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Association between maternal obesity and offspring Apgar score or cord pH: a systematic review and meta-analysis

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Previous results are inconsistent regarding the association between maternal obesity and Apgar score or cord pH in humans. The aim of this study was to investigate the association between maternal pre-pregnancy and pregnancy body mass index (BMI) and infant Apgar score or cord pH. We conducted a systematic review of studies published in English before 20 August 2015 using PubMed, EMBASE, and Cochrane Library. Eleven cohort studies with a total of 2,586,265 participants finally met our inclusion criteria. Pooled results revealed the following factors associated with Apgar score <7 at 5 minutes: overweight (odds ratio [OR] 1.13; 95% confidence interval [CI], 1.08–1.20), obese (OR 1.40; 95% CI, 1.27–1.54), and very obese (OR 1.71; 95% CI, 1.55–1.89). The pooled analysis also revealed that maternal overweight or obesity increased the risk for Apgar score <7 at 1 minute. There was no association between maternal BMI and neonatal cord pH. Thus, this study suggests that maternal overweight and obesity affect baby's condition immediately after birth in general. More studies are needed to confirm these results and detect the influence of variables across studies.

The prevalence of female obesity at child-bearing ages has continuously increased in recent years¹. Maternal baseline body mass index (BMI) values are categorized by standard conventions: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese (BMI ≥ 30 kg/m²). Maternal obesity is further stratified into three classes: class I (BMI 30–34.9 kg/m²), class II (BMI 35–39.9 kg/m²), and class III (BMI ≥ 40 kg/m²)². Accumulating evidence has suggested that maternal obesity before and during pregnancy can result in pregnancy-induced hypertension, pre-eclampsia, gestational diabetes, and caesarean delivery, as well as foetal and neonatal complications, such as macrosomia, intrauterine growth retardation, foetal death, stillbirth, and infant death^{3,4}, but the underlying mechanisms have not been well established.

The Apgar score was introduced by Virginia Apgar in 1953 and is evaluated at 1, 5, and 10 minutes after birth. The Apgar score is used as an index to evaluate the neonate's overall status and response to resuscitation, as well as its prognosis beyond the neonatal period⁵. Furthermore, previous studies have observed that low Apgar scores at birth increased the risk for later motor control and perception difficulties, cognitive developmental delays, learning disabilities, cerebral palsy, autism, attention-deficit/hyperactivity disorder, and epilepsy^{6,7}.

In addition, cord pH is a more sensitive measure for high risk neonates that may be at risk for poor neurologic outcomes, as most cerebral palsy patients have normal Apgar scores at birth⁸. Cord pH is one assessment of neonatal metabolic status. Cord pH decreases when hydrogen ions from anaerobic metabolism overwhelm the foetus's buffer capacity, which is an important indicator of birth asphyxia⁹. Birth asphyxia, although the correct definition is imprecise, is an insult to the foetal or newborn due to failure to breath or breathing poorly leading to decrease oxygen perfusion to various organs¹⁰. It remains a persistent worldwide problem occurring in 20 per 1000 term live births¹⁰. According to WHO survey, up to 23% of neonatal deaths in low-income countries are due to birth asphyxia¹¹. In addition, it is also one of the leading causes of neonatal deaths within 24 hours¹². Thus, determination

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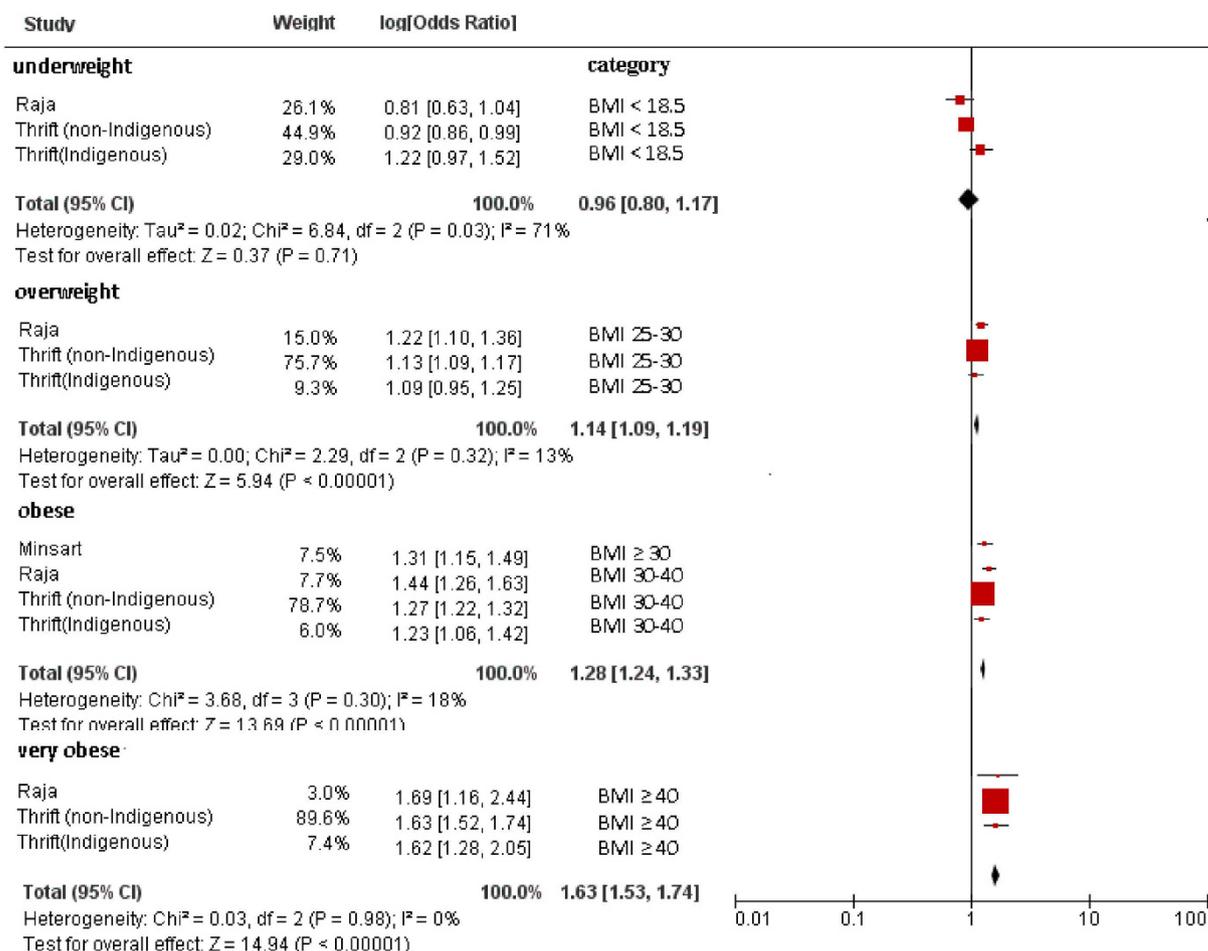


Figure 1. Forest plot of pooled analyses of maternal BMI categories and an Apgar score <7 at 1 minute.

Maternal overweight, obesity and very obesity by BMI categories was significantly associated with Apgar score <7. Maternal underweight categories showed nonsignificant trends toward increased an Apgar score <7. Note that obesity group compared with non-obese controls (BMI < 30) in the Minsart *et al.* study. In others studies, ORs are for each category as compared with the “normal weight” category (BMI 18–25).

of maternal factors that may affect Apgar score and cord pH will improve the understanding of the influence of maternal obesity and provide evidence for predicting serious conditions in order to plan appropriate neonatal care.

To date, many human studies have published inconsistent results on the impact of maternal obesity on Apgar score and cord pH at birth. Thus, we conducted a systematic review and meta-analysis to evaluate their association. We hypothesized that neonates exposed to maternal obesity would have lower Apgar scores and cord pH than would normal controls.

Results

Literature search. We identified 205 potential studies: 132 from PubMed, 63 from EMBASE, 4 from the Cochrane Database, and 9 additional references from reviewing references in relevant articles. After careful screening, 11 studies were selected for inclusion in this study^{3,4,13–21}. Supplemental Fig. 1 shows the reasons for exclusion. The extracted data from the 11 included studies are presented in Table 1.

Characteristics and quality of included studies. The included studies were published between 2008 and 2015. All were cohort studies. The sample sizes varied, from a maximum of 1764403²¹ to a minimum of 1996⁴. Of the included studies, eight selected consecutive singleton births without gestational age restrictions for analysis^{3,14–20}, and three were limited to full-term infants^{4,13,21}. Regarding timing of maternal BMI assessment, seven studies assessed BMI at the first antenatal visit^{13,15,17–21}, one study at the early second trimester (13–18 weeks)¹⁴, and three at pre-pregnancy^{3,4,16}. Most studies used normal weight status as the reference, one¹⁴ used BMI < 25 kg/m², one used non-obese participants¹⁸, and one used class I obesity¹⁶.

For data sources of maternal BMI, seven studies used self-reported maternal weight and height^{4,13,15–18,20,21}, one was measured by a physician¹⁹, and three determined BMI from medical records or registry data^{3,14,17}. For Apgar score and cord pH, all studies identified them from registry data or medical records. All studies were controlled statistically for a number of potentially confounding variables. The results of the quality assessment of the included studies are shown in Table 1. All included studies were of high quality (NOS > 5).

| Author, year | country | Study design | size | GA | Ascertainment of Exposure; Outcome | Primary outcome | Comments | Risk of bias; quality |
|-----------------------------|----------------|----------------------|--------|------|---|--|---|---|
| Nohr 2008 ¹³ | Danish | Retrospective cohort | 58126 | term | Self-report; registry data | Apgar score (<8) at 5 min BMI < 18.5, OR = 0.8 (CI, 0.5–1.3) BMI 25–30, OR = 1.3 (CI, 1.0–1.6) BMI ≥ 30, OR = 1.8 (CI, 1.3–2.4) | GWG, maternal age, parity, height, smoking, alcohol consumption, social status, exercise, GA, and BW | Different methods of exposure, only preterm neonates; NOS:6 |
| CHEN 2010 ¹⁴ | United States | retrospective cohort | 58089 | all | Registry data | Apgar score (4–6) at 5 min BMI 25–30, OR = 1.2 (CI, 0.99–1.4) BMI 30–40, OR = 1.4 (CI, 1.1–1.7) BMI ≥ 40, OR = 2.0 (CI, 1.5–2.7) Apgar score (0–3) at 5 min BMI 25–30, OR = 1.0 (CI, 0.7–1.4) BMI 30–40, OR = 1.1 (CI, 0.8–1.6) BMI ≥ 40, OR = 0.8 (CI, 0.4–1.6) | Maternal age, maternal education, smoking, preexisting diabetes mellitus, chronic hypertension, maternal fever at delivery, parity, previous preterm or small-for gestational age newborn, birth year | Different methods of exposure; NOS:8 |
| Choi 2011 ³ | Korean | retrospective cohort | 2454 | all | Medical record | Apgar score (<7) at 1 min or 5 min BMI < 18.5, OR = 1.39 (CI, 0.91–2.12) BMI 23–25, OR = 1.96 (CI, 1.20–3.18) BMI ≥ 25, OR = 1.98 (CI, 1.19–3.29) | Maternal age, parity, numbers of fetuses, GA, and medical history | Different methods of exposure; NOS:8 |
| Ovesen 2011 ¹⁵ | Danish | retrospective cohort | 369347 | all | Self-report; registry data | Apgar score < 7 at 5 min BMI < 18.5, OR = 0.8 (CI, 0.65–1.04) BMI 25–29, OR = 1.32 (CI, 1.19–1.47) BMI 30–34, OR = 1.41 (CI, 1.22–1.64) BMI ≥ 35, OR = 1.94 (CI, 1.63–2.32) | Maternal age, parity, smoking during pregnancy, GA, BW, gestational diabetes mellitus, sex, and birth year | Different methods of exposure; NOS:7 |
| Marshall 2012 ¹⁶ | United States | retrospective cohort | 64272 | all | Self-report; medical record | Apgar score < 7 at 5 min BMI 40–49.9, OR = 1.0 (CI, 0.8–1.4) BMI ≥ 50, OR = 1.9 (CI, 1.1–3.2) | smoking, medicaid, age (18–34 years), education, prenatal care, married, nulliparous, repeat cesarean delivery, scheduled primary cesarean delivery, and race | Different methods of exposure; NOS:7 |
| Raja 2012 ¹⁷ | United Kingdom | retrospective cohort | 27668 | all | Medical record | Apgar score < 8 at 1 min BMI < 18.5, OR = 0.81 (CI, 0.63–1.04) BMI 25–30, OR = 1.22 (CI, 1.10–1.36) BMI 30–40, OR = 1.44 (CI, 1.26–1.63) BMI ≥ 40, OR = 1.69 (CI, 1.16–2.44) Apgar score < 8 at 5 min BMI < 18.5, OR = 1.00 (CI, 0.56–1.77) BMI 25–30, OR = 1.35 (CI, 1.06–1.73) BMI 30–40, OR = 1.57 (CI, 1.16–2.11) BMI ≥ 40, OR = 1.53 (CI, 0.62–3.79) Cord pH < 7.10 BMI < 18.5, OR = 1.18 (CI, 0.55–2.51) BMI 25–30, OR = 1.12 (CI, 0.81–1.55) BMI 30–40, OR = 1.11 (CI, 0.73–1.68) BMI ≥ 40, OR = 0.61 (CI, 0.14–2.58) | maternal age, ethnicity, parity and smoking | Different methods of exposure; NOS:8 |
| Minsart 2013 ¹⁸ | Belgian | Retrospective cohort | 38675 | all | Registry data or self-report; registry data | Apgar score < 7 at 1 min BMI ≥ 30, OR = 1.31 (CI, 1.15–1.49) | maternal age, parity, GWG, height, multiple birth, hypertension, diabetes, macrosomia, gestational age, maternal origin, education, employment, cohabiting status | Different methods of exposure; NOS:7 |
| Continued | | | | | | | | |

| Author, year | country | Study design | size | GA | Ascertainment of Exposure; Outcome | Primary outcome | Comments | Risk of bias; quality |
|------------------------------|---------------|----------------------|---------|------|------------------------------------|---|--|---|
| MAGANN 2013 ¹⁹ | United States | Prospective cohort | 4490 | all | Measured; medical data | Apgar score (0–4) at 5 min BMI < 18.5, OR = 1.24 (CI, 0.75–2.08) BMI 35–39.9, OR = 1.32 (CI, 0.81–2.15) BMI 40–44.9, OR = 1.51 (CI, 0.86–2.64) BMI ≥ 45, OR = 0.97 (CI, 0.51–1.85) Cord pH < 7.1 BMI < 18.5, OR = 1.13 (CI, 0.56–2.37) BMI 25–29.9, OR = 0.51 (CI, 0.30–1.07) BMI 30–34.9, OR = 0.34 (CI, 0.15–0.77) BMI 35–39.9, OR = 0.55 (CI, 0.25–1.21) BMI 40–44.9, OR = 1.20 (CI, 0.59–2.45) BMI ≥ 45, OR = 1.40 (CI, 0.74–2.77) | maternal age, ethnicity, nullparity, pre-existing hypertension, pre-existing diabetes, induction of labour, caesarean delivery, gestational age, post-term delivery, caesarean delivery, meconium, shoulder dystocia | Different methods of exposure; NOS:8 |
| Thrift 2014 ²⁰ | Australia | Retrospective cohort | 37752 | all | Self-report; registry data | Apgar score < 7 at 1 min Indigenous BMI < 18.5, OR = 1.22 (CI, 0.97–1.52) BMI 25–30, OR = 1.09 (CI, 0.95–1.25) BMI 30–39.9, OR = 1.23 (CI, 1.06–1.42) BMI ≥ 40, OR = 1.62 (CI, 1.28–2.05) Non-indigenous BMI < 18.5, OR = 0.92 (CI, 0.86–0.99) BMI 25–30, OR = 1.13 (CI, 1.09–1.17) BMI 30–39.9, OR = 1.27 (CI, 1.22–1.32) BMI ≥ 40, OR = 1.63 (CI, 1.52–1.74) Apgar score < 7 at 5 min BMI < 18.5, OR = 1.71 (CI, 1.15–2.54) BMI 25–30, OR = 1.06 (CI, 0.80–1.42) BMI 30–39.9, OR = 1.22 (CI, 0.92–1.63) BMI ≥ 40, OR = 1.85 (CI, 1.18–2.88) Non-indigenous BMI < 18.5, OR = 0.95 (CI, 0.81–1.11) BMI 25–30, OR = 1.02 (CI, 0.94–1.10) BMI 30–39.9, OR = 1.26 (CI, 1.16–1.36) BMI ≥ 40, OR = 1.70 (CI, 1.46–1.98) | maternal age, nullparity Accessibility/ Remoteness Index of Australia category and smoking status. | Different methods of exposure; NOS:7 |
| Persson 2014 ²¹ | Sweden | Prospective cohort | 1764403 | term | Self-report; registry data | Apgar score (0–3) at 5 min BMI < 18.5, OR = 0.74 (CI, 0.43–1.25) BMI 25–30, OR = 1.39 (CI, 1.20–1.61) BMI 30–35, OR = 1.60 (CI, 1.28–1.98) BMI 35–40, OR = 1.61 (CI, 1.11–2.34) BMI ≥ 40, OR = 2.40 (CI, 1.42–4.04) Apgar score (0–3) at 10 min BMI < 18.5, OR = 0.91 (CI, 0.52–1.59) BMI 25–30, OR = 1.28 (CI, 1.07–1.54) BMI 30–35, OR = 1.42 (CI, 1.06–1.89) BMI 35–40, OR = 1.68 (CI, 1.04–2.72) BMI ≥ 40, OR = 3.30 (CI, 1.80–6.03) | maternal country of birth, smoking in early pregnancy, education, parity, height, maternal age, infant year of birth, and mode of delivery | Different methods of exposure, only preterm neonates; NOS:6 |
| Vinturache 2015 ⁴ | Canada | prospective cohort | 1996 | term | Self-report; medical records | Apgar score < 7 at 5 min BMI 25–30, OR = 2.0 (CI, 0.6–6.2) BMI ≥ 30, OR = 1.9 (CI, 0.4–8.9) | pregnancy complications, type of labour onset, mode of delivery, and meconium in the amniotic fluid | Different methods of exposure, only preterm neonates; NOS:6 |

Table 1. Characteristics of Included Studies. GWG, gestational weight gain; GA, gestational age; BW, birth weight; BMI, body mass index; OR, odds ratios; NOS, score of Newcastle-Ottawa scale; min, minute.

Maternal BMI and Apgar score. The original outcomes of the included studies are presented in Table 1. Considering the studies' heterogeneity, we performed a separate pooled analysis of Apgar scores < 3 at 5 min from those < 7. Compared with infants born to normal-weight mothers, the pooled results of maternal BMI for Apgar scores < 7 at 1 minute were as follows: underweight (odds ratio [OR] = 0.96; 95% confidence interval [CI], 0.80–1.17; $P = 0.71$), overweight (OR = 1.14; 95% CI, 1.09–1.19; $P < 0.001$), obese (OR = 1.28; 95% CI, 1.24–1.33; $P < 0.001$), and very obese (OR = 1.63; 95% CI, 1.53–1.74; $P < 0.001$) (Fig. 1).

Figure 2 shows the association between maternal BMI and Apgar score < 3 at 5 minutes: underweight (OR = 0.96; 95% CI, 0.58–1.61; $P = 0.88$), overweight (OR = 1.23; 95% CI, 0.90–1.68; $P = 0.19$), obese (OR = 1.43; 95% CI, 1.20–1.71; $P < 0.001$), and very obese (OR = 1.48; 95% CI, 0.81–2.68; $P = 0.20$).

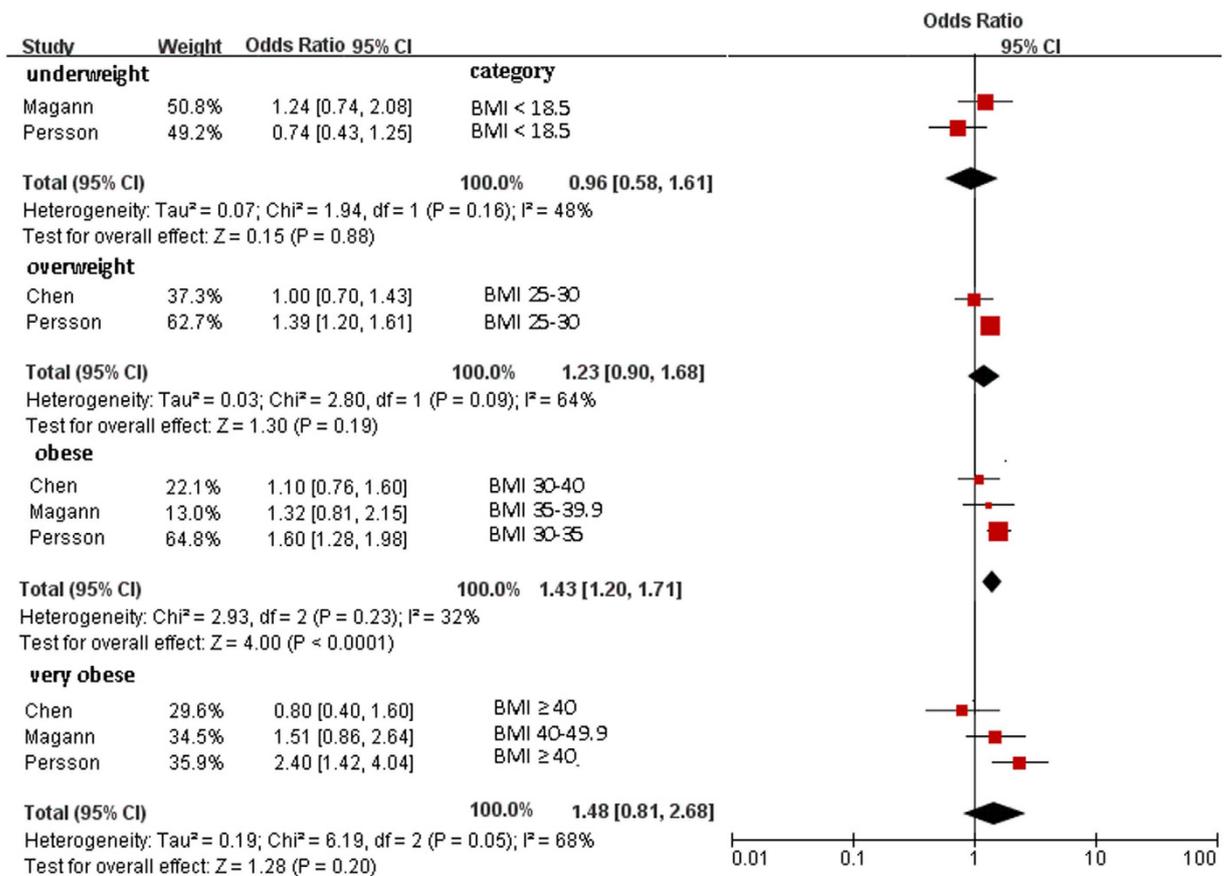


Figure 2. Forest plot of pooled analyses of maternal BMI categories and an Apgar score < 3 at 5 minute. Maternal obesity by BMI categories was significantly associated with Apgar score < 3. Maternal underweight, overweight, and very obesity categories showed nonsignificant trends toward increased an Apgar score < 3. Note that ORs are for each category as compared with different reference category (Chen *et al.*, BMI < 25; Magann *et al.*, BMI 18–25; Persson *et al.*, BMI 18.5–34.9).

Maternal BMI showed significant trends for Apgar scores < 7 at 5 minutes: underweight (OR = 0.99; 95% CI, 0.79–1.25; $P = 0.96$), overweight (OR = 1.22; 95% CI, 1.08–1.39; $P = 0.002$), obese (OR = 1.34; 95% CI, 1.26–1.42; $P < 0.001$), and very obese (OR = 1.66; 95% CI, 1.36–2.02; $P < 0.001$) (Fig. 3).

We identified one study²¹ that reported a significant association between Apgar score < 4 at 10 minutes and maternal overweight or obesity (BMI 25–29.9: 1.32 (1.10–1.58); BMI 30–34.9: 1.57 (1.20–2.07); BMI 35–39.9: 1.80 (1.15–2.82); and BMI 40: 3.41 (1.91–6.09)).

Maternal BMI and cord pH. Two studies reported ORs by BMI categories for cord pH < 7.1^{18,20}. The pooled analysis showed no significant association with maternal BMI: underweight (OR = 1.16; 95% CI, 0.69–1.94; $P = 0.59$), overweight (OR = 0.81; 95% CI, 0.38–1.72; $P = 0.59$), obese (OR = 0.65; 95% CI, 0.20–2.06; $P = 0.46$), and very obese (OR = 1.05; 95% CI, 0.55–1.99; $P = 0.88$) (Fig. 4).

Publication bias. A funnel plot was used for visual assessment of publication bias only when at least 10 studies were included in the meta-analysis. Thus, an adjusted Begger's test was implemented to evaluate asymmetry and publication bias. The pooled results showed no evidence of publication bias (supplemental Table 6).

Subgroup analysis and sensitivity analysis. We carried out a subgroup analysis for pooled results if at least two studies existed for each group. For Apgar score < 7 at 5 minutes, a higher OR was observed in studies including only full-term infants (1.80, 95% CI, 1.33–2.43; $P < 0.001$) than in other studies (1.32, 95% CI, 1.24–1.40; $P < 0.001$) for analyses of the association between Apgar score and obese mothers. For timing of measurement of maternal BMI, there was a higher OR in studies with pre-pregnancy BMI assessment (1.97, 95% CI 1.22–3.20; $P = 0.006$) than in others (1.33, 95% CI 1.25–1.41; $P < 0.001$) for the association with obese mothers. These results are similar to those for the association with overweight mothers (for more details, see the supplemental Table 5).

Considering the small number of studies in our pooled analysis, we performed a sensitivity analysis for Apgar score < 7 at 5 minutes by omitting one study at a time. Every BMI category maintained similar results during the sensitivity analysis. For underweight, significant heterogeneity disappeared ($P = 0.7$; $I^2 = 0\%$) when excluding the outcomes related to indigenous pregnancy from the Thrift *et al.* study²⁰. For overweight, heterogeneity decreased to 68% ($P = 0.004$), 58% ($P = 0.03$), and 18% ($P = 0.29$), when the Choi *et al.*³, Ovesen *et al.*¹⁵, and non-indigenous

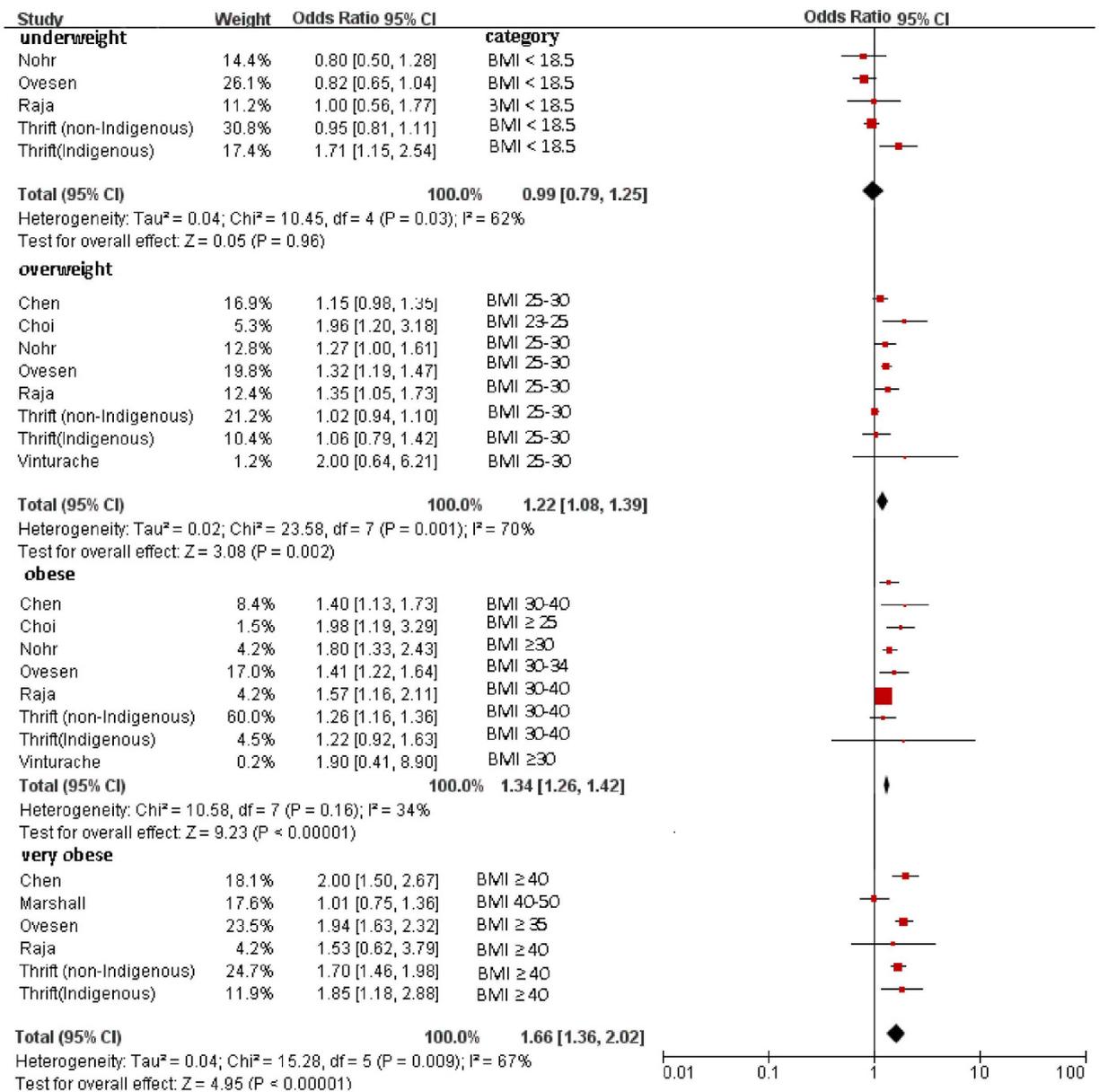


Figure 3. Forest plot of pooled analyses of maternal BMI categories and an Apgar score <7 at 5 minute. Maternal overweight, obesity and very obesity by BMI categories was significantly associated with Apgar score <7. Maternal underweight categories showed nonsignificant trends toward increased an Apgar score <7. Note that reference category was BMI < 25 in Chen *et al.* study. In other studies, ORs are for each category as compared with the “normal weight” category (BMI 18–25).

Thrift *et al.*²⁰ studies were excluded, respectively. For obesity, heterogeneity decreased to 27% ($P = 0.22$) and 9% ($P = 0.36$) when the Choi *et al.*³ and Nohr *et al.*¹³ studies were excluded, respectively. In addition, no evidence of heterogeneity was observed among the remaining studies when the outcomes related to non-indigenous pregnancy in Thrift *et al.* study²⁰ were excluded ($P = 0.16$, $I^2 = 0\%$). For the very obese category, heterogeneity decreased ($P = 0.77$, $I^2 = 0\%$) only when the Marshall *et al.*¹⁶ study was excluded.

Discussion

The results of this systematic review and meta-analysis of 11 cohort studies with a total of 2,586,265 participants showed that infants whose mothers had a BMI ≥ 25 kg/m² during pregnancy had an increased risk of low Apgar scores at 1 and 5 minutes. Maternal underweight (defined by BMI) was not associated with low Apgar scores. Maternal BMI was not associated with cord pH. However, these pooled results may have been underpowered because of the small number of studies included. The subgroup analysis and sensitivity analysis showed the stability of pooled results.

The Apgar score at 5 minutes was shown to be more predictive of neonatal survival than that at 1 minute²². Low Apgar score at 5 minutes was associated with an increased risk of neonatal and infant death, with a higher

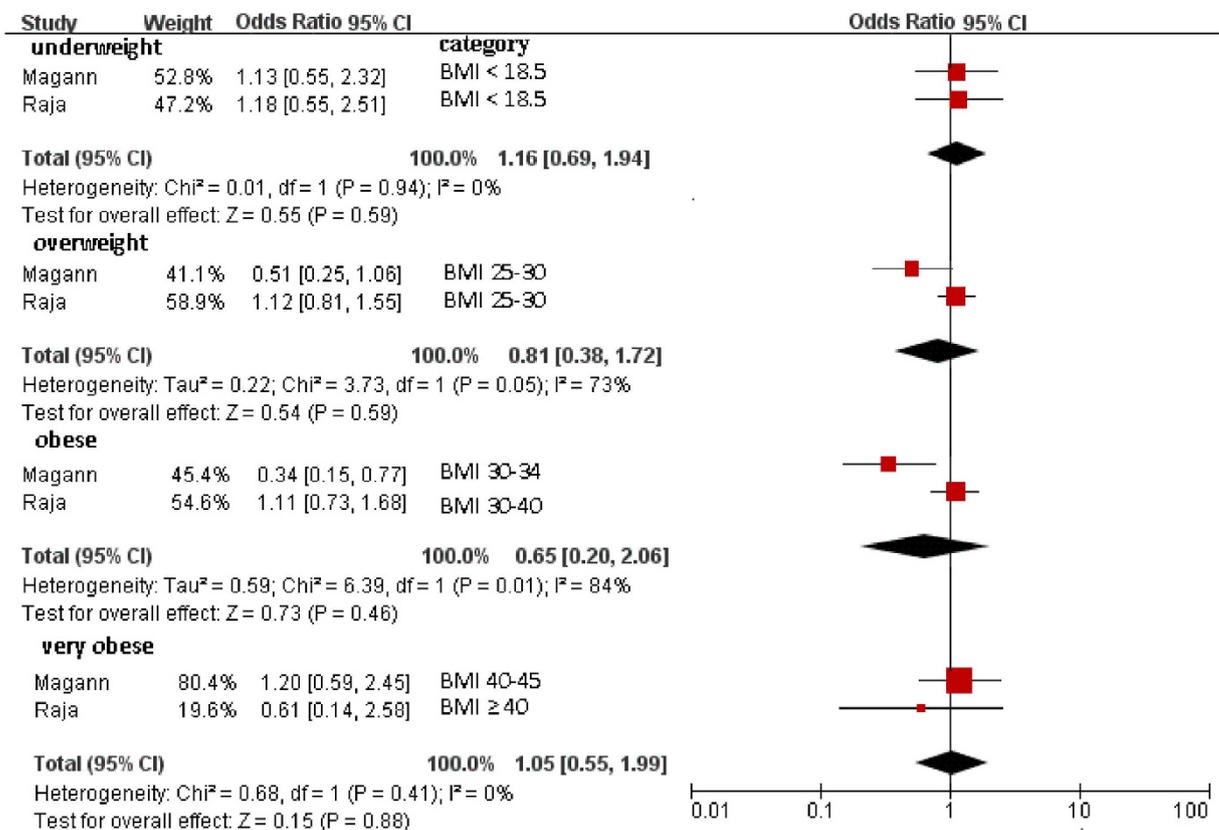


Figure 4. Forest plot of pooled analyses of maternal BMI categories and cord pH < 7.1. Maternal BMI in different categories showed nonsignificant associations with cord pH < 7.1. Note that ORs are for each category as compared with the “normal weight” category (BMI 18–25).

magnitude for very low Apgar (0–3) compared with intermediate scores (4–6). Furthermore, the strength of these association was strongest for full-term infants²³. Previous studies have observed that maternal BMI was related to risks of infant mortality primarily in full-term births²⁴. Our study suggested that maternal obesity was associated with low Apgar scores at 1 and 5 minutes. In a subgroup analysis, the risk of maternal obesity and overweight was higher for Apgar score < 7 at 5 minutes in full-term infants and time of measurement of maternal BMI at pre-pregnancy. However, these two groups contained overlapping studies, so it cannot be concluded that a high BMI assessed pre-pregnancy is more harmful than that assessed during early pregnancy. Also, weight gain during pregnancy was associated with neonatal adverse events^{25,26}. Of the included studies, more than half of studies assessed maternal BMI at the first antenatal visit without exact time. Thus some women may receive their first check-up in the middle or late stage of pregnancy, and gain certain weights by her pregnancy. Future studies are warranted to detect the influence of these variables.

Cord pH is considered a crucial outcome measure for monitoring foetal conditions. Malin *et al.* concluded that low arterial pH was strongly associated with long-term adverse outcomes in a systematic review of outcomes for 481,753 infants²⁷. However, the clinically meaningful pH level is unknown. Yeh *et al.* suggested that the threshold pH for adverse neurological outcomes is 7.10 and the ‘ideal’ cord pH is 7.26–7.30. Above 7.00, however, neonatal acidemia is weakly associated with adverse outcomes²⁸. Our results did not show any association between umbilical cord pH < 7.1 and maternal BMI. However, measurement of umbilical cord pH is not part of routine care in some obstetrics facilities, so we only had two applicable studies. Heterogeneity existed among these studies. Further, the lack of other cut-off criteria besides pH < 7.1 for cord pH might explain the absence of an association. Thus, more clinical studies are required to assess the relationship between arterial umbilical cord pH and maternal BMI.

Maternal obesity might affect the neonatal condition immediately after birth through multiple pathways. Many studies have demonstrated that obesity in pregnancy is associated with a wide spectrum of maternal complications, including postpartum haemorrhage, higher risks of maternal hypertension, and gestational diabetes. Obesity in pregnancy has also been shown to be associated with foetal macrosomia, post-term pregnancy, increased caesarean section rates, and need for labour induction^{25,26,29}.

Maternal BMI in early pregnancy is strongly associated with fat mass, which includes visceral fat mass. The placenta is prone to obesity-associated lipid accretion^{30,31}. Previous studies have observed that maternal obesity is associated with elevated total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides, and lower high-density lipoprotein cholesterol³². Placentas from obese women show 50% more lipids than do placentas from lean women³³. Alternatively, lipotoxicity may influence the pathogenesis of the placenta through inflammation and oxidative stress. Compared with full-term control placentas, placentas of

obese women showed disorders of redox balance, as indicated by increased lipid peroxidation (malondialdehyde measurement) and activity of antioxidant enzymes, such as the superoxide dismutases, catalase, and glutathione peroxidase³⁴. Finally, increasing lipotoxicity, inflammation, and oxidative stress in the placenta could disrupt placental morphology, cell proliferation, and angiogenesis³². Placental dysfunction could impair fetal health condition in the uterus.

Substantial heterogeneity was observed in the pooled analysis, but this was not surprising because of the limited number of included studies and differences in various aspects across studies. The sensitivity analysis suggested that the heterogeneity might come from specific studies. In the Choi *et al.* study³, low Apgar scores were defined as scores less than 7 at 1 or 5 minutes, which may lead to overestimated results. In fact, the OR reported by that study was evidently higher than that in the other studies. Similarly, Nohr *et al.*¹³ included Apgar scores < 8, which might account for their results. Marshall *et al.*¹⁶ reported ORs for very obese which was compared to mothers BMI ranged from 30 to 39.9. In addition to differences in the features of the study populations, Thrift *et al.*²⁰ conducted a study with indigenous or non-indigenous pregnancies, which contributed to the high heterogeneity. The ethnicity basis for association between overweight or obesity and adverse neonatal outcome remain unclearly.

One of major strengths of our study is that all included original studies used a cohort design, eliminating the possibility of reverse causation. Moreover, in the sensitivity analysis, the combined results of the associations between maternal overweight and obesity with the risk of low Apgar scores persisted and remained statistically significant. In addition, with the large sample size, we had enhanced statistical power to provide more precise and reliable risk estimates. The major limitation of our meta-analysis was that currently available published studies in this area are not sufficient. Additionally, we included only articles published in English. For studies on maternal BMI, cord pH, and Apgar scores at 1 minute, only 2 to 3 studies were eligible for analysis under each category.

In conclusion, our pooled analyses provide evidence that maternal overweight and obesity are significantly associated with low Apgar scores. There was no association with low cord pH. However, the associations could not be definitively concluded to indicate risk factors. More studies are needed to focused on this topic.

Methods

Retrieval of studies. We searched PubMed, EMBASE, and Cochrane Library in order to located related studies. The literature search was completed before August 2015. The search was performed by combining Medical Subject Heading (MeSH) terms combined with free-text words for birth asphyxia, such as asphyxia neonatorum and Apgar score, or keywords, such as birth asphyxia and cord pH, and using “OR” for connecting relevant text within the concept. To acquire studies related to maternal weight status we combined these terms using “AND” with a combination of key word, such as maternal obesity, maternal body mass index, and gestational weight. We restricted the search to human studies published in English. Titles and abstracts of the retrieved studies were scanned to exclude studies that were clearly irrelevant. Then, two authors independently read the full text of remaining studies to determine their eligibility according to our inclusion criteria. Disagreements were resolved by a third author, who independently examined the studies, and then consensus was reached. The reference lists of the included studies and relevant reviews were manually searched for further additional articles.

Study selection. Inclusion criteria for our study were as follows: (1) those that investigated maternal BMI during pregnancy and risk of low Apgar score and cord pH; (2) case-control or cohort studies; (3) those that described the assessment of exposure and outcome; and (4) those that provided adjusted relative risk (RR) estimates, such as risk ratios, incidence rate ratios, hazard ratios, or ORs and 95% CIs for different categories of BMI.

Exclusion criteria for the study were as follows: (1) case series; (2) studies with overlapping data; (3) those that provided crude ORs or original data; (4) those in which Apgar scores and cord pH were expressed as means and standard deviations.

Data extraction. Two investigators independently extracted data from the studies, including first author, publication date, country, study design, sample size, assessment method for maternal BMI and birth asphyxia parameters, primary outcome, and adjusted confounders. We included the single study with the largest sample size if participants overlapped between studies. When data extraction was completed, we compared the results of two authors, and any disagreement was independently reviewed by a third author until consensus was reached.

Quality evaluation. All included studies were examined for their methodological quality by two authors independently using the Newcastle-Ottawa scale (NOS). The NOS is recommended for both cohort studies and case-control studies, where scores vary between 0 and 9³⁵. This scale consists of a eight-term process for assessing the selection of the study population, comparability, and the evaluation of exposure and outcome. Studies with scores of at least 5 were deemed to be high-quality studies. Any disagreement was resolved in the manner previously described.

Statistical analysis. Included studies used ORs to assess the association between maternal BMI and risk of low Apgar score and cord pH. We pooled the ORs across studies using the Mantel–Haenszel formula (fixed-effect model) or the DerSimonian–Laird formula (random-effect model). A fixed-effect model was adopted when heterogeneity existed; otherwise, a random-effect model was used. The I^2 and Q statistics were used to detect statistical heterogeneity between studies. The Q statistic was considered significant if $P < 0.1$, and $I^2 > 50\%$ indicated high heterogeneity. A forest plot was used to show the ORs and 95% CIs for each study, as well as the pooled ORs and 95% CIs. We conducted subgroup analyses in studies where participants were restricted based on gestational age (full-term infant or not) and time of measurement of maternal BMI (pre-pregnancy or during pregnancy). We performed the sensitivity analysis by removing one study at a time. Publication bias was visually assessed with funnel plots and the Begg-adjusted rank correlation test, where a value of $P < 0.05$ was considered statistically

significant. All analyses were performed with Review Manager software (RevMan, version 5.3) or Stata software (version 12).

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Author Contributions

T.T.Z. and J.T. contributed equally. T.T.Z. and J.T. conceived and designed the study. F.Y.Z and Y.Q. performed literature searches and data collection. T.T.Z. and J.T. conducted statistical analysis and wrote manuscript. D.Z.M. revised the manuscript.

Additional Information

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