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REVIEW ARTICLE

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Age at adiposity rebound and the relevance for obesity: a systematic review and meta-analysis

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OBJECTIVES: To understand the sex difference in age at adiposity rebound (AR), integrate the prevalence of early AR (EAR), and provide a quantitative association between early age at AR and overweight/obesity.
METHODS: Literature review was conducted in different databases, including the Web of Science, PubMed, EMBASE, Wiley, Chinese National Knowledge Infrastructure, and ScienceDirect databases up to August 2021. Studies that reported data related to AR were considered for inclusion. Pooled effect sizes and their respective 95% confidence intervals (CIs) were calculated using random effects models, depending on the size of heterogeneity. Heterogeneity was tested by using the I^2 statistics.
RESULTS: 28 studies with a combined sample size of 106,397 people were included in the final meta-analysis. Girls had a significantly earlier age of AR than boys (mean difference = 3.38 months; 95% CI 2.14–4.63). The overall prevalence of EAR was 40% (95% CI 31% to 50%), and the prevalence in girls was 5% higher than that in boys based on the definition of age at AR < 5.0–5.1 years. The overall pooled prevalence of EAR showed an increasing trend by child's birth year [1934–1973]: 29% (95% CI 22% to 37%), 1991–2001: 35% (95% CI 26% to 44%), and 2002–2009: 52% (95% CI 40–63%). Early age at AR (age at AR < 5.0–5.1 years) was associated with a significantly increased risk of overweight/obesity (OR = 5.07; 95% CI 3.60–7.12), overweight (OR = 3.10; 95% CI 1.69–5.70), and obesity (OR = 6.97; 95% CI 4.32–11.26) from the preschool period to adulthood.
CONCLUSIONS: The overall prevalence of EAR is increasing, and girls experience AR earlier than boys. The early age at AR in children may be an early and effective marker of obesity.

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INTRODUCTION

Obesity is a major challenge facing global health in the 21st century. It has been recognized that adult obesity is associated with a series of chronic non-communicable diseases (NCDs), including type II diabetes, cardiovascular disease, and cancer, and the incidence and mortality of NCDs are significantly increasing [1–3]. For children and adolescents, a study involving 200 countries from 1975 to 2016 found that the global age-standard obesity prevalence rate increased from 0.7% in 1975 to 5.6% in 2016 among girls and from 0.9% in 1975 to 7.8% in 2016 among boys [4]. Especially in 2016, approximately 124 million children and adolescents aged 5 to 19 were obese, and 213 million were overweight [4].

Although childhood obesity also predicts adolescent and adult obesity [5] and is related to many long-term negative metabolic effects [6–8], most children with obesity will not become adults with obesity. Similarly, some adults with obesity did not show obesity characteristics in children, especially in early childhood [9]. Therefore, BMI status in early childhood may not be an ideal predictor of adult obesity [10].

Many researchers have revealed that individuals with an early age at adiposity rebound (AR) tend to be overweight or obese [10, 11]. Body mass index (BMI) shows a specific physiological trend in human early growth and development. It rises rapidly within 9 to 12 months after birth and then declines gradually [10]. Generally, the lowest BMI value appears at 3–8 years old and then rises again. In 1984, Rolland-Cachera et al. [10] first defined the point of minimal BMI as AR. Age at AR is a critical marker and may be one of the early effective predictors of obesity in later childhood, adolescence, and adulthood [9, 10]. Studies have shown that early adiposity rebound (EAR) increases the risk of obesity that initiates in childhood [12–17] and is closely associated with metabolic syndrome [17, 18] and cardiovascular diseases [19, 20]. The age at AR for children seems to be getting earlier. Dorosty et al. [21] found that AR in England occurred earlier than it was several decades ago. In Poland, studies also revealed that children's age at AR was younger in 2010 than in 1983 and that this phenomenon occurred not only in the 85th percentile of BMI but also in the 50th and 15th percentiles of BMI [22, 23]. Between 1934 and 1944, the average age of AR was 5.8 years, and the proportion of AR < 5 years old was 32.4% in Finland [24]. In contrast, the average age at AR in children born in Portugal from April 2005 to August 2006 was 5.16 years old, 42.6% of whom

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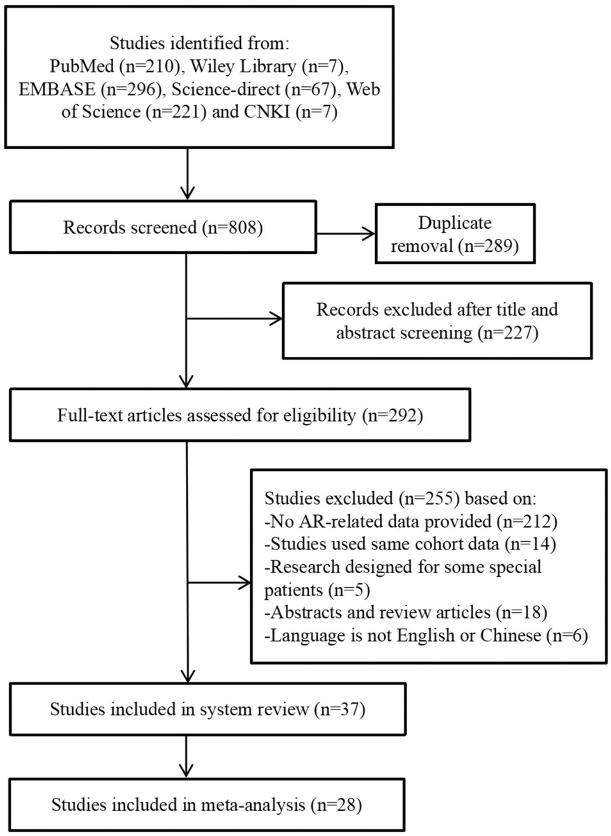

Fig. 1 Flow chart of the data extraction.

were under 5 years old [25]. Data from the longitudinal national cohort of South Korea showed that the proportion of children born in 2008–2012 with AR < 57 months was 77.2% [26]. In China, a national birth cohort found that 43.5% of children had AR before 4 years [17].

However, no study has systematically integrated age at AR or quantified the prevalence of EAR and its secular trend. The quantitative association between age at AR and subsequent fatness is not clear. In the current study, we summarized the published literature related to AR to provide an overview of the sex difference in the average age at AR and the prevalence of EAR and to investigate the relationship between age at AR and overweight/obesity.

SUBJECTS AND METHODS

This systematic review protocol has been registered on PROSPERO as CRD42021246140. This study followed the recommendations for conducting and reporting the meta-analysis (PRISMA) [27, 28].

Data sources and literature search

Two investigators (Ji-Xing Zhou, Fu Zhang) performed comprehensive literature searches independently on PubMed, EMBASE, Web of Science, ELSEVIER ScienceDirect (SDOS), Wiley Online Library, and Chinese National Knowledge Infrastructure (CNKI) of all published papers up to August 2021. The search terms were ‘adiposity rebound’, ‘BMI rebound’, and ‘body mass index rebound’. Similar Chinese technical terms were adopted to search for eligible articles in CNKI.

Original studies with data related to AR were considered for inclusion. The following criteria were used to include published studies: (1) Design: longitudinal studies; (2) Participants: children with multiple repeated measures of BMI (height and weight); (3) Effect size: ① mean age and standard deviation (SD) at AR in different sexes; ② prevalence of EAR and the definition of EAR; ③ odds ratios (ORs) and the 95% confidence intervals (CIs) or sufficient data to calculate an effective size between earlier at AR and later overweight/obesity; (4) Others: reporting the children’s birth year (or when the study started), and for AR reporting both the case population and the normal population, we only extracted data from the normal population. In addition, the following criteria were used to exclude published studies: (1) studies designed for particular patients; (2) abstracts and review articles; (3) animal studies; (4) written in neither English nor Chinese; (5) focus on late AR; (6) other AR-related research not related to research goals. For some studies using the same cohort data or database, we used a study with more complete data and a larger sample size.

Study selection and data extraction

All data were independently extracted by the two reviewers. In case of disputes during data collection, consensus should be reached through conferral. First, we searched papers in six databases using the proposed search formula. After retrieval, all articles were imported into EndNote X8.2, and duplicate studies were removed. Then, irrelevant literature was excluded by reading the titles and abstracts. Finally, the relevant data were extracted by reading the full text and references.

When describing the prevalence of EAR and mean age at AR by sex, available information, including the first author’s name, publication year, birth year, country, sample size, the definition of EAR, prevalence of EAR, and the mean age and SD at AR in different sexes, was extracted. To understand the relationship between age at AR and later obesity, the information we extracted or calculated included the first author’s name, publication year, birth year, country, sample size, the definition of early age at AR, age, and criteria for overweight/obesity assessment, and ORs and their 95% CIs between early age at AR and overweight/obesity. The definition of overweight/obesity was based on internationally or nationally recognized standards.

Quality assessment

Two reviewers independently assessed study quality using the Newcastle–Ottawa Scale (NOS) [29]. The NOS criteria covered three aspects, i.e., selection, comparability, and exposure. The total NOS score ranged from 0 to 9, and a score of 7 or higher was regarded as high quality.

For studies reporting the prevalence of EAR that were eventually included in the meta-analysis, we also assessed the quality and risk of bias of studies using the Joanna Briggs Institute (JBI) tool [30], which was used by authors conducting systematic reviews, particularly on prevalence. This tool consists of a rating list with ten criteria, which can be assessed as ‘yes’ (= 1); ‘no’ (= 0), ‘not applicable’ (= NA) or ‘unclear’ (=?); Therefore, the score for each study ranged from 0 to 10. Based on this score, we divided each study into low-risk (7–10), moderate-risk (4–6), or high-risk of bias (1–3).

At the end of the quality review, in the absence of consensus, the third reviewer (Xiao-yun Qin) evaluated the quality of the study and made the most correct evaluation based on the results of the previous two reviewers.

Statistical analysis

The analysis was conducted using STATA (version 15.0). $P < 0.05$ was considered statistically significant.

In studies that reported the mean age at AR and SD for boys and girls, pooled mean differences and 95% CIs were calculated to compare the differences in AR between the sexes. Then, we conducted a subgroup analysis stratified by birth years (born between 1934 and 1988; born between 1988 and 1998; born between 1999 and 2009).

Table 1. Characteristics of selected studies.

Authors; Country	Sample size (boy/girl)	Birth year	Definition of EAR	Results			Quality score
				Prevalence of EAR (boy/girl)	Mean age at AR (SD) by sex (year)	Age for weight assessment; OR (95%CI)	
Characteristics of studies included in the meta-analysis							
Eriksson et al. [24], 2003; Finland	6,060 (NI / NI)	1934–1944	Before 5 years old	32% (NI / NI)	NI	NI	9
Koivuaho et al. [35], 2019; Finland	1,010 (NI / NI)	1966	Before 5.1 years old	25% (NI / NI)	NI	NI	9
Bhargava et al. [36], 2004; India	1,243 (NI / NI)	1969	Before 5 years old	19% (NI / NI)	NI	NI	8
Williams and Goulding [37], 2009; New Zealand	458 (239 / 219)	1972–1973	Before 5.5 years old (boys) / Before 5 years old (girls)	NI (19% / 23%)	NI	**26 years old** [b] *Obesity:*5.91(3.03,11.55)[*]; *Overweight:* 2.7(3.03,11.55)	7
Freedman et al. [38], 2001; America	105 (46 / 59)	1969	Before 5 years old	53% (46% / 59%)	NI	NI	7
Hughes et al. [39] 2014; Britain	907 (NI / NI)	1991–1992	Before 5.08 years old	27% (NI / NI)	NI	**15 years old** [c] *Obesity:*3.31(1.98,5.55) *Overweight:*2.04(1.20,3.48)	8
Campbell et al. [40], 2011; Australia	299 (146 / 153)	1998–2000	Before 5 years old	27% (21% / 33%)	NI	**6.5 years old** [d] *Overweight&Obesity:*15.31(7.74,30.30)	7
Taylor et al. [41], 2004; New Zealand	39 (- / NI)	1998–2001	Before 5 years old	49% (NI / NI)	NI	**9 years old** [NI] *Overweight:*3.64(2.84,6.89)	7
Börnhorst et al. [42], 2017; European countries	4,373 (2,239 / 2,134)	2005–2006	Before 5 years old	37% (42% / 33%)	NI	**9.2 years old** [d] *Obesity:*22.37(10.90,46.35); *Overweight:*8.20(6.60,10.19)	9
Gonzalez et al. [43], 2014; Chile	910 (455 / 455)	2002–2003	Before 5 years old	44% (41% / 47%)	NI	NI	8
Hubbard et al. [44], 2021; America	49,062 (26,413 / 22,649)	2006–2010	Before 5 years old	67% (65% / 68%)	NI	NI	9
Ip et al. [45], 2017; America	190 (89 / 101)	2008–2009	Before 5 years old	69% (65% / 72%)	NI	**Years 2 after AR** [e] *Obesity:* 6.87(2.69,17.55); *Overweight:* 2.18(0.95,5.01) **Years 1 after AR** [e] *Obesity:* 4.25(1.73,10.46); *Overweight:* 1.91(0.83,4.41)	7
Freedman et al. [46], 2021; America	17,077 (8,971 / 8,106)	2006	Before 5 years old	51% (47% / 55%)	NI	**13 years old** [e] *Obesity:*8.70(7.87,9.63)	8
Koyama et al. [18], 2014; Japan	271 (147 / 124)	1995–1996	Before 5 years old	43% (44% / 43%)	*Boy* 4.8(1.4); *Girl* 4.7 (1.5)	NI	7
Günther et al. [47], 2006; Germany	313 (161 / 152)	1985	Before 4 years old	27% (NI / NI)	*Boy* 5.6(1.5); *Girl* 5.2 (1.7)	NI	8
Fonseca et al. [25], 2021; Portugal	3,372 (1,750 / 1,622)	2005–2006	Before 5 years old	43% (42% / 44%)	*Boy* 5.19(1.28); *Girl* 5.12(1.33)	NI	9
Sabo et al. [48], 2017; America	647 (328 / 319)	1929	NI	NI	*Boy* 5.89(2.28); *Girl* 5.93(3.70)	NI	7
Guzzardi et al. [49], 2016; Finland	1,080 (471 / 609)	1934–1944	NI	NI	*Boy* 5.9(0.9); *Girl* 5.8 (1.0)	NI	8
Sovio et al. [20], 2014; Finland	4,228 (2,116 / 2,112)	1966	NI	NI	*Boy* 5.8(0.9); *Girl* 5.6 (1.0)	NI	8
Whitaker et al. [14], 1998; America	390 (155 / 235)	1965–1971	Before 4.8 years old	33% (NI / NI)	*Boy* 5.8 (1.9); *Girl* 5.4 (1.7)	**20–29 years old** [a] *Obesity:*3.16(1.78,5.61) [*]	7
Williams et al. [50], 1998; New Zealand	922 (474 / 448)	1972–1973	NI	NI	*Boy* 6.0(1.04); *Girl* 5.6(0.99)	NI	8

Table 1. continued

Authors; Country	Sample size (boy/girl)	Birth year	Definition of EAR	Results			Quality score
				Prevalence of EAR (boy/girl)	Mean age at AR (SD) by sex (year)	Age for weight assessment; OR (95%CI)	
Warrington et al. [51], 2013; Britain	**Avon:**6,867 (3,642 / 3,225) **Raine:**1,344 (697 / 647)	1991–1992;1989–1991	NI	NI	*Boy* 6.07 (1.02); *Girl* 5.61 (1.16) *Boy* 5.30 (1.05); *Girl* 4.64 (1.10)	NI	8
Salvi et al. [52], 2012; Italy	558 (281 / 277)	1992–1995	NI	NI	*Boy* 4.8(1.2); *Girl* 4.5 (1.6)	NI	7
Skinner et al. [53], 2004; USA	70 (37 / 33)	1992	NI	NI	*Boy* 4.7(1.5); *Girl* 4.5 (1.1)	NI	7
Di Gravio et al. [54], 2019; UK	545 (259 / 286)	1997–1998	NI	NI	*Boy* 6.1(1.08); *Girl* 5.9(1.23)	NI	8
Wen et al. [55], 2012; America	3,190 (1,643 / 1,547)	1998	NI	NI	*Boy* 4.1(0.99); *Girl* 3.9(0.92)	NI	8
Aris et al. [56], 2019; America	804 (417 / 387)	1999–2002	NI	NI	*Boy* 5.31(1.76); *Girl* 4.82(1.71)	NI	7
Marakaki et al. [57], 2017; Greece	63 (48 / 15)	2009	NI	NI	*Boy* 4.93(1.36); *Girl* 5.1(1.5)	NI	7
Characteristics of studies included in the systematic review but not in meta-analysis							
Rolland-Cachera et al. [58], 1987; France	113 (54 / 59)	1953	Before 5.5 years old	31% (NI / NI)	NI	NI	7
Ohlsson et al. [15], 2012; Spain	573 (NI / NI)	1992–1994	Before 5.4 years old	33.3% (NI / NI)	NI	**18–20 years old [b]** *Obesity:*4.10 (1.20,13.90)*;* *Overweight:*3.2 (1.9–5.2)	8
Giussani et al. [59], 2013; America	1,310 (682 / 628)	1996–2005	Before 5.5 years old	15% (NI / NI)	NI	NI	8
Roche et al. [13], 2020; France	1,055 (546 / 509)	2003–2005	Before 5.5 years old	40% (NI / NI)	NI	**6–8 years old [d]** *Obesity&Overweight:* 4.81(3.29,7.03)	8
Fang et al. [60], 2020; China	342 (NI / NI)	2005	Before 5.67 years old	34% (NI / NI)	NI	NI	7
Sun et al. [61], 2017; China	802 (NI / NI)	2006–2008	Before 5.67 years old	26% (NI / NI)	NI	**8–9 years old [g]** *Obesity:*1.92(1.31,2.80) *Overweight:*1.60(1.06,2.42)	8
Hwang et al. [12], 2020; Korea	11,106 (NI / NI)	2008–2012	Before 4.75 years old	77% (NI / NI)	NI	**5 years old [f]** *Obesity:*3.71(3.20,4.29) * *Overweight:*1.76 (1.57,1.96)	9
Cao et al. [17], 2020; China	720 (NI / NI)	2013–2014	Before 4 years old	43% (NI / NI)	NI	**5 years old [h]** *Obesity&Overweight:*2.71(1.81,4.05) *	8
Haga et al. [62], 2021; Japan	1,438 (714 / 724)	2001–2007	*Before 6 years old*	39% (NI / NI)	NI	**14 years old [d]** *Obesity:*8.04(3.76,17.17) *(boys)*; 3.57 (1.91,6.66) *(girls)*	8

Criteria for Diagnosis of overweight and obesity: a Adult obesity was defined as an average BMI ≥ 27.8 in men and ≥27.3 in women; **b** Obesity: BMI ≥ / > 30 kg/m2, overweight (BMI 25–29.9 kg/m2); **c** Weight status was defined by using BMI-z-scores relative to UK 1990 BMI reference data: overweight (BMI z score≥1.04 and<1.64, equivalent to 85th–94th percentiles) and obesity (BMI z score≥1.64, equivalent to 94th percentile); **d** Weight status classification using the International Obesity Task Force (IOTF) criteria or extended criteria; **e** Overweight was defined as BMI ≥ 85th percentile but<95th percentile and obesity was defined as a BMI ≥ 95th percentile of the CDC growth charts (or, equivalently, a z-score ≥1.645) for a child's sex and age; **f** BMI percentile curves for the male Korean Standard (overweight, 85^{th} percentile ≤BMI < 95th percentile; Obesity, BMI ≥ 95th percentile); **g** Beijing Institute of Pediatrics and Peking University Institute of children and adolescents jointly developed the reference value of BMI percentile for Chinese.
European countries: Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Sweden, Spain;
EAR: early adiposity rebound;
NI: no information;
*: OR was adjusted for birth weight or BMI at AR or child's sex.

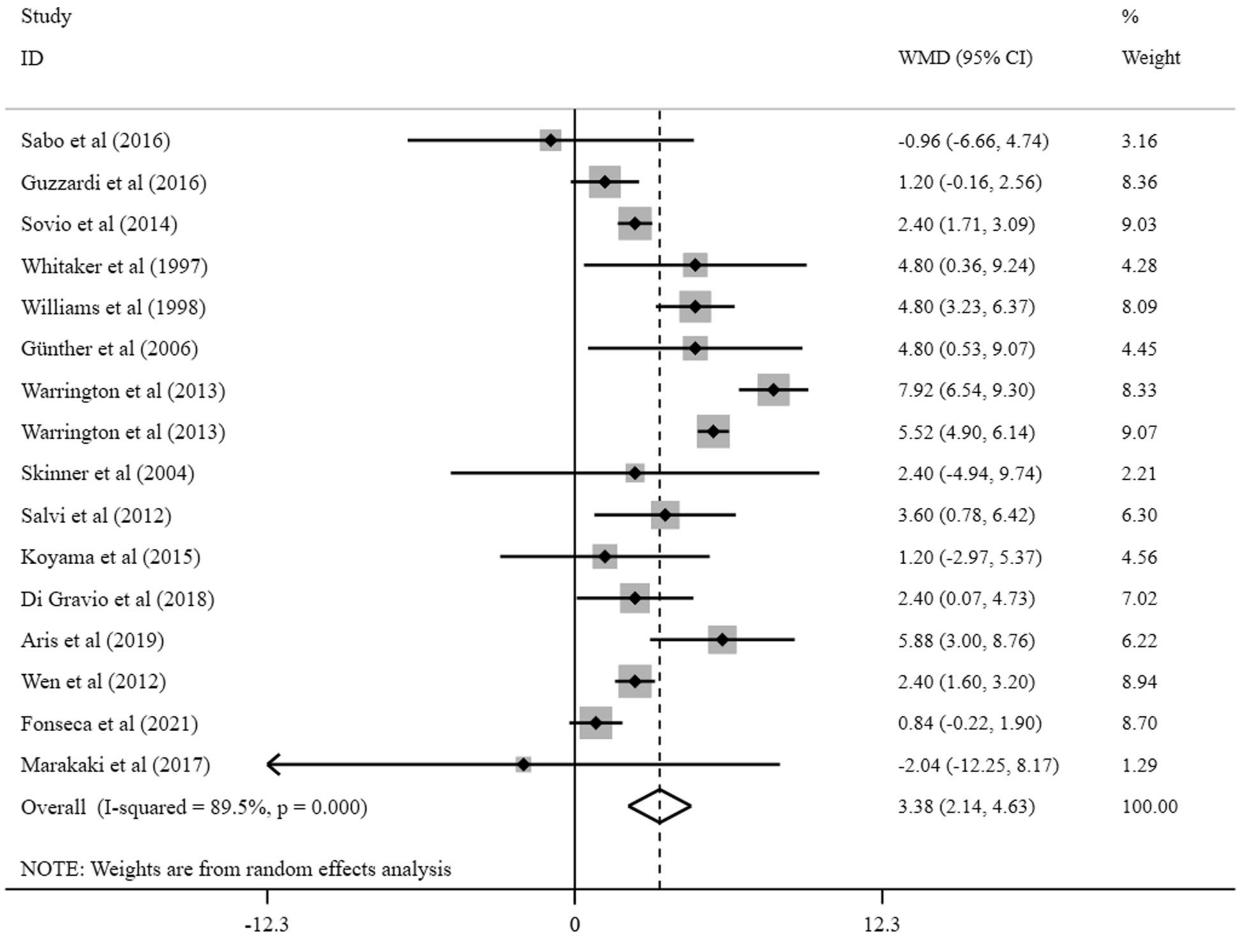

Fig. 2 Forest plot of studies assessing the mean difference in age (months) at AR between boys and girls.

There were no uniform criteria for defining EAR in the included studies. Since most studies used the age at AR < 5.0–5.1 years as the definition of EAR, we only pooled the overall and sex-specific prevalence of EAR under this definition. In addition, we conducted a subgroup analysis stratified by different birth years (between 1934 and 1973; between 1991 and 2001; between 2002 and 2009) for the overall prevalence of EAR.

Pooled ORs and 95% CIs were combined to assess the association between early age at AR (age at AR < 5.0–5.1 years) and subsequent overweight/obesity. We performed four subgroup analyses: (i) type of weight status (overweight and obesity); (ii) age (preschool and school-age, adolescence, and adulthood); (iii) birth year (born before 2001; born after 2001); and (vi) any adjusted data (adjusted findings; unadjusted findings).

The results are presented as forest plots or tables. The degree of heterogeneity among the studies was analyzed by the I^2 statistic. We considered that heterogeneity was present when the I^2 statistic was > 50% [31, 32]. If there was heterogeneity, the random effect model was used; otherwise, the fixed effect model was adopted [33]. The assessment of publication bias applied to sex differences in age at AR and the relationship between age at AR and obesity. The existence of publication bias was judged by a funnel plot. The quantitative analysis of publication bias was performed by Begg's test and Egger's test [34]. We used sensitivity analysis to investigate the stability of the outcome. Every study included in this meta-analysis was deleted each time to define its influence on the pooled ORs and mean differences. If the corresponding pooled ORs and mean differences were not fundamentally altered, it would suggest that the results be statistically robust.

RESULTS

Search results

A total of 808 studies were retrieved. After repeated checks and initial screening of titles and abstracts, 516 of 808 studies were excluded. Then, after reading the full text of the remaining literature, a total of 37 articles were eligible for inclusion in the systematic review, of which 28, involving 106,397 participants, were used for meta-analysis. The study selection process is presented in Fig. 1.

Characteristics of included studies

Detailed characteristics of the included studies are summarized in Table 1. The included studies were published between 1987 and 2021, with sample sizes ranging from 39 to 49,062. Regarding the prevalence of EAR and the mean age at AR (SD) by sex, 13 studies [24, 35–46] only reported the former, 3 studies [18, 25, 47] reported both outcomes, 12 studies [14, 20, 48–57] only reported the latter, and 7 studies [12, 13, 17, 58–62] did not perform a meta-analysis of these two outcomes because the definition of EAR was not < 5.0–5.1 years. For early age at AR and later overweight/obesity, a total of 11 studies [12–15, 17, 37, 39, 42, 45, 46, 61] reported its association, 7 of which were used for meta-analysis using an EAR of <5.0–5.1 years as a criterion [37, 39–42, 45, 46]. The included studies used 7 different criteria for defining obesity,

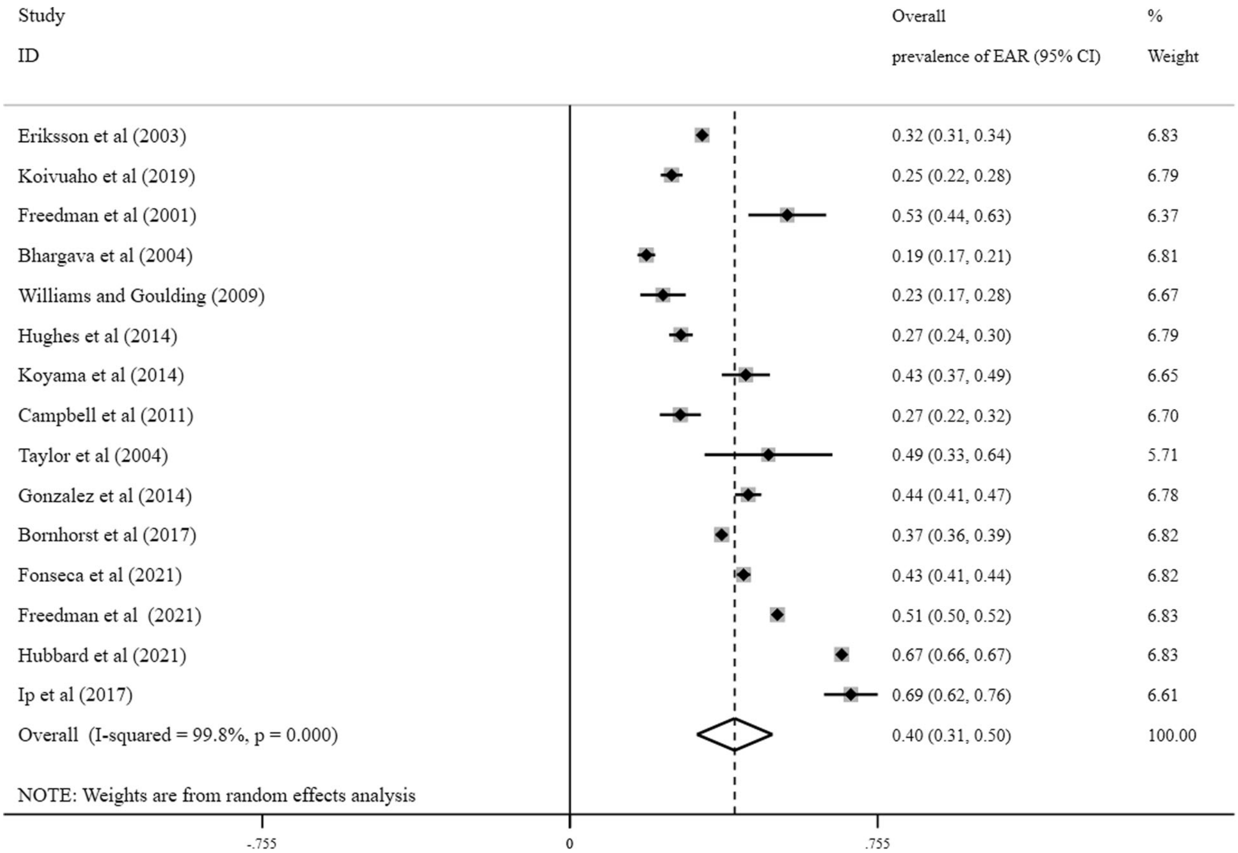

Fig. 3 Forest plot of studies assessing the prevalence of EAR.

and the quality scores of all the included studies were 7 or above (Table 1).

Meta-analysis

Mean differences in age at AR by sex. A total of 16 studies involving 10 countries reported the mean (SD) age at AR by sex. The participants were born between 1929 and 2009. When girls served as the reference group in examining the pooled mean difference in age at AR, it was found that the mean age at AR in boys was older by 3.38 months (95% CI: 2.14–4.63) (Fig. 2). The result from the I^2 statistic showed that there was heterogeneity among the studies (89.5%; $P < 0.001$). Thus, the random-effects model was used to calculate the pooled effect.

In the sub-analysis according to birth year, compared to boys, the pooled mean difference in age at AR in girls was 2.87 months earlier (95% CI: 1.44–4.30) born before 1988, 4.52 months earlier (95% CI: 2.64–6.39) in those born between 1988 and 1998, and 2.40 months earlier (95% CI: 0.60–4.21) in girls born between 1999 and 2009 (S Fig. 1).

Prevalence of EAR. A total of 15 studies involving 10 countries reported the prevalence of EAR (studies with EAR defined as age at AR < 5.0–5.1 years) were included in the meta-analysis. The majority of studies were conducted in developed countries. In these studies, the prevalence of EAR ranged from 19 to 69%, yielding an overall pooled prevalence of 40% (95% CI 31% to 50%) (Fig. 3). The result from the I^2 statistic showed that there was heterogeneity among the studies analyzed (99.8%; $P < 0.001$). Thus, the pooled prevalence with 95% CI was calculated using a random-effects model. For the sex-specific prevalence of EAR, girls were 5% higher than boys (Fig. 4).

When stratified by birth year, the overall prevalence of EAR showed an increasing trend over time. The overall pooled prevalence was 29% (95% CI 22 to 37%) in children born between 1934 and 1973, 35% (95% CI 26 to 44%) in children born between 1991 and 2001, and 52% (95% CI 40% to 63%) in those born between 2002 and 2009 (Fig. 5).

Early age at AR and overweight/obesity. A total of 7 studies involving 12 countries were pooled to analyze the association between early age at AR and overweight/obesity. Children with age at AR > 5.0–5.1 years served as the control group. Overweight/obesity was measured between 6 and 29 years old. Early age at AR was found to be significantly associated with overweight/obesity (OR = 5.07; 95% CI 3.60 to 7.12) ($I^2 = 87.9\%$, $P < 0.001$) by using the random effects model ($I^2 = 96.0\%$, $P < 0.001$) (Fig. 6).

The association between early age at AR and later overweight/obesity was significant in all subgroup analyses (Table S1). For weight type, early age at AR was more associated with obesity (OR = 6.97; 95% CI 4.32 to 11.26) ($I^2 = 78.7\%$, $P < 0.001$) than with overweight (OR = 3.10; 95% CI 1.69 to 5.70) ($I^2 = 89.2\%$, $P < 0.001$) (Fig. 7). Subgroup analysis by age showed that early age at AR was more strongly associated with preschool and school-age (OR = 5.93; 95% CI 3.52 to 9.98) ($I^2 = 83.9\%$, $P < 0.001$) than overweight/obesity in adolescence (OR = 3.99; 95% CI 1.50 to 10.61) ($I^2 = 94.9\%$, $P < 0.001$) and adulthood (OR = 3.90; 95% CI 1.81–8.39) ($I^2 = 68.2\%$, $P < 0.001$). For birth year, the pooled effect size was OR = 4.13 (95% CI 2.50 to 6.84) ($I^2 = 79.8\%$, $P < 0.001$) in children born before 2001 and OR = 6.43 (95% CI 4.44–9.29) ($I^2 = 81.3\%$, $P < 0.001$) in those born after 2001. In addition, the association weakened when adjusting for any potential confounding factors (OR = 3.90; 95% CI: 1.81–8.37) ($I^2 = 68.2\%$, $P < 0.001$) compared with unadjusted findings (OR = 5.31; 95% CI: 3.69–7.66) ($I^2 = 88.2\%$, $P < 0.001$).

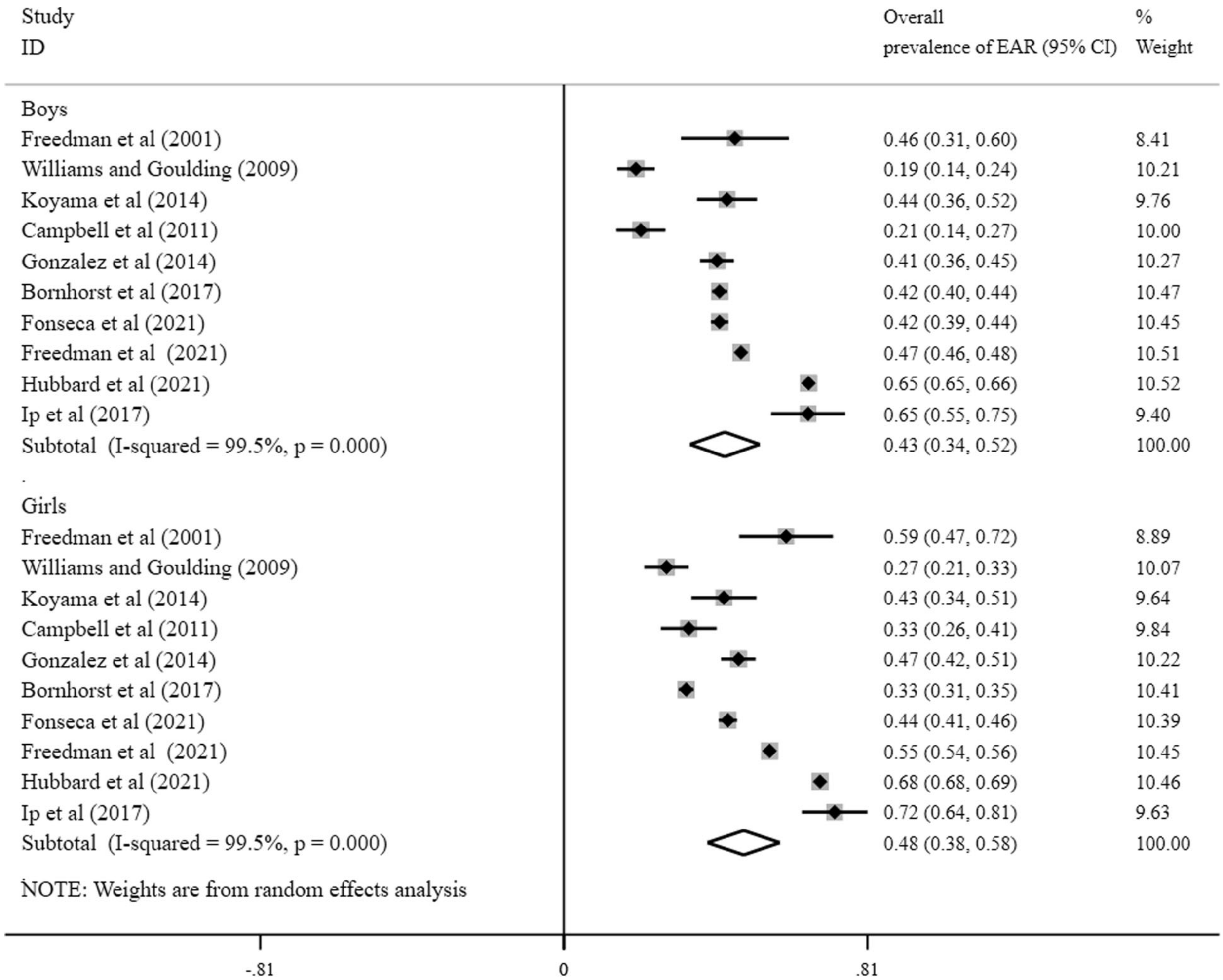

Fig. 4 Forest plot of studies assessing the prevalence of EAR by sex.

Sensitivity analysis and bias diagnostics

In the analyses of sex differences in the average age at AR, no publication bias was found according to the funnel plot, Begg's test ($P = 0.964$), or Egger's test ($P = 0.766$). The sensitivity analysis showed that the pooled effect size did not exceed the original confidence interval after removing each study and indicated that the result was stable.

After assessing the risk of bias of EAR using the JBI tool [63], 4 studies were classified as the moderate risk of bias, and 11 studies were classified as low risk (Table S2). For the pooled prevalence of EAR, no significant publication bias was identified according to the funnel plot, Begg's test ($P = 0.373$), or Egger's test ($P = 0.050$), and the sensitivity analysis showed that the result was stable.

In the analysis of the relationship between early age at AR and later overweight/obesity, no significant publication bias was identified according to the funnel plot, Begg's test ($P = 0.119$), or Egger's test ($P = 0.153$). The sensitivity analysis showed that the result was stable.

DISCUSSION

The present study indicates that the overall prevalence of EAR has reached 40% based on the criterion of < 5.0–5.1 years old. Girls had a relatively earlier age at AR than boys. Early age at AR was found to be significantly associated with later overweight and obesity.

Possible factors for the secular trend of EAR

The prevalence of EAR shows a significantly increasing trend by birth year in the current study, suggesting that the age at AR in humans may be advancing compared to the past. The potential mechanism underlying the occurrence of EAR is unclear. The following reasons might be proposed. First, breastfeeding and protein intake were considered potential dietary causes that contributed to the early age of AR. Exclusive breastfeeding over 4 months is a protective behavior to prevent the development of EAR and adolescent obesity [64]. However, the global breastfeeding scorecard, which assessed 194 countries, showed that only 40% of children under six months of age are exclusively breastfed, and only 23 countries had exclusive breastfeeding rates above 60% [65]. An adequate supply of protein and essential amino acids is essential for children's growth and development, but it is also the case that the recommendations for infant protein intake are often on the high side, which increases a large margin of safety in the estimated nutritional needs [66]. In recent years, most studies have reported a higher proportion of protein to energy and lower fat intake in infants' diets [67–69]. Protein intake was associated with faster weight gain in infancy and proved to be a risk factor for later obesity [70, 71]. The higher the protein intake in the first 2 years is, the earlier the AR is, and the higher the subsequent BMI level will be [72]. Second, prenatal maternal-fetal factors may be another important way to explain the increasing prevalence of EAR. Studies have found that birth outcomes may have a certain

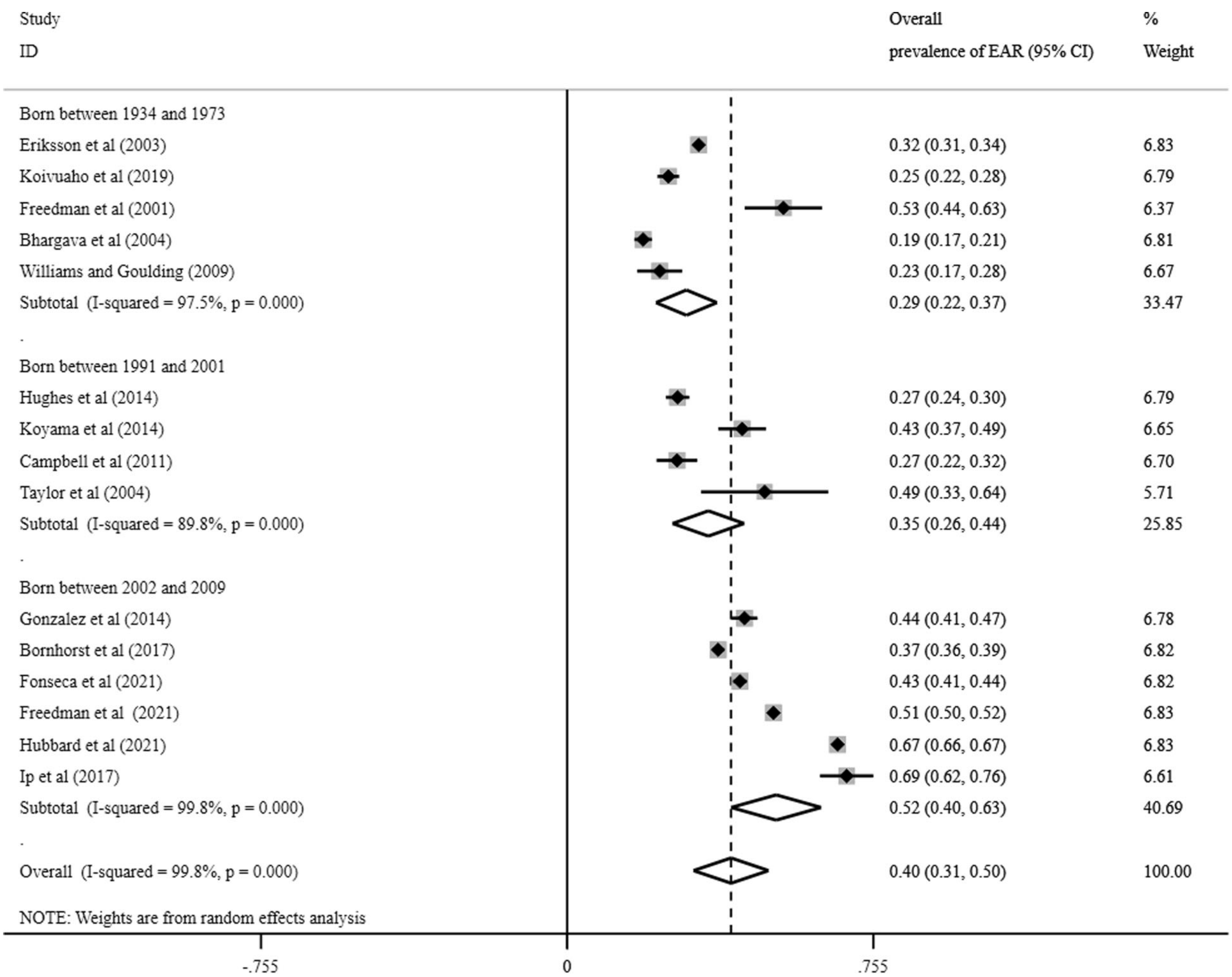

Fig. 5 Forest plot of studies assessing the prevalence of EAR stratified by birth year.

influence on age at AR [73, 74]. The global preterm birth rate is generally rising [75, 76], and a cohort study of preterm births from Italy pointed out that preterm birth is an independent risk factor for EAR [74]. The EDEN mother-child cohort study reported that for children born small for gestational age (SGA), the average age at AR is lower than that of children born appropriate for gestational age (AGA) and large for gestational age (LGA) [77]. Evidence from cohort studies also found that the timing of adiposity rebound occurred significantly earlier in children with maternal diabetes and high BMI during pregnancy [77–80]. The high prevalence of maternal obesity and diabetes during pregnancy may be synchronized with the increasing rate of EAR [81], especially for gestational diabetes mellitus (GDM), which has continued to increase globally over the past few decades [82]. Third, factors that affect obesity, such as outdoor activity, sleep duration, and physical activity, may also affect the trajectory of early childhood BMI and its special milestone AR [83–86].

Sex differences in age at AR

Our study shows that girls have a younger age at AR than boys. This difference may be determined by the physiological attributes of physical development between males and females. Studies have revealed that age at AR is related to the age of puberty onset [37, 87]. Puberty is not an isolated event in the process of human development, and its initiation time is closely related to the physical condition of early humans [88]. William et al. [89] suggested that the age at the onset of AR is related to the age at menarche and proposed that the age at AR would be a predictor of physiological maturity. Girls typically start puberty earlier than boys [90]. One may suppose that the difference in age at AR between boys and girls might influence the subsequent rate of physical development and be linked to the timing of puberty onset. The potential association between age at AR and puberty timing and whether the magnitude of the difference in AR between sexes at different birth years is synchronized with changes in the pubertal onset timing gap requires further verification.

The essence of the AR phenomenon

The BMI trajectory corresponds to the trend in the size of human adipocytes, i.e., increases first and then decreases in the early stage [91]. Rolland-Cachera et al. [10] suggested that EAR might constitute a marker for generalized growth acceleration and cell hyperplasia. Two main growth trajectories associated with adult obesity were advanced: one with high BMI at all ages, which reflected both high lean and fat body masses, and the other with low or normal BMI followed by an EAR reflecting fat mass increase rather than lean body mass [91]. Studies found that children undergoing EAR gained fat at a faster rate than children who rebounded at a later age [41]. The change in BMI during AR is considered to be caused by the change in body fat, not by the increase in lean weight [41, 92, 93]. The characteristic of "AR" during this period is that the lean mass

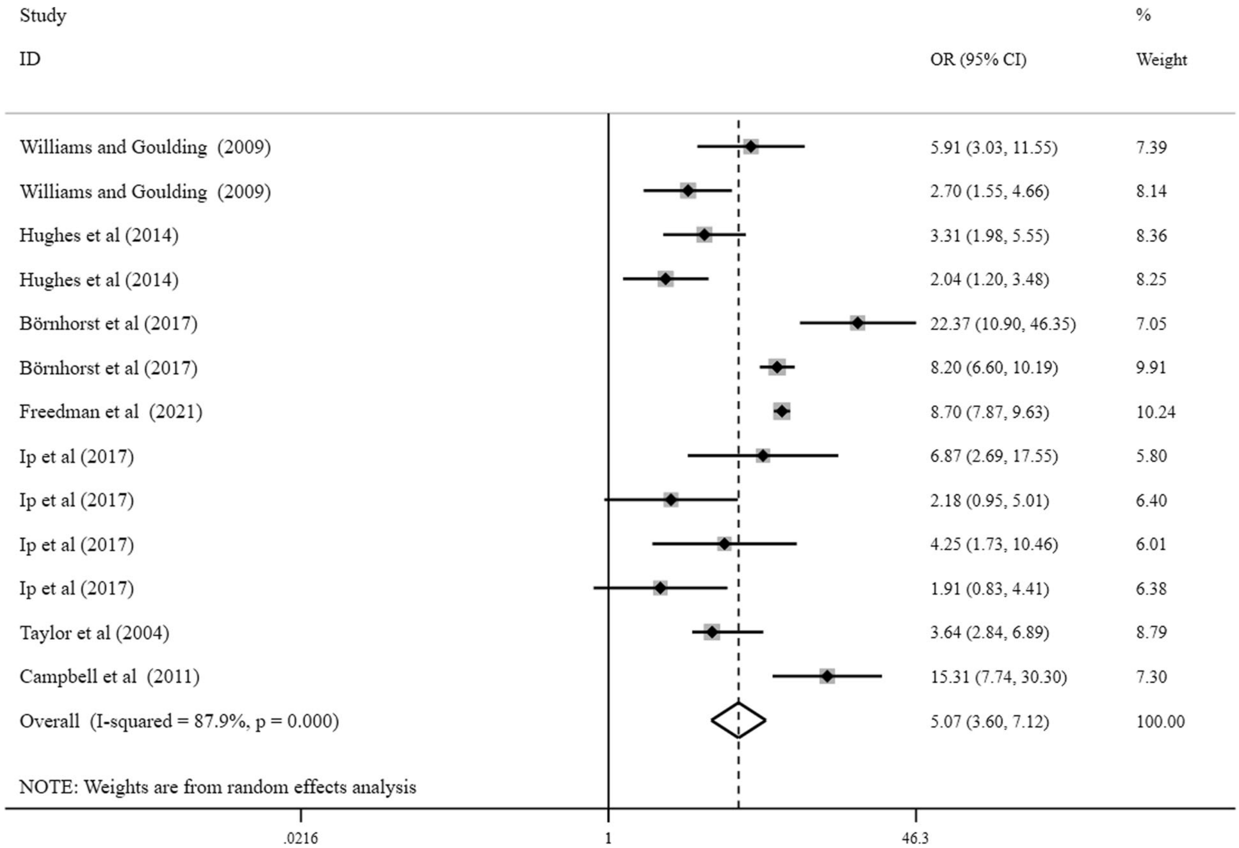

Fig. 6 Forest plot of the association between EAR and overweight/obesity.

index (LMI) continues to increase, while the fat mass index (FMI) stops decreasing, which makes the children's BMI value rise [40].

The association between AR and obesity

The rapid accumulation of body fat may contribute to the development of obesity later in life [94]. As a possible early marker of obesity, AR has been confirmed by many studies. Our findings also indicated a lifelong impact of early age at AR on overweight and obesity. Although some scholars argue that the association between the time of AR and obesity is an epiphenomenon and that the real impact on obesity is BMI at AR [11, 95], more studies suggest that the time of AR is an independent predictor of the risk of later obesity [9, 22, 23]. The predictive effect of EAR on the risk of obesity does not depend on the percentage of body fat at the time of AR [11, 14, 96]. The link between age at AR and BMI at AR is hard to explain. It is generally accepted that both age at AR and BMI at AR impact later obesity [11]. As Cole's understanding of early AR, with its coexisting with high BMI or markedly increasing BMI in terms of z scores, it seems to put children at the forefront of the "horse" race for obesity [11]. Rolland-Cachera and Cole [96] also pointed out that AR itself is not a critical period. Exploring the factors that contribute to EAR should help to shed light on the early mechanism of obesity development.

Strengths and limitations

The current study has some advantages. This is the first study to comprehensively summarize all available published literature and report the prevalence of EAR and the sex differences in age at AR in different birth years. Second, the data of the current study mainly came from birth cohorts, national registration systems, and medical records. The rates of loss to follow-up were low in these cohorts, and the data from registration and medical notes were considered accurate and reliable. Third, the quality of the included studies was relatively high, which improved the reliability of the results.

Several limitations must be acknowledged. On the one hand, in most of the literature we included, the cut-off value of EAR was approximately 5 years, but some studies defined EAR as the occurrence of AR before 4.0, 5.5, or 5.6 years of age. Therefore, to make the results as accurate as possible when pooling the prevalence of EAR and pooling the OR between early age at AR and overweight/obesity, we only analyzed studies that judged EAR based on < 5.0–5.1 years. On the other hand, the determination of age at AR is influenced by the number of repeated BMI measurements as well as the identification methods [97]. There is no doubt that the more frequently BMI measurements are taken around the AR, the more accurate the AR age will be. The methods to determine the time of AR in the current study mainly included visual inspection, random coefficient models, and polynomial models [97]. However, there may be slight differences in AR age results estimated by different methods [97].

CONCLUSION

In conclusion, the overall prevalence of EAR may be increasing, and girls have AR earlier than boys. Early AR in children may be an early and effective marker of obesity. Both the causes of EAR and possible interventions deserve further exploration.

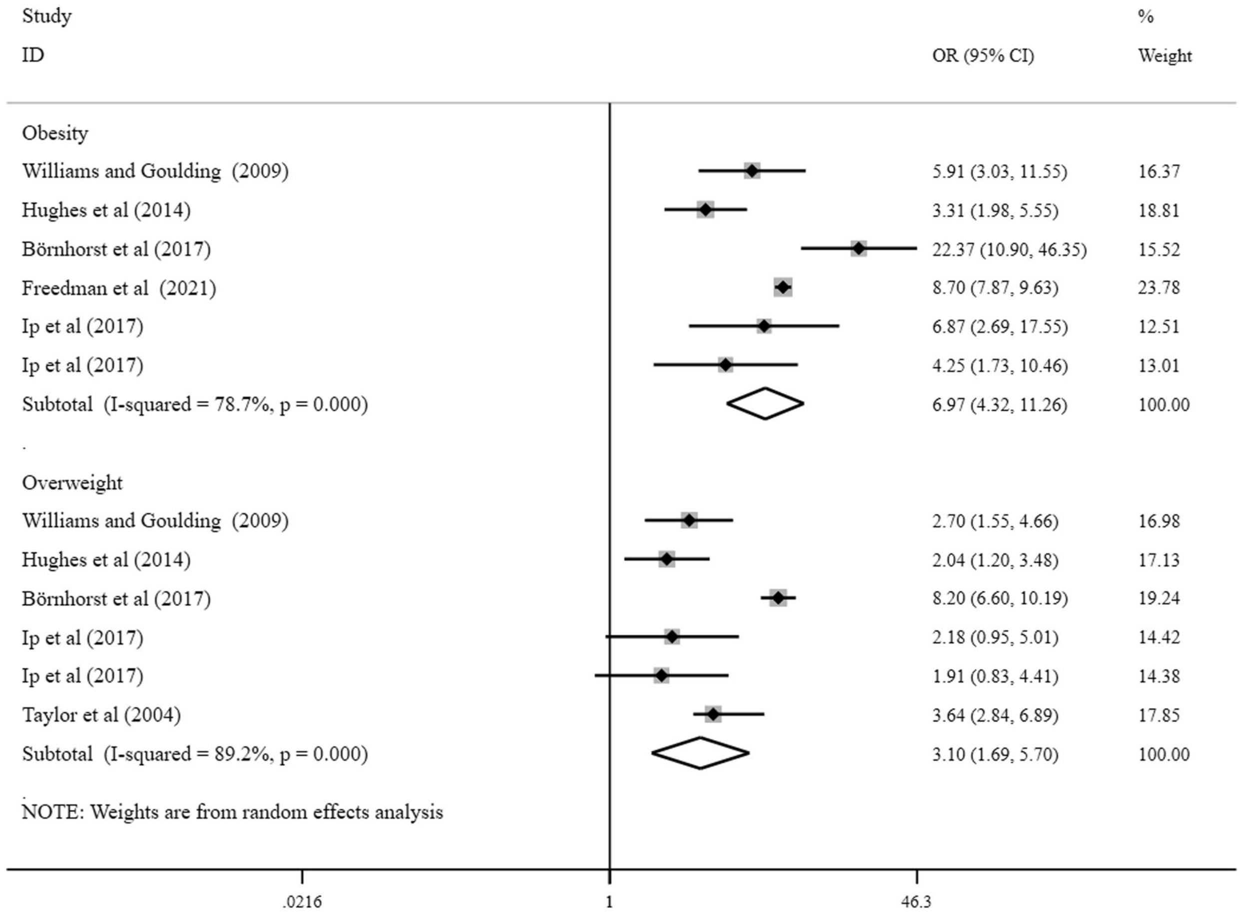

Fig. 7 Forest plot of the association between EAR and overweight/obesity by weight status.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

All authors conceived and designed the study. JXZ, FZ, and XYQ were responsible for data collection. JXZ and PXL analysed the data. JXZ and KH drafted the manuscript. YZT, SSZ, FBT, and KH provided feedback on the report. All authors revised the manuscript, contributed to the intellectual content and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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