesity based on a specified definition.

2. Methods and materials

2.1. Search strategy

A literature search was performed for prospective cohort studies published before March 1, 2015 concerning the association between the age at introduction of complementary food and the risk of becoming overweight and/or obese during childhood on the PubMed (Medline), Embase and Cochrane databases. The PubMed search terms used were "("infant" OR "baby") AND ("solid food" OR "complementary food" OR "complementary feeding") AND ("overweight" OR "body mass index" OR "BMI" OR "body weight" OR "weight" OR "obese" OR "obesity")", and similar search terms were used for the Embase and Cochrane databases. The references from relevant primary papers and review articles were searched to identify additional relevant studies. The design, implementation, analysis, and reporting of this meta-analysis were performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) protocol [27].

2.2. Study selection

The criteria necessary for studies to be included in this meta-analysis consisted of having a prospective study design, a focus on the age at introduction of complementary or solid food, occurrence of children aged 2 to 12 years being overweight or obese as a quantified outcome, all measurements related to outcome taken by health professionals or trained investigators rather than self-reported, and RRs for being overweight and obese calculated with 95% CIs for at least 2 quantitative ages at which solid food was introduced or provided the original data allowing calculation of these estimates. Any retrospective, cross-sectional, non-human, and/or non-primary (eg, reviews, editorials, protocols, letters and guidelines) studies were excluded. Furthermore, studies that failed to report the incidence of participants being overweight or obese as an outcome or the age at introduction of complementary feeding as an exposure, or included pre-term infants and infants with conditions that can influence growth were excluded. Fig. 1 illustrates the study selection process.

2.3. Data extraction

Data extraction was carried out independently by 2 authors (Yuanjue Wu and Rui Liu) using a standard extraction form. The following information was mined from each study that met the selection criteria: basic information (ie, the first author, year of publication, and country of the study conducted), study characteristics (number of participants, number of cases and length of follow-up), outcomes (being overweight or obese), definitions of outcome, and categories of age at introduction of complementary foods and RRs

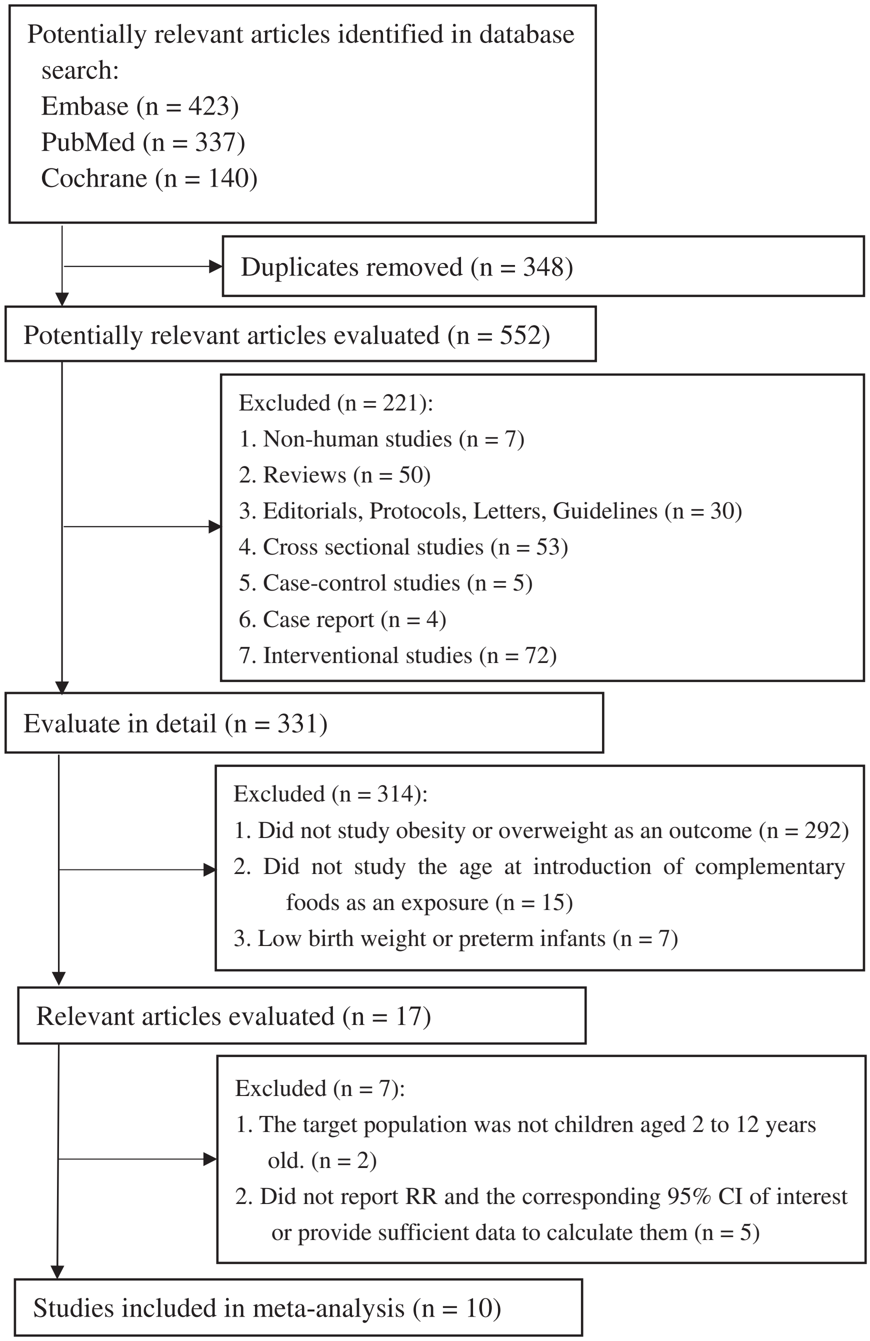

Fig. 1 – Flow diagram of literature search and study selection.

with 95% CIs of being overweight or obesity. If studies had several adjustment models, the information extracted was from the maximum extent of adjustment for potentially confounding variables.

Quality assessment was performed by 2 authors (Yuanjue Wu and Rui Liu) independently according to the Newcastle-Ottawa Quality Assessment Scale for non-randomized studies in meta-analyses [28]. This scale awards a maximum of 9 points to each study as follows: a maximum of 4 points for selection of participants and measurement of exposure, a maximum of 2 points for comparability of cohorts based on study design or analysis, and a maximum of 3 points for the assessment of outcomes and adequacy of follow-up. Scores of 0 to 3, 4 to 6, and 7 to 9 were considered low-, moderate-, and high-quality studies, respectively.

2.4. *Definitions of complementary foods and overweight or obesity*

The definitions used for complementary foods vary from study to study. In the present article, the terms “complementary foods” and “solid foods” were defined as any firm, soft or liquid food or drink besides breast milk or infant formula. This definition differs from the WHO definition, which includes any food or liquid given along with breast milk [21]. The “complementary feeding” and “introduction of solid foods” described the transition from milk feeding to the family diet. The “age at introduction of complementary feeding” was defined as the age at introduction complementary foods, which was measured in weeks or months and categorized as <4 months, 4-6 months, or ≥6 months.

The definitions for overweight or obesity were not uniform across studies included in this meta-analysis. Although all studies included in this analysis measured BMI as an index of outcome, the criteria defining overweight or obesity often differed. Three studies [17,18,22] used the age- and sex-specific BMI cut off points proposed by International Obesity Task Force (IOTF) [29]. Meanwhile, several other studies used BMI percentiles as the cutoff values for overweight or obesity. For example, some studies reported a BMI ≥85th percentile was overweight and a BMI ≥95th percentile was obese [15,16,30]. Other studies stated a BMI ≥90th percentile [31] or BMI Z-score ≥1 SD was overweight, and a BMI z-score ≥2 SD [9,14] or a BMI ≥85th percentile and triceps and subscapular skinfolds ≥90th percentile was obese [23]. Subgroup analyses were conducted to evaluate the influence of these different definitions on the accuracy of the estimate.

2.5. *Statistical analyses*

In this meta-analysis, the effect variables were measured by RRs and corresponding 95% CIs for all included studies; odds ratios (ORs) were deemed equivalent to RRs. The RRs and corresponding 95% CIs from data comparing the introduction of complementary foods before 4 months of age or after 6 months of age versus at 4 to 6 months of age were collected from each study. If these values were not available because the ages at the introduction of complementary foods differed from those defined above, they were computed from original data. Those articles reporting both overweight and obesity were treated as two separate reports. Heterogeneity across studies was evaluated using the χ^2 test and I^2 statistic, where significance was $P \le .05$ for χ^2 test or $I^2 > 50\%$ [32]. The I^2 statistic assesses the percentages of variability across studies that are attributable to heterogeneity rather than chance. For the I^2 metric, we designated low, moderate, and high I^2 values to be 25%, 50%, and 75%, respectively [32,33]. A fixed effect model, Mantel-Haenszel method, was used to evaluate the pooled estimate when the heterogeneity was negligible, and a random effect model, the Der Simonian and Laird method, was used when the heterogeneity was significant [34]. Stratified analyses were performed to assess how the associations varied by countries, definitions of outcomes, length of follow-up and number of participants. Additionally, sensitivity analyses were performed by consecutively omitting every article from the meta- analysis in turn to evaluate the effect of each study on the overall estimate. Publication bias was assessed using a funnel plot and Begg’s and Egger’s test [35,36]. Power calculation was conducted using the methodology described by Cafri et al [37]. All statistical analyses were performed using Stata version 10 (Stata Corp LP, College Station, TX, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA). All reported P values are 2 sided and $P < .05$ was regarded as statistically significant.

3. Results

3.1. *Literature search*

Four hundred and twenty-three articles were identified from Embase, 337 articles from PubMed and 140 articles from Cochrane in a process illustrated in Fig. 1. After exclusion of 348 duplicate studies, 552 articles remained. The titles and abstracts were screened, and 535 were excluded primarily because they were case-control, cross-sectional, non-human, and/or irrelevant studies, or reviews, editorials, or protocols. Seventeen seemingly relevant articles remained following this screening process. After a full-text review of these 17 articles, 2 articles [38,39] were excluded that examined the association between the age of introduction of complementary feeding and the risk of being overweight or obese in adulthood, and 5 articles [10–13,24] were excluded because they did not report the RRs and the corresponding 95% CIs of interest or provide sufficient data by which to calculate them. Of the remaining 10 articles, 3 were separated by outcomes measured into overweight and obesity [9,15,23], where each study was regarded as two separate studies. In 5 other articles, only being overweight, and not being obese, was looked at as an outcome [14,17,18,22,31], while 2 articles only looked at being obese, and not being overweight, as an outcome [16,30]. In total, 10 articles consisting of 13 studies were included in this meta-analysis.

3.2. *Study characteristics*

The characteristics of the studies included in this analysis are presented in Table 1. In total, 10 articles reported 13 results based on the inclusion of different outcomes. These studies were published between May 2005 and February 2015. Of these reports, 3 were conducted in the United Kingdom, 2 in the United States, 2 in China, 1 in Brazil, 1 in India, and 1 in Australia. All included studies were population-based birth cohort studies with the number of participants ranging from 307 to 40,510 with a total of 53,605 for overweight and from 847 to 40,510 with a total of 56,136 for obesity. Overweight and obesity were determined by BMI, which was calculated from measurements of bodyweight (kg) and height (m). Age at introduction of complementary foods was recorded by self-administered or interviewer-administered questionnaire. The age of the participants ranged from 3 to 11 years old. When assessing quality, all studies received scores of 6 or higher on the Newcastle-Ottawa Quality Assessment Scale with an average score of 8.1 and, therefore, were considered to be of high methodological quality.

3.3. *Association between the age at introduction of complementary feeding and risk of being overweight*

Eight studies included in the analysis evaluated the risk of children being overweight following the early introduction of complementary foods at <4 months compared to a later introduction at 4 to 6 months. Fig. 2a presents the results from the random-effects model of combining the risk estimates. Of these 8 studies, 5 identified a significant direct

Table 1 – Characteristics of studies in the meta-analysis of the age at introduction of complementary foods in relation to risk of childhood overweight or obesity.

First author	Publication Year	Country	Length of follow-up	Number of participants	Number of cases	Outcomes	Definitions of outcome	Categories of age at introduction of complementary foods and RRs (95% CIs)
Zheng [9]	2015	China	4.5	40,510	5911	Overweight	BMI z-score ≥1 SD	≤3 mo, population: 26,229 (case: 3983); 4-6 mo, population: 13,106 (case: 1761); >6 mo, population: 1175 (case: 167)
Lin [22]	2013	China	5	3571	553	Overweight	IOTF age- and sex-specific BMI cutoff points	<3 mo,RR: 0.95 (0.29 3.17) 3-4 mo,RR: 0.92 (0.60-1.43) 5-6 mo,RR: 1 (reference) 7-8 mo,RR: 1.08 (0.70,1.67) >8 mo,RR: 1.14 (0.69,1.86)
Caleyachetty [31]	2013	Indian	5	529	54	overweight	Age- and sex-specific BMI >90th percentile	≤3 mo, population: 100 (case: 12); 4-5 mo, population: 346 (case: 35) ≥6 mo, population: 83 (case: 7)
Abraham [14]	2012	Scotland	3	3460	421	Overweight	BMI Z-score ≥1.04	0-3 mo,OR: 1 (reference); 4-5 mo, OR: 0.74 (0.57-0.97); 6-10 mo, OR: 0.72 (0.48-1.09) 0-3 mo, population: 522 (case: 86); 4-5 mo, population: 2319 (case: 269); 6-10 mo, population: 619 (case: 66)
Huh [15]	2011	USA	3	847	223	Overweight	Age- and sex-specific BMI ≥85th percentile	<4 mo, population: 134 (case: 50); 4-5 mo, population: 590 (case: 146); ≥6 mo, population: 123 (case: 27)
Seach [17]	2010	Australia	10	307	85	Overweight	IOTF age- and sex-specific BMI cutoff points	≤5 mo, population: 170 (case: 59); 5-6 mo, population: 70 (case: 13); ≥6 mo, population: 67 (case: 13)
Neutzling [23]	2009	Brazil	11	1204	280	Overweight	Age- and sex-specific BMI ≥85th percentile	<4 mo,RR: 0.77 (0.58-1.02); ≥4 mo, RR: 1 (reference);
Hawkins [18]	2009	UK	3	13,177	3085	Overweight	IOTF age- and sex-specific BMI cutoff points	<4 mo,OR: 1.12 (1.02,1.23); ≥4 mo,OR: 1 (reference)
Zheng [9]	2015	China	4.5	40,510	1288	Obesity	BMI z-score ≥2 SD	≤3 mo, OR: 1.03 (0.91-1.18); 4-6 mo, OR: 1 (reference); >6 mo, OR: 0.96 (0.64-1.42)
Gooze [16]	2011	USA	5	6800	1183	Obesity	Age- and sex-specific BMI ≥95th percentile	≤3 mo, population: 1350 (case: 294); 4-5 mo, population: 3200 (case: 518); ≥6 mo, population: 2250 (case: 371)
Huh [15]	2011	USA	3	847	75	Obesity	Age- and sex-specific BMI ≥95th percentile	<4 mo, population: 134 (case: 26); 4-5 mo, population: 590 (case: 38); ≥6 mo, population: 123 (case: 11)
Neutzling [23]	2009	Brazil	11	1204	140	Obesity	Age- and sex-specific BMI ≥85th percentile, and triceps and subscapular skinfolds ≥90th percentile	<4 mo, RR: 0.88 (0.55 1.41); ≥4 mo,RR: 1 (reference);
Reilly [30]	2005	UK	7	6775	560	Obesity	Age- and sex-specific BMI ≥95th percentile	<1 mo, OR: 0.88 (0.42-1.87); 1-2 mo, OR: 1.08 (0.50-2.32); 2-3 mo, OR: 1.48 (1.01-2.16); 3-4 mo, OR: 1.08 (0.831.39); 4-6 mo, OR: 1 (reference)

association between the age at introduction of complementary feeding and being overweight, while 3 did not find a significant relationship. Overall, children who started complementary feeding before 4 months of age had a higher risk of being overweight compared to children who started at 4 to 6 months (the pooled RR, 1.18; 95% CI, 1.06-1.31). Statistically significant heterogeneity was observed across these studies (P = .004, I^2 = 65.9%).

Due to insufficient dichotomous data, only 6 of the 8 studies were included in the analysis of the risk of subjects

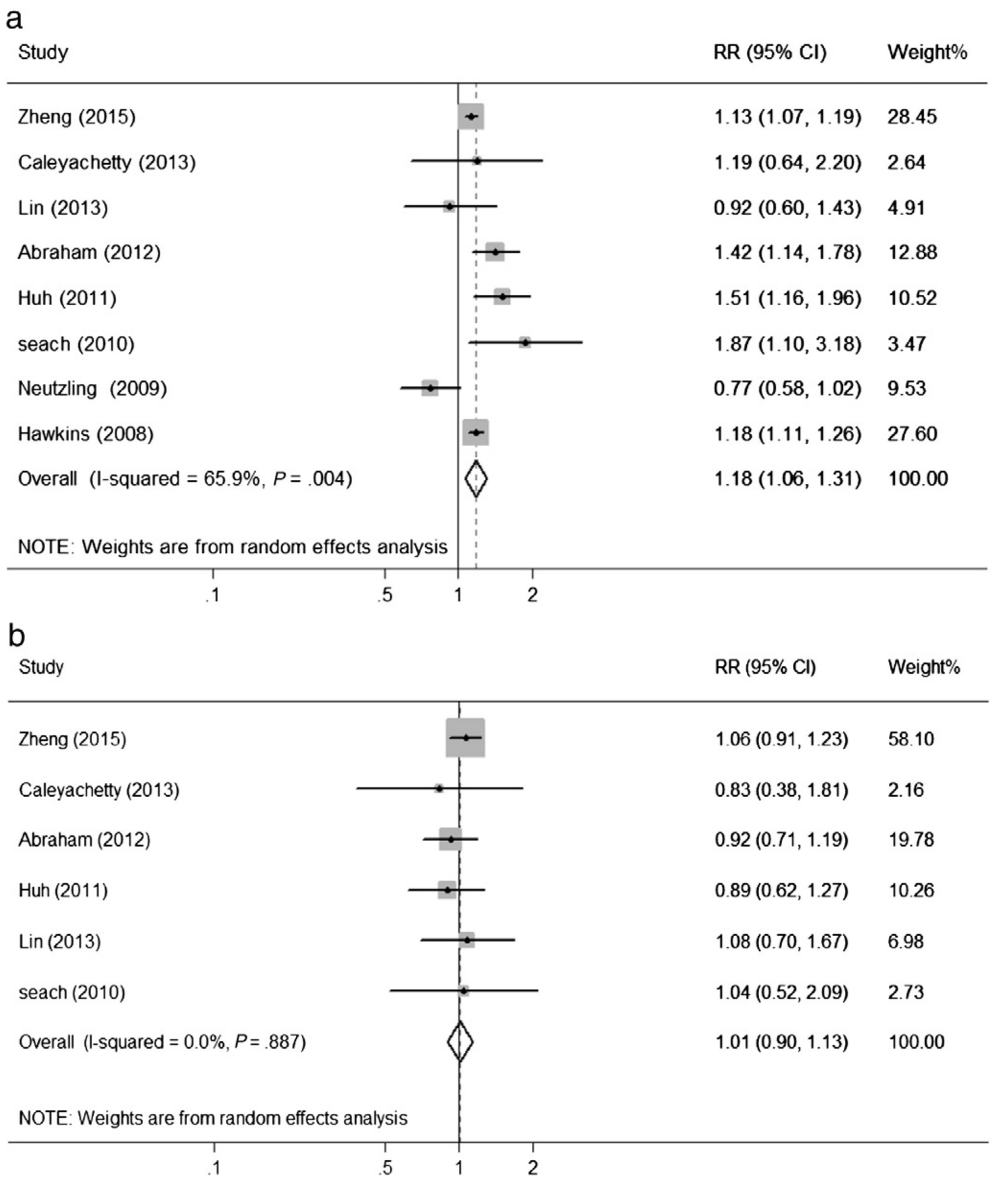

Fig. 2 – Forest plots of the associations between the age at introduction of complementary foods and risk of childhood overweight. a, Forest plot of the risk of childhood overweight associated with the age at introduction of complementary foods <4 months versus at 4 to 6 months. b, Forest plot of the risk of childhood overweight associated with the age at introduction of complementary foods ≥6 months versus at 4 to 6 months.

being overweight following a delayed introduction of complementary foods at ≥6 months compared to 4 to 6 months. The fixed-effects model combining the risk estimates is presented in Fig. 2b. The pooled RR of being overweight was 1.01 with a 95% CI of 0.90 to 1.13. No effect of heterogeneity on the RRs was observed ($P = .887$, $I^2 = 0.00\%$).

3.4. *Association between age at introduction of complementary feeding and risk of being obese*

This meta-analysis included five studies on the risk of children becoming obese following an early introduction of complementary foods at <4 months compared to 4 to 6 months. The random-effects model combining the risk estimates is shown in Fig. 3a. Of these 5 studies, 3 detected a significant direct relationship, while 2 did not. Overall, children introduced to complementary foods early at <4 months compared to 4 to 6 months had a higher risk of obesity (the pooled RR, 1.33; 95% CI, 1.07-1.64). Statistically significant heterogeneity was observed across the included studies ($P < .001$, $I^2 = 81.9\%$).

Due to insufficient dichotomous data, only 3 of the 5 studies were included in the analysis of the risk of obesity in children with a late introduction to complementary foods at ≥6 months compared to 4 to 6 months. The fixed-effects model combining the risk estimates is shown in Fig. 3b. The pooled RR of obesity was 1.02 with a 95% CI of 0.91 to 1.14. No effect of heterogeneity on the RRs was observed ($P = .525$, $I^2 = 0.00\%$).

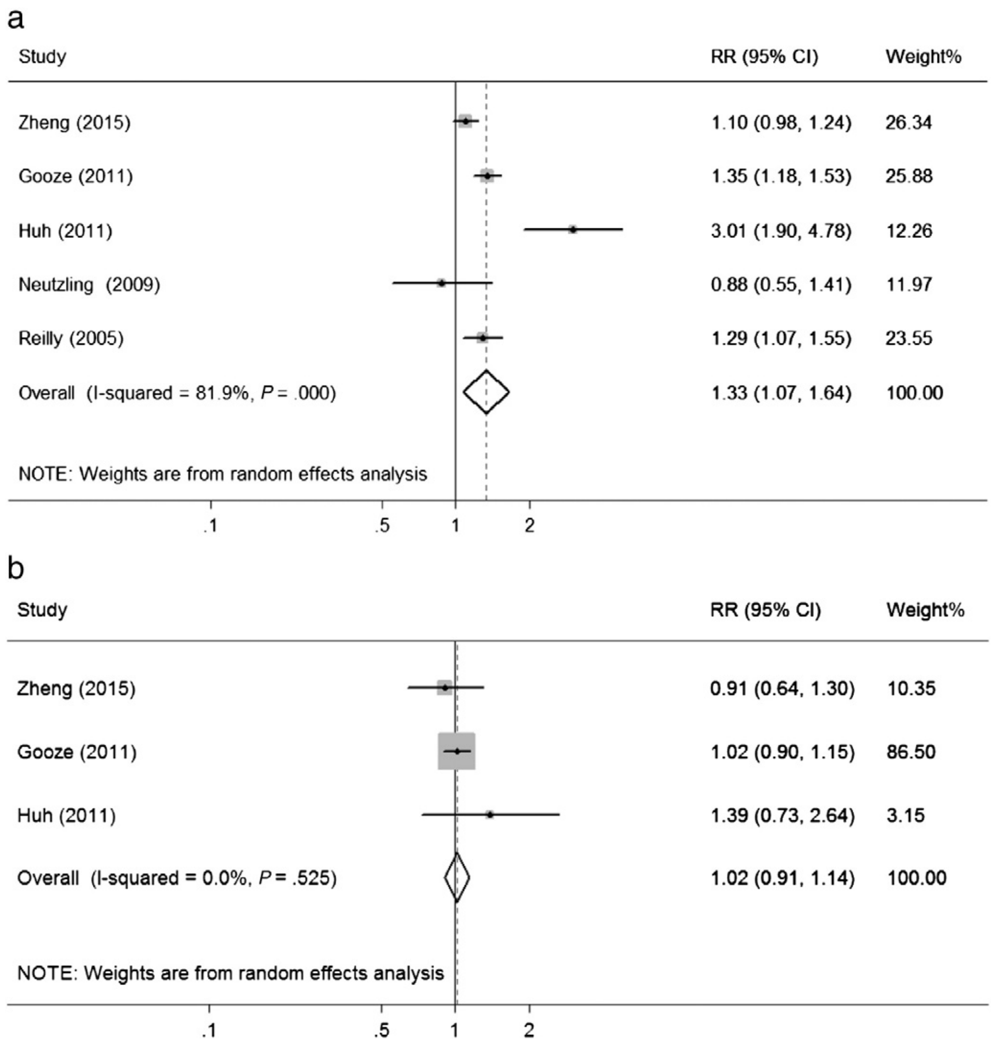

Fig. 3 – Forest plots of the associations between the age at introduction of complementary foods and risk of childhood obesity. a, Forest plot of the risk of childhood obesity associated with the age at introduction of complementary foods <4 months versus at 4 to 6 months. b, Forest plot of the risk of childhood obesity associated with the age at introduction of complementary foods ≥6 months versus at 4 to 6 months.

3.5. *Subgroup and sensitivity analyses*

To explore the possible sources of heterogeneity among subgroups, stratified analyses were performed on countries, definitions of outcomes, length of follow-up and number of participants. As shown in Table 2, when being overweight was the measured outcome, the early introduction of complementary foods was significantly associated with an increased risk of being overweight for children in developed counties, where the definition of being overweight was other than by IOTF or BMI ≥85th percentile, length of follow-up was <6 years and the number of participants was ≥5000. Furthermore, the relatively higher heterogeneity was observed between groups from developing and developed countries, where the definition of overweight was BMI ≥85th percentile, length of follow-up was ≥6 years and the number of participants <5000 (I^2 was 60.7%-91.5%). Evaluation of obesity yielded similar findings, which the early introduction of complementary foods significantly increased the risk of obesity in children in developed counties, where the definition of obesity was BMI ≥95th percentile, and length of follow-up was <6 years. However, higher heterogeneity was also found between these subgroups (I^2 was 82.7% to 89.9%).

The results of the sensitivity analyses are shown in Table 3. When focusing on being overweight as the outcome, the heterogeneity between studies was reduced when the study conducted by Neutzling et al was excluded (I^2 = 51.6%, P = .054), but the overall effect size did not drastically change (RR, 1.22; 95% CI, 1.11-1.33). When obesity was the outcome, the heterogeneity between the studies was reduced when Huh's study was omitted from the meta-analysis (I^2 = 59.8%, P = .058), and the association between the early introduction of complementary foods and the risk of obesity was still significant (RR, 1.21; 95% CI, 1.05-1.38).

Table 2 – Subgroup analyses of risk of childhood overweight or obesity and the age at introduction of complementary foods (<4 months vs 4-6 months).

	Number of studies	RR (95% CI)	*P* for heterogeneity [a]	I^2
Overweight				
Total	8	1.18 (1.06-1.31)	.004**	65.9%
Countries				
Developing counties	4	0.99 (0.78-1.25)	.054	60.7%
Developed counties	4	1.36 (1.14-1.63)	.049*	61.9%
Definitions of overweight				
IOTF	3	1.21 (0.92-1.59)	.125	51.8%
BMI ≥85th percentile	2	1.08 (0.56-2.09)	.001**	91.5%
Others	3	1.22 (1.03-1.44)	.147	47.9%
Length of follow-up				
<6 y	6	1.19 (1.10-1.29)	.096	46.5%
≥6 y	2	1.16 (0.49-2.77)	.004**	88.1%
Number of participants				
≥5000	2	1.15 (1.10-1.20)	.305	5.0%
<5000	6	1.21 (0.92-1.60)	.002**	73.2%
Obesity				
Total	5	1.33 (1.07-1.64)	<.001***	81.9%
Countries				
Developing counties	2	1.09 (0.97-1.22)	.367	0.0%
Developed counties	3	1.58 (1.07-2.14)	.003**	82.7%
Definitions of obesity				
BMI ≥95th percentile	3	1.58 (1.17-2.14)	.003**	82.7%
Others	2	1.09 (0.97-1.22)	.367	0.0%
Length of follow-up				
<6 y	3	1.49 (1.08-2.05)	<.001***	89.9%
≥6 y	2	1.14 (0.80-1.62)	.138	54.5%
Number of participants				
≥5000	3	1.23 (1.08-1.42)	.059	64.6%
<5000	2	1.63 (0.49-5.44)	<.001***	92.5%

a. **P* < .05; ***P* < .01; ****P* < .001.

3.6. *Publication bias and power analysis*

Visual inspection of a funnel plot, shown in Fig. 4, failed to identify substantial asymmetry. Begg rank correlation and Egger linear regression tests also gave no evidence of publication bias among the studies. For studies where the outcome was being overweight, Begg's $Z = 0.25$ and $P = .805$, and Egger's test $t = 0.47$ and $P = .662$. When obesity was the outcome, Begg's $Z = 0.73$ and $P = .462$, and Egger's test $t = 1.19$ and $P = .321$. Power analysis was conducted following the methodology provided by previous study [37]. The power of the estimate of early complementary feeding (before 4 months of age) with risk of childhood overweight and obesity was 13.71% and 11.23%, respectively.

4. Discussion

The data from ten prospective studies was reanalyzed to determine if there is an association between the age at which complementary foods are introduced to infants and the risk of being overweight or obese in children aged 3 to 11 years old. It was found that the introduction of complementary foods before 4 months of age was associated with an increased risk of being overweight or obese during childhood, but delaying this introduction after 6 months showed no relationship with overweight or obesity.

The mechanisms behind this association between an earlier introduction to solid foods and a higher risk of being overweight or obese are uncharacterized. One possibility is that an early introduction to solids is associated with an increased intake of calories [40] and protein [41] during infancy, which, when occurring during the first year of life, is predictive of greater weight gain and percent body fat in childhood [42]. Another potential mechanism is related to the intricate interactions between breastfeeding and complementary feeding. A number of studies have determined breastfeeding for a longer duration is protective against childhood obesity [43,44], and an earlier introduction of solid foods increases the likelihood of premature termination of breastfeeding [45,46]. Furthermore, formula-fed children are typically given an earlier introduction to solid foods than breastfed children, and, therefore, seem to be more affected by the timing of complementary feeding [40,47]. This hypothesis is supported by Huh's study [15], which reports that introducing solid food before 4 months was associated with an almost 6-fold increase in the risk of obesity among 3-year-old formula-fed infants, but not in breastfed infants. Other mechanisms may involve biological alternations directly related to weight regulation, such as adipogenesis [48], appetite control [48], and food preferences [49]. Interestingly, several studies demonstrated that alterations in gut flora resulting from the introduction of specific dietary components in solid foods may lead to epigenetic modification of metabolism genes, thus increasing the likelihood of obesity [50,51]. Taken together, our work in conjunction with other studies suggests that an early introduction to complementary foods increases the susceptibility of individuals to an obesogenic environment. Further investigations are needed on the role of these mechanisms underlying the effect of timing of complementary foods introduction on the risk of obesity.

Findings in the present study concerning the association between the age at which complementary feeding started and the risk of being overweight or obese in childhood were consistent with the findings of a number of previous publications [9–18,30], but not others [22–24,31]. Two recent systematic reviews have been conducted on this topic. One review was by Moorcroft et al in 2011 and included 24 studies conducted in developed countries. They found no clear association between the age at which solid food was introduced, and the risk of being overweight or obese during infancy and childhood [26]. The other systematic review was conducted by Pearce et al in 2013, and covered 23 studies conducted in both developed and developing countries. This review drew a similar conclusion to Moorcroft's study that there was no clear association between the age at introduction of complementary foods and being overweight or obese in childhood, although some evidence suggested that a very early introduction at or before 4 months of age, rather than at

Table 3 – Sensitivity analyses of risk of childhood overweight or obesity and the age at introduction of complementary foods (<4 months vs 4-6 months).

First author	Publication year	RR (95% CI)	*P* for heterogeneity [a]	I^2
Overweight				
None	—	1.18 (1.06-1.31)	.004**	65.9%
Hawkins [18]	2008	1.19 (0.99-1.43)	.003**	69.9%
Neutzling [23]	2009	1.22 (1.11-1.33)	.054	51.6%
Seach [17]	2010	1.16 (1.05-1.29)	.008**	65.5%
Huh [15]	2011	1.15 (1.03-1.27)	.011*	63.6%
Abraham [14]	2012	1.15 (1.03-1.28)	.009**	65.1%
Lin [22]	2013	1.20 (1.07-1.33)	.003**	69.2%
Caleyachetty [31]	2013	1.18 (1.06-1.32)	.002**	70.8%
Zheng [9]	2015	1.20 (1.01-1.44)	.004**	68.3%
Obesity				
None	—	1.33 (1.07-1.64)	<.001***	81.9%
Reilly [30]	2005	1.35 (1.02-1.80)	<.001***	86.3%
Neutzling [23]	2009	1.40 (1.12-1.78)	<.001***	84.9%
Huh [15]	2011	1.21 (1.05-1.38)	.058	59.8%
Gooze [16]	2011	1.34 (0.98-1.84)	<.001***	84.7%
Zheng [9]	2015	1.43 (1.07-1.90)	.002**	80.0%

a. *P < .05; **P < .01; ***P < .001.

4 to 6 months or >6 months, may increase the risk of being overweight as a child [25]. It is important to note that the study design, the categories of age at introduction of complementary food and outcome measurements differed between studies included in these 2 reviews. The heterogeneity among these studies made drawing a clear or

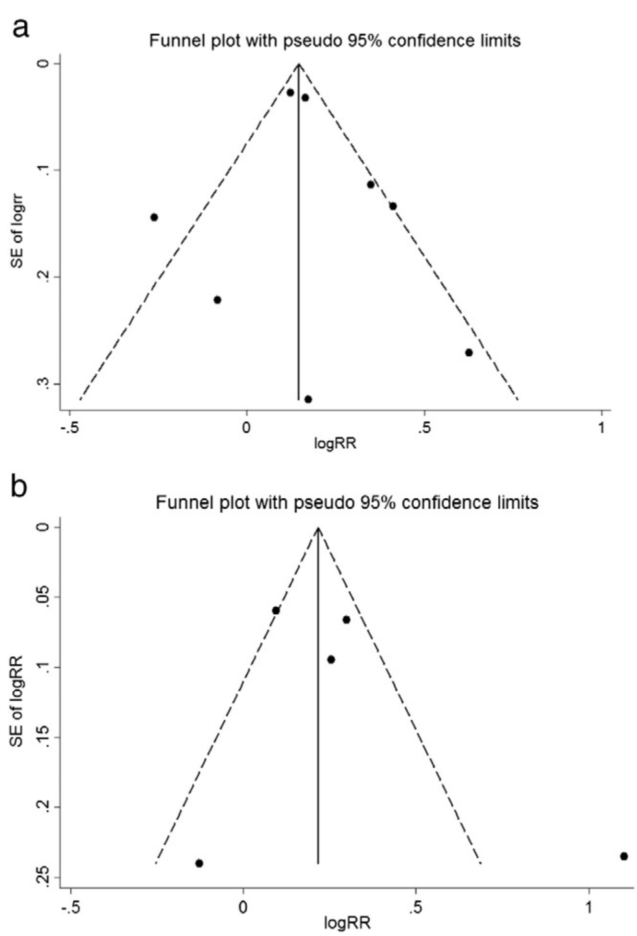

Fig. 4 – Funnel plot of standard error by log relative risks of childhood overweight or obesity associated with the age at introduction of complementary foods <4 months versus at 4 to 6 months. a, Funnel plot of standard error by log relative risk for overweight b. Funnel plot of standard error by log relative risk for obesity.

quantitative conclusion challenging, despite the rigorous systematic methods was used in these 2 reviews.

To the best of the authors' knowledge, this meta-analysis is the first attempt to quantitatively assess the relationship between the age when complementary foods are introduced and the risk of being overweight or obese as a child. Accordingly, the present study used different eligibility criteria and study methodologies from previous systematic reviews [25,26,52]. First, data was collected only from prospective cohort studies, which had more potential to assess causality than case-control studies or cross-sectional studies. Furthermore, analysis of only studies that reported RRs and 95% CIs or original data from which RRs and 95% CIs could be calculated allowed quantitative analysis. Second, a relatively consistent cut-off age was used to define an early (<4 months or ≤3 months) versus late (≥6 months) introduction to complementary foods. In addition, the information on infant feeding was collected during infancy and early childhood (<2 y), minimizing the likelihood of recall bias. Finally, outcomes measured were defined as being overweight or obese, and all studies stated specific definitions of these outcomes. Studies excluded from this analysis were those that only reported predetermined relevant measures (such as bodyweight gain, BMI or Z score, body composition, skinfold or ponderal index) [53–58] without a specific definition for overweight or obese. These studies were excluded with the aim of making the effect estimates more precise.

Despite the above described design, analyses of heterogeneity still found that definitions of overweight and obesity, length of follow-up and number of participants were potential sources of heterogeneity. The definitions of being overweight and obese differed between studies as there was no widely accepted standard until recently [59]. Every definition of overweight and obesity has advantages and limitations. For example, setting the 85th or 95th percentile of BMI as a cut-off for being overweight or obese was arbitrarily based on US data that may not be applicable to the Asian population [60]. However, all directions of the association based on any definitions were the same (RR >1.00), suggesting the association between the timing of introduction of complementary foods and overweight or obesity risk may be true. The discrepancy in length of follow-up may affect results, and longer follow-up duration may dilute the associations examined as later dietary factors contribute more to the risk of being overweight or obese. Regarding the high degree of heterogeneity in the sample size of studies, a relatively small sample size in a cohort study, where the sample size is <5000 subjects, may lead to an unstable result because the significant association may be a chance finding.

Due to the complexity of the causes of children being overweight or obese, identifying and adjusting for confounding variables is necessary. In the present meta-analysis, all included studies measured potential confounders, such as maternal BMI, level of education, socioeconomic status, smoking during pregnancy, infant sex, birth weight, and breastfeeding status, but only a few studies adjusted for them [22,23]. Furthermore, some RRs that were calculated in this analysis from original data were not adjusted for confounding factors because the categories for age at introduction of complementary foods in those studies did not conform to our definitions. This may affect the validity of the findings.

Two other limitations in this meta-analysis should be noted. First, some studies were omitted from analyses based on inclusion/exclusion criteria, which is the methodological limitation for systematic reviews or meta-analyses. Four recently published cohort studies [10–13] were not included in this meta-analysis due to the data being categorized by different age groups for when solid foods were introduced and for which RRs were calculated than defined in our analyses. However, it is unlikely this would significantly affect the results of this analysis, because 3 of 4 of those studies reported similar findings to ours. Second, a dose-response or trend analysis was not performed to provide further evidence for limited eligible studies. Thus, further meta-analysis of longitudinal observational studies are needed to determine if there is a dose-response between the age at introduction of complementary feeding and the risk of being overweight or obese as a child.

In summary, our meta-analysis of prospective cohort studies firstly shows a significant positive association between the introduction of complementary food before 4 months of age and risk of being overweight or obese in childhood. Based on the results, avoidance of very early introduction of complementary foods needs to be promoted in the infant feeding practice. Meanwhile, this present study found no significant protection from being overweight or obese during childhood by delaying the introduction of complementary foods after the infant had reached 6 months. Further studies using larger sample sizes and controlled for appropriate confounders are warranted to verify these findings.

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