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Body Mass Index at 11–13 Weeks' Gestation and Pregnancy Complications

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Key Words
Body mass index · First-trimester screening · Miscarriage · Stillbirth · Preeclampsia · Diabetes mellitus, gestational · Preterm delivery · Birth weight · Cesarean section

Abstract
Objective: To examine the association between body mass index (BMI) at 11–13 weeks' gestation and a wide range of adverse pregnancy outcomes after adjustment for confounding factors in obstetric history and maternal characteristics. ***Methods:*** This was a prospective screening study for adverse obstetric outcomes in women with singleton pregnancies attending for their first routine hospital visit at 11^{+0}–13^{+6} weeks of gestation. The maternal weight and height were measured and the BMI was calculated. Regression analysis was performed to examine the association between BMI and each of the adverse pregnancy outcomes. ***Results:*** We examined 41,577 pregnancies with a live fetus at 11–13 weeks. There was a significant contribution from maternal BMI, in addition to maternal characteristics and obstetric history, in the prediction of subsequent miscarriage, stillbirth, preeclampsia, gestational hypertension, gestational diabetes mellitus, delivery of small and large for gestational age neonates, and both elective and emergency cesarean section, but not spontaneous preterm delivery. The risk for each pregnancy complication increased exponentially with BMI, except for delivery of small for gestational age neonates which decreased with BMI. ***Conclusions:*** Maternal BMI at 11–13 weeks can be combined with other maternal characteristics and obstetric history to estimate patient-specific risks for many pregnancy complications.

Introduction

The proportion of overweight and obese pregnant women is increasing and in such women, compared to those with normal body mass index (BMI), the risk for many pregnancy complications is increased [1–7]. However, comparison of the prevalence of pregnancy complications between different BMI groups does not allow estimation of accurate patient-specific risks which requires BMI to be treated as a continuous variable. Additionally, there were great differences between studies reporting on the association between BMI and pregnancy complications [1–7]. The method of recording maternal BMI varied between studies from self-reporting to accurate measurement of weight and/or height before or during different gestations in pregnancy. The categories of BMI that were compared were not the same in the various published reports. Additionally, the criteria for the diagnosis of pregnancy complications varied between studies. For exam-

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ple, some studies provided data only for total rather than elective and emergency cesarean section, the same was the case in preterm delivery in which data were given as total or separately for iatrogenic and spontaneous. The definitions of small and large neonates varied with some studies using cutoffs of birth weight regardless of gestation at delivery and others percentiles of weight for gestational age.

The aim of this study was to use BMI, calculated from accurate measurement of weight and height at 11–13 weeks' gestation, as a continuous variable to estimate patient-specific risk for a wide range of adverse pregnancy outcomes after adjustment for confounding factors in obstetric history and maternal characteristics.

Materials and Methods

Screening Study Population

This was a prospective screening study for adverse obstetric outcomes in pregnant women attending for their first routine hospital visit at King's College Hospital, London, UK, and Medway Maritime Hospital, Kent, UK. This visit, which was held at 11^{+0}–13^{+6} weeks of gestation, included recording of maternal demographic characteristics and previous obstetric and medical history, measurement of maternal weight and height and calculation of BMI (kg/m^2), and ultrasound examination for the measurement of the fetal crown-rump length (CRL) to determine gestational age [8], measurement of the fetal nuchal translucency thickness as part of screening for aneuploidies [9], and examination of the fetal anatomy for the diagnosis of major fetal defects [10]. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

A second ultrasound examination for fetal biometry and examination of the fetal anatomy was carried out at 20–24 weeks. In the neonatal period all babies were examined by a pediatrician. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women.

Maternal Characteristics and Obstetric History

Patients completed a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), method of conception (spontaneous or assisted), cigarette smoking during pregnancy, history of chronic hypertension, history of type 1 or 2 diabetes mellitus, and obstetric history including the outcome of each previous pregnancy. The questionnaire was then reviewed by a doctor together with the patient.

Outcome Measures

In this study we examined the relationship between BMI recorded at 11^{+0}–13^{+6} weeks with (1) miscarriage or stillbirth, (2) development of preeclampsia (PE) or gestational hypertension (GH), (3) development of gestational diabetes mellitus (GDM), (4) spontaneous preterm delivery before 34 and before 37 weeks, (5) delivery of a small for gestational age (SGA) or large for gestational age (LGA) neonate, and (6) delivery by elective or emergency cesarean section.

We excluded pregnancies conceived by intrauterine insemination because we did not have data on whether or not they had received ovulation-inducing drugs, pregnancies with fetal aneuploidies or major defects diagnosed either prenatally or in the neonatal period, and pregnancies ending in termination for psychosocial reasons.

Miscarriage and Stillbirth

Miscarriage included spontaneous miscarriage and fetal death before 24 weeks. Stillbirths were fetal deaths at or after 24 weeks.

Preeclampsia and Gestational Hypertension

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy [11]. We also subdivided PE according to gestational age at delivery into early-PE (<34 weeks), middle-PE (34–37 weeks) and late-PE (>37 weeks). In the investigation of the relationship between BMI and PE or GH we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Gestational Diabetes

Screening for GDM in our hospitals was based on a two-step approach. In all women random plasma glucose was measured at 24–28 weeks of gestation, and if the concentration was >6.7 mmol/l, an oral glucose tolerance test was carried out within the subsequent 2 weeks. The diagnosis of GDM was made if the fasting plasma glucose level was at least 6 mmol/l or the plasma glucose level 2 h after the oral administration of 75 g glucose was 7.8 mmol/l or more [12]. In women with normal random blood sugar an oral glucose tolerance test was performed if they had persistent glucosuria, they developed polyhydramnios, or the fetus became macrosomic. In the investigation of the relationship between BMI and GDM we excluded pregnancies with pre-pregnancy diabetes mellitus type 1 or 2 and those ending in miscarriage or delivery before 30 weeks because they may not have had screening and diagnosis of GDM.

Spontaneous Preterm Delivery

Spontaneous preterm deliveries included those with spontaneous onset of labor and those with preterm pre-labor rupture of membranes occurring before 34 completed weeks (238 days) and before 37 completed weeks (259 days). In the investigation of the relationship between BMI and spontaneous preterm delivery we excluded pregnancies ending in miscarriage or stillbirth and those with iatrogenic delivery before 34 and 37 weeks, respectively.

Small and Large for Gestational Age

SGA and LGA neonates were defined as those with birth weight below the 5th percentile or above the 95th percentile for gestation, respectively [13]. In the investigation of the relationship between BMI and SGA or LGA we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Elective or Emergency Cesarean Section

Emergency cesarean section included all cases where such delivery was undertaken after the onset of labor, usually for failure to progress, fetal distress or intrapartum hemorrhage. This group also included cases of antepartum hemorrhage requiring cesarean section. Elective cesarean section was performed before the onset

Table 1. Univariable logistic regression analysis on the association between the maternal body mass index recorded at 11^{+0}–13^{+6} weeks and pregnancy complications

Outcome	OR (95% CI)	p
Hypertensive disorders	1.08 (1.07–1.09)	<0.001
Preeclampsia	1.09 (1.08–1.10)	<0.001
Early preeclampsia	1.08 (1.06–1.11)	<0.001
Middle preeclampsia	1.09 (1.07–1.11)	<0.001
Late preeclampsia	1.09 (1.07–1.10)	<0.001
Gestational hypertension	1.07 (1.06–1.08)	<0.001
Gestational diabetes	1.11 (1.10–1.12)	<0.001
Fetal loss	1.06 (1.04–1.07)	<0.001
Miscarriage	1.05 (1.04–1.07)	<0.001
Stillbirth	1.06 (1.04–1.09)	<0.001
Abnormal growth	–	
Large for gestation >95th centile	1.09 (1.08–1.10)	<0.001
Large for gestation >90th centile	1.08 (1.07–1.08)	<0.001
Small for gestation <10th centile	0.97 (0.96–0.97)	<0.001
Small for gestation <5th centile	0.97 (0.96–0.97)	<0.001
Delivery before 34 weeks	1.03 (1.01–1.04)	<0.001
Spontaneous	–	0.245
Iatrogenic	1.06 (1.04–1.08)	<0.001
Cesarean section	1.06 (1.06–1.07)	<0.001
Elective	1.06 (1.06–1.07)	<0.001
Emergency	1.06 (1.05–1.06)	<0.001

OR = Odds ratio; CI = confidence interval.

of labor for obstetrical or medical indications or at the request of the mother. In the investigation of the relationship between BMI and elective or emergency cesarean section we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Statistical Analysis

Univariable logistic regression analysis was performed to examine the association between BMI and each of the adverse pregnancy outcomes. The risk for each of the pregnancy outcomes was then calculated from the formula: odds/(1 + odds), where odds = e^Y, and Y was derived from the univariable logistic regression analysis. Multivariable logistic regression analysis was performed for the prediction of each pregnancy outcome from BMI, maternal age, racial origin, mode of conception, smoking, history of chronic hypertension or diabetes, and previous history of adverse pregnancy outcome or family history of PE.

In a separate analysis BMI was converted into categorical variables, with four categories: <25, 25–29.9, 30–34.9 and ≥35. The adjusted odds ratios (ORs) for pregnancy complications in each BMI group were derived by multivariable logistic regression analysis which included the maternal factors as described above.

The statistical software package PASW Statistics 18.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Literature Search

We searched MEDLINE and EMBASE from 1996 to November 2010 to identify English language articles reporting the relationship between specific BMI groups and adverse pregnancy outcomes. We included all case-control and cohort studies which reported data from singleton pregnancies regarding the primary outcome measures: miscarriage, stillbirth, PE, GH, GDM, preterm delivery, birth of SGA or LGA neonates, and delivery by elective or emergency cesarean section. We excluded duplicate publications.

Two independent reviewers extracted the data from each article and these were then examined by a third reviewer. ORs with 95% confidence intervals (CI) were calculated for each outcome in each study. Forrest plots were constructed and a random-effects model, which takes into account the random variation within studies, was used to calculate weighted summary ORs by taking into account the weight of each study.

Forrest plots and summary ORs were generated using Medcalc software version 9.6.2.0 (MedCalc Software, Mariakerke, Belgium).

Results

Study Population

During the study period we carried out an ultrasound examination at 11–13 weeks in 45,191 singleton pregnancies with a live fetus and CRL of 45–84 mm. We excluded from further analysis 77 (0.2%) cases because they conceived by intrauterine insemination, 2,739 (6.1%) because there were no or incomplete data on pregnancy outcome and 682 (1.5%) because of the prenatal or postnatal diagnosis of aneuploidies or major defects, and 116 (0.3%) because of pregnancy termination for psychosocial reasons.

In the 41,577 cases included in the study the median maternal age was 31.2 (range 14.3–51.2) years, the median BMI was 24.4 (range 15–63.3), the racial origin of the women was Caucasian in 31,413 (75.5%), African in 6,682 (16.1%), South Asian in 1,694 (4.1%), East Asian in 733 (1.8%), and mixed in 1,055 (2.5%). In 4,554 (10.9%) cases the women were cigarette smokers, 442 (1.1%) had a history of chronic hypertension, 317 (0.8%) had a history of diabetes type 1 or 2, and in 1,819 (4.4%) their mother had developed PE.

Pregnancy Complications

Univariable logistic regression analysis demonstrated that the maternal BMI recorded at 11^{+0}–13^{+6} weeks was significantly associated with subsequent miscarriage, stillbirth, PE, GH, GDM, delivery of SGA and LGA neonates, and both elective and emergency cesarean section, but not spontaneous delivery before 34 weeks (table 1; fig. 1, 2).

Table 2. Logistic regression analysis for the prediction of miscarriage and stillbirth by maternal factors and obstetric history

Independent variable	Miscarriage		Stillbirth	
	OR (95% CI)	p	OR (95% CI)	p
Body mass index	1.03 (1.01–1.05)	0.001	1.05 (1.03–1.08)	<0.001
Maternal age, years	1.04 (1.02–1.05)	<0.001	1.01 (0.98–1.04)	0.422
Ethnic origin				
Caucasian	1		1	
African	3.40 (2.74–4.20)	<0.001	1.91 (1.35–2.70)	<0.001
South Asian	1.22 (0.69–2.14)	0.497	1.53 (0.74–3.15)	0.252
East Asian	1.08 (0.44–2.63)	0.867	0.92 (0.23–3.76)	0.912
Mixed	2.58 (1.60–4.16)	<0.001	1.33 (0.54–3.27)	0.532
Conception				
Spontaneous	1		1	
Ovulation drugs	5.38 (3.72–7.78)	<0.001	2.12 (0.93–4.83)	0.073
IVF	1.19 (0.58–2.46)	0.630	1.58 (0.58–4.32)	0.370
Cigarette smoking	1.45 (1.06–1.97)	0.020	1.91 (1.29–2.84)	0.001
History of chronic hypertension	1.06 (0.54–2.05)	0.868	3.33 (1.65–6.71)	0.001
History of preexisting diabetes				
None	1		1	
Type 1 diabetes mellitus	2.44 (0.89–6.68)	0.082	3.56 (1.12–11.33)	0.032
Type 2 diabetes mellitus	1.44 (0.55–3.73)	0.459	1.83 (0.43–7.69)	0.410
Parity				
Nulliparous without previous miscarriage	1			
Nulliparous with previous miscarriage <16 weeks	1.69 (1.25–2.27)	0.001		
Nulliparous with previous miscarriage 16–23 weeks	10.34 (5.91–18.11)	<0.001		
Parous without previous miscarriage	1.02 (0.79–1.32)	0.854		
Parous with previous miscarriage <16 weeks	1.08 (0.74–1.58)	0.700		
Parous with previous miscarriage 16–23 weeks	4.10 (2.37–7.07)	<0.001		
Nulliparous			1	
Parous without previous stillbirth			0.71 (0.53–0.96)	0.026
Parous with previous stillbirth			1.71 (0.62–4.75)	0.300

Note that the classification of parity used for the two outcome measures was different. OR = Odds ratio; CI = confidence interval; IVF = in vitro fertilization.

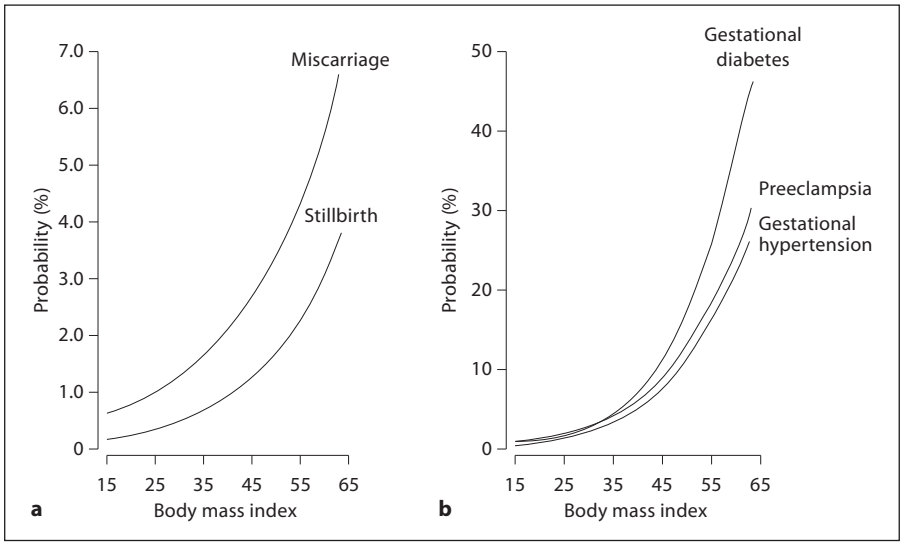


Fig. 1. Predictive probability of miscarriage and stillbirth (**a**), gestational diabetes mellitus, preeclampsia and gestational hypertension (**b**) plotted against body mass index.

Table 3. Logistic regression analysis for the prediction of preeclampsia and gestational hypertension by maternal factors and obstetric history

Independent variable	Preeclampsia		Gestational hypertension	
	OR (95% CI)	p	OR (95% CI)	p
Body mass index	1.07 (1.06–1.08)	<0.001	1.07 (1.06–1.08)	<0.001
Maternal age, years	1.02 (1.01–1.03)	0.002	1.03 (1.02–1.04)	<0.001
Ethnic origin				
Caucasian	1		1	
African	2.77 (2.37–3.24)	<0.001	1.46 (1.24–1.71)	<0.001
South Asian	2.07 (1.50–2.84)	<0.001	1.09 (0.77–1.53)	0.631
East Asian	1.61 (0.95–2.72)	0.077	1.14 (0.69–1.88)	0.620
Mixed	1.41 (0.90–2.21)	0.130	1.06 (0.70–1.61)	0.773
Conception				
Spontaneous	1		1	
Ovulation drugs	1.30 (0.80–2.13)	0.287	1.07 (0.66–1.72)	0.786
IVF	1.72 (1.12–2.65)	0.013	1.38 (0.92–2.06)	0.115
Cigarette smoking	0.81 (0.61–1.06)	0.125	0.56 (0.43.0.74)	<0.001
History of chronic hypertension	3.96 (2.93–5.36)	<0.001	0.77 (0.46–1.28)	0.311
History of preexisting diabetes				
None	1		1	
Type 1 diabetes mellitus	1.79 (0.85–3.77)	0.144	1.65 (0.80–3.39)	0.176
Type 2 diabetes mellitus	0.74 (0.30–1.84)	0.646	0.82 (0.32–2.08)	0.672
Parity				
Nulliparous	1		1	
Parous without previous PE	0.30 (0.25–0.35)	<0.001	0.34 (0.29–0.39)	<0.001
Parous with previous PE	1.96 (1.55–2.49)	<0.001	1.82 (1.44–2.29)	<0.001
Maternal history of PE	1.69 (1.30–2.19)	<0.001	1.98 (1.58–2.48)	<0.001

OR = Odds ratio; CI = confidence interval; IVF = in vitro fertilization; PE = preeclampsia.

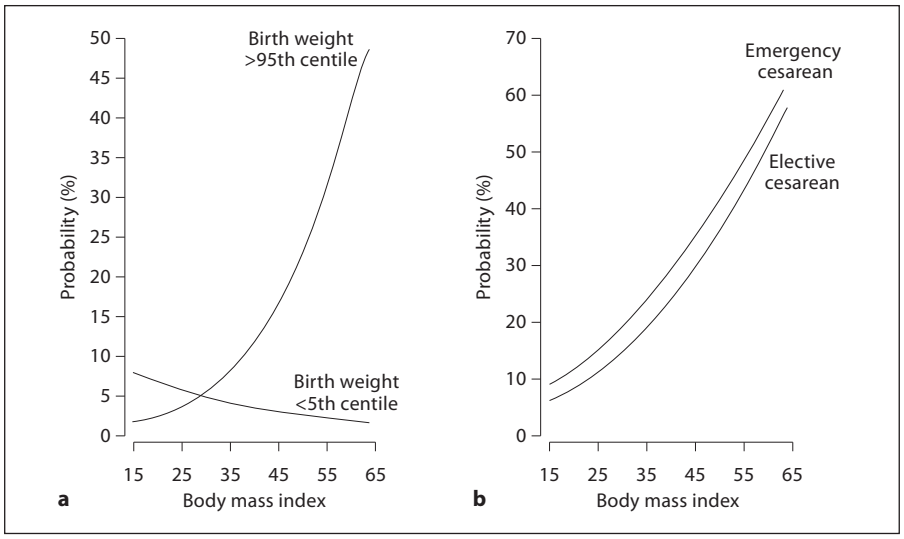


Fig. 2. Predictive probability of small and large for dates neonates (**a**), elective cesarean section and emergency cesarean section (**b**) plotted against body mass index.

Table 4. Logistic regression analysis for the prediction of small and large for gestational age neonates and gestational diabetes by maternal factors and obstetric history

Independent variable	Small for gestational age		Large for gestational age		Gestational diabetes	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Body mass index	0.97 (0.96–0.98)	<0.001	1.08 (1.07–1.09)	<0.001	1.11 (1.10–1.12)	<0.001
Maternal age, years	1.01 (1.00–1.02)	0.052	1.01 (1.00–1.02)	0.035	1.07 (1.05–1.08)	<0.001
Ethnic origin						
Caucasian	1		1		1	
African	2.19 (1.95–2.46)	<0.001	0.62 (0.53–0.71)	<0.001	1.41 (1.18–1.69)	0.001
South Asian	3.11 (2.62–3.68)	<0.001	0.46 (0.32–0.66)	<0.001	2.86 (2.15–3.81)	<0.001
East Asian	2.05 (1.54–2.71)	<0.001	0.65 (0.40–1.05)	0.077	3.59 (2.43–5.29)	<0.001
Mixed	1.64 (1.27–2.12)	<0.001	0.72 (0.51–1.02)	0.066	1.19 (0.74–1.93)	0.477
Conception						
Spontaneous	1		1		1	
Ovulation drugs	1.79 (1.33–2.42)	<0.001	0.97 (0.66–1.42)	0.872	1.54 (0.97–2.44)	0.066
IVF	1.37 (0.98–1.91)	0.062	1.07 (0.71–1.62)	0.735	1.37 (0.84–2.23)	0.211
Cigarette smoking	2.70 (2.40–3.03)	<0.001	0.58 (0.48–0.70)	<0.001	1.02 (0.78–1.32)	0.905
History of chronic hypertension	2.06 (1.45–2.93)	<0.001	0.90 (0.60–1.36)	0.625	0.99 (0.60–1.64)	0.970
History of preexisting diabetes					–	–
None	1		1			
Type 1 diabetes mellitus	0.25 (0.06–1.00)	0.049	6.93 (4.89–9.82)	<0.001		
Type 2 diabetes mellitus	1.48 (0.70–3.11)	0.306	2.74 (1.66–4.53)	<0.001		
Parity						
Nulliparous	1		1		1	
Parous without previous SGA	0.45 (0.40–0.49)	<0.001				
Parous with previous SGA	1.88 (1.61–2.19)	<0.001				
Parous without previous LGA			1.40 (1.25–1.57)	<0.001	0.81 (0.69–0.96)	0.012
Parous with previous LGA			6.24 (5.26–7.42)	<0.001	1.94 (1.46–2.57)	<0.001

OR = Odds ratio; CI = confidence interval; IVF = in vitro fertilization; SGA = small for gestational age; LGA = large for gestational age.

The results of multivariable logistic regression analysis for the prediction of miscarriage (Nagelkerke R^2 = 0.070, $p < 0.001$) and stillbirth (Nagelkerke R^2 = 0.026, $p < 0.001$), PE (Nagelkerke $R^2 = 0.110$, $p < 0.001$) and GH (Nagelkerke R^2 = 0.068, $p < 0.001$), GDM (Nagelkerke $R^2 = 0.083$, $p < 0.001$), delivery of SGA (Nagelkerke R^2 = 0.074, $p < 0.001$) or LGA neonates (Nagelkerke $R^2 = 0.087$, $p < 0.001$), and elective (Nagelkerke $R^2 = 0.205$, $p < 0.001$) or emergency cesarean section (Nagelkerke R^2 = 0.135, $p < 0.001$) from BMI, maternal age, racial origin, mode of conception, smoking, history of chronic hypertension or diabetes, and previous obstetric history are summarized in tables 2–5.

Literature Search

Forrest plots of ORs from previous reports and our study for stillbirth, PE, GH, GDM, preterm delivery before 34 or 37 weeks, delivery of SGA neonate with birth weight below the 5th and 10th percentile, delivery of LGA neonate with birth weight above the 90th and 95th percentile and delivery by cesarean section are shown in figures 3–11 [1, 3, 14–46]. In the case of early delivery in our study we selected spontaneous delivery before 34 and 37 weeks, but in most previous studies the outcome measure included a combination of spontaneous and iatrogenic preterm delivery. In our study we had data on both elective and emergency cesarean section, but most previous studies provided data only for total cesarean section.

Discussion

This was a prospective screening study in a large heterogeneous inner-city population in which the BMI at 11–13 weeks was derived from accurate measurement of weight and height. The findings demonstrate that with

Table 5. Logistic regression analysis for the prediction of elective and emergency cesarean section by maternal factors and obstetric history

Independent variable	Elective cesarean section		Emergency cesarean section	
	OR (95% CI)	p	OR (95% CI)	p
Body mass index	1.05 (1.04–1.06)	<0.001	1.06 (1.06–1.07)	<0.001
Maternal age, years	1.07 (1.07–1.08)	<0.001	1.05 (1.05.1.06)	<0.001
Ethnic origin				
Caucasian	1		1	
African	0.94 (0.85–1.04)	0.246	1.24 (1.14–1.34)	<0.001
South Asian	1.31 (1.11–1.54)	0.002	1.34 (1.16–1.55)	<0.001
East Asian	1.33 (1.04–1.70)	0.023	1.12 (0.89–1.40)	0.333
Mixed	0.91 (0.72–1.14)	0.412	0.93 (0.77–1.13)	0.477
Conception				
Spontaneous	1		1	
Ovulation drugs	1.21 (0.94–1.56)	0.133	0.91 (0.72–1.15)	0.427
IVF	1.46 (1.14–1.85)	0.002	1.15 (0.93–1.41)	0.194
Cigarette smoking	0.92 (0.82–1.05)	0.215	1.18 (1.07–1.30)	0.001
History of chronic hypertension	1.72 (1.31–2.25)	<0.001	1.33 (1.02–1.74)	0.038
History of preexisting diabetes				
None	1		1	
Type 1 diabetes mellitus	4.64 (3.05–7.07)	<0.001	5.56 (3.87–7.99)	<0.001
Type 2 diabetes mellitus	2.29 (1.39–3.77)	0.001	1.88 (1.16–3.05)	0.011
Parity				
Nulliparous	1		1	
Parous with one or more VD only	0.95 (0.88–1.03)	0.237	0.26 (0.24–0.28)	<0.001
Parous with one CS only	9.89 (8.77–11.14)	<0.001	2.76 (2.45–3.10)	<0.001
Parous with one CS plus one or more VD	3.72 (2.98–4.65)	<0.001	0.51 (0.38–0.69)	<0.001
Parous with two or more CSs only	71.77 (48.88–105.39)	<0.001	2.45 (1.45–4.11)	0.001
Parous with two or more CSs plus one or more VD	20.18 (10.66–38.18)	<0.001	1.03 (0.38–2.77)	0.958

OR = Odds ratio; CI = confidence interval; IVF = in vitro fertilization; VD = vaginal delivery; CS = cesarean section.

increasing maternal BMI, after adjustment for other maternal characteristics and obstetric history, there is a significant increase in the rate of subsequent miscarriage, stillbirth, PE, GH, GDM, delivery of LGA neonates, and both elective and emergency cesarean section, and a decrease in the rate of a delivery of SGA neonates.

Our results are in general agreement with those of previous studies which examined BMI in its relation to pregnancy complications as a categorical rather than continuous variable. Although such analysis does not allow accurate estimation of patient-specific risks, it makes it possible to combine data from several studies and calculate ORs for pregnancy complications for the various classes of BMI. As illustrated in figures 3–11, there is a stepwise increase in risk for several pregnancy complications with each class of increasing BMI.

The algorithms derived from multivariable logistic regression analysis, which combine BMI as a continuous variable with other maternal factors, can form the basis for a suggested new approach to antenatal care, whereby the patient-specific risk for a wide variety of pregnancy complications is estimated at a first hospital visit at 11–13 weeks' gestation [47]. Early estimation of risks for these pregnancy complications could potentially improve pregnancy outcome by shifting antenatal care from a series of routine visits to a more individualized patient- and disease-specific approach both in terms of the schedule and content of such visits.

The management of patients would not be dictated by their BMI class but rather by their estimated risk for a given condition, derived from their individual BMI in combination with other characteristics and obstetric history as well as the results of biophysical and biochemical tests. For example, at 11–13 weeks the estimated risk for

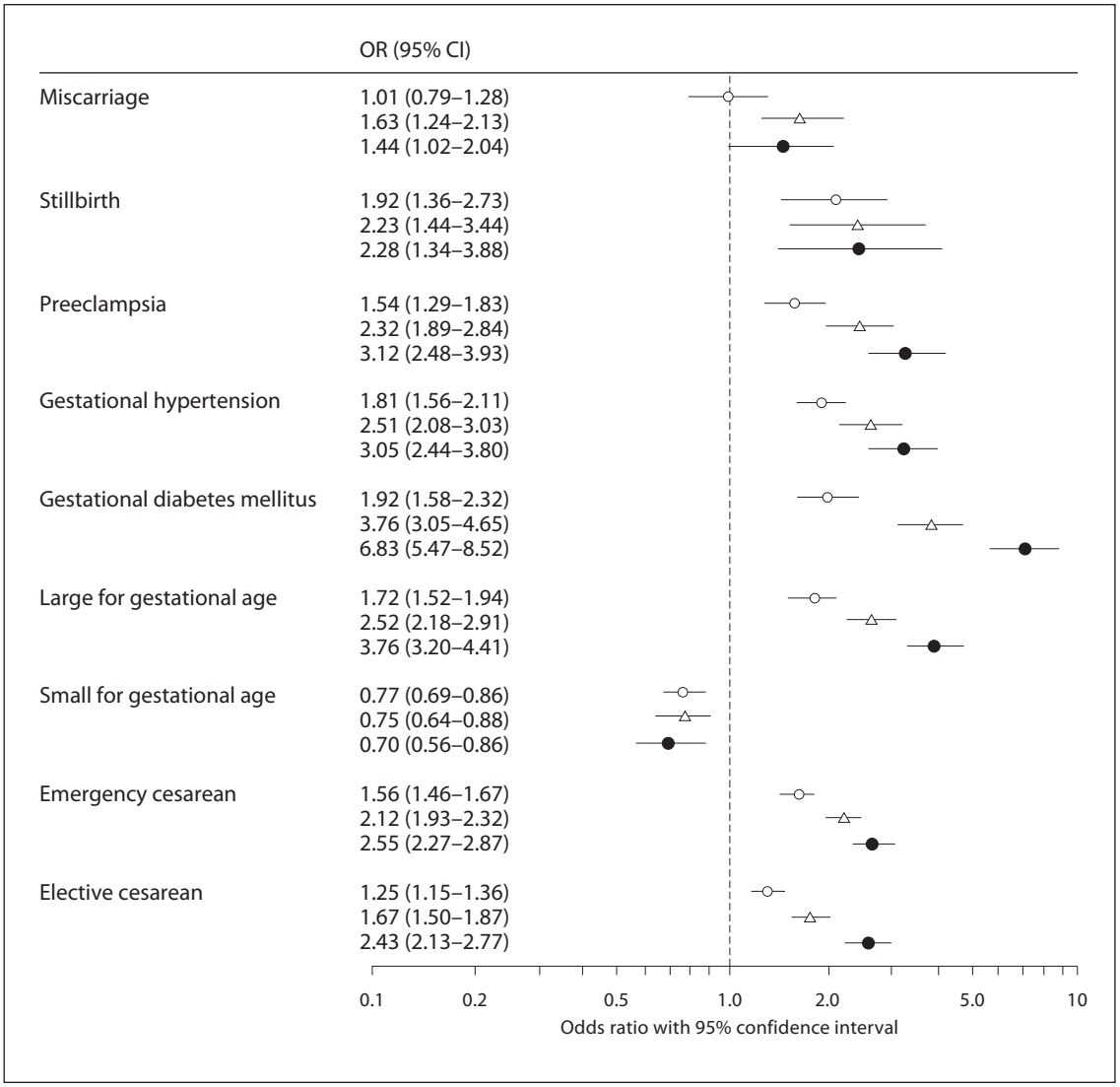


Fig. 3. Forrest plot of odds ratios and confidence intervals, after adjustment for maternal characteristics and obstetric history, for the risk of pregnancy complications in our study according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

subsequent development of PE depends on maternal BMI, as well as age, race, method of conception, history of chronic hypertension and whether in previous pregnancies they had PE or not. This maternal factor-related risk can be modified by the measurements of mean arterial pressure, uterine artery pulsatility index and serum pregnancy-associated plasma protein-A and placental growth factor at 11–13 weeks [48]. On the basis of such first-trimester combined testing, a group with an estimated high risk for PE could be treated prophylactically by low-dose aspirin [49] and have closer monitoring of their blood pressure for early diagnosis of PE should this develop.

Similarly, the estimated risk for stillbirth could be derived at 11–13 weeks by a combination of BMI with race, smoking, history of chronic hypertension and diabetes mellitus, whether they had a previous stillbirth or not, as well as the level of maternal serum pregnancy-associated plasma protein-A and the blood flow pattern in the fetal ductus venosus at 11–13 weeks [50]. Possible mechanisms for the association of obesity with stillbirth include fetal hyperglycemia and metabolic acidosis due to maternal

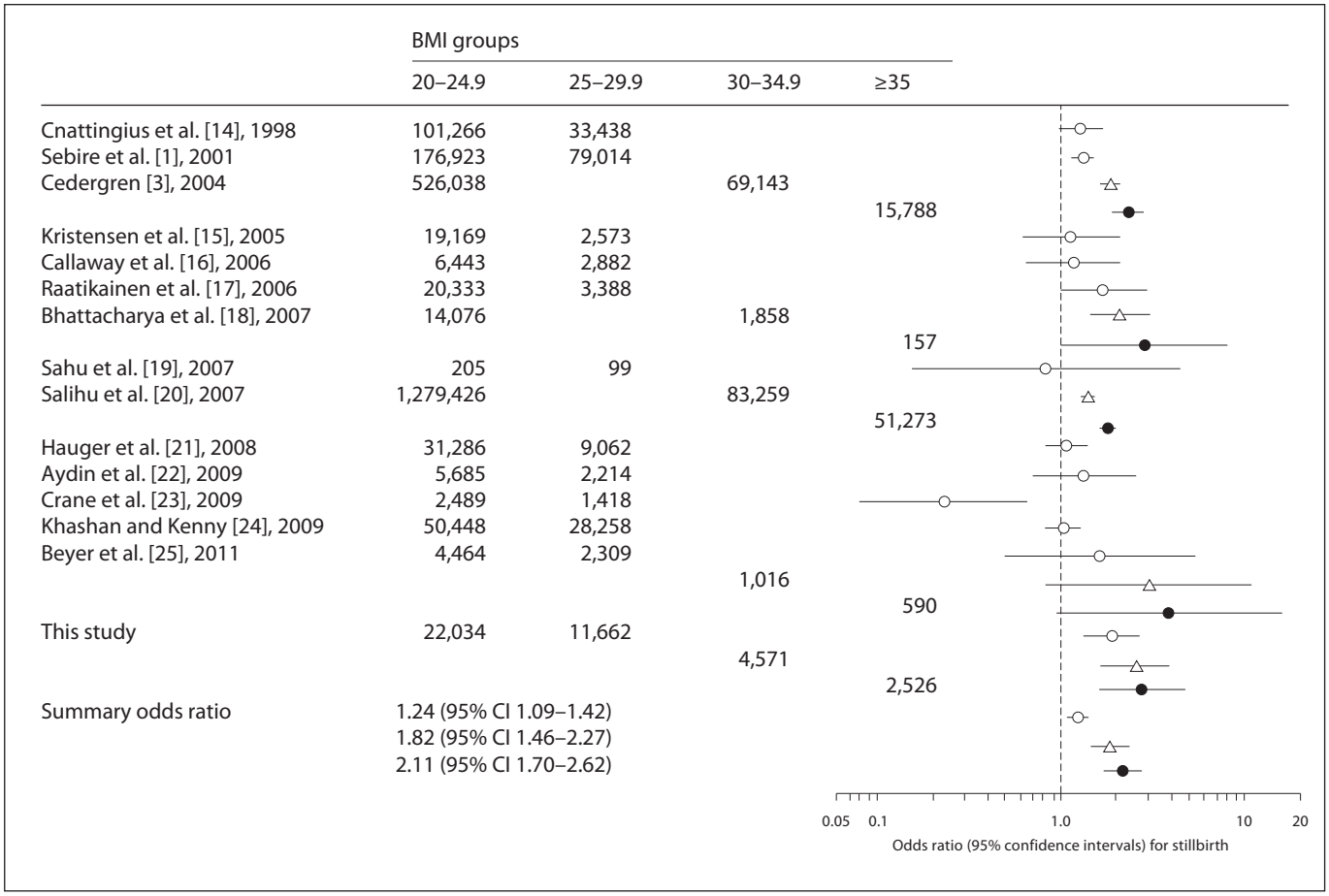
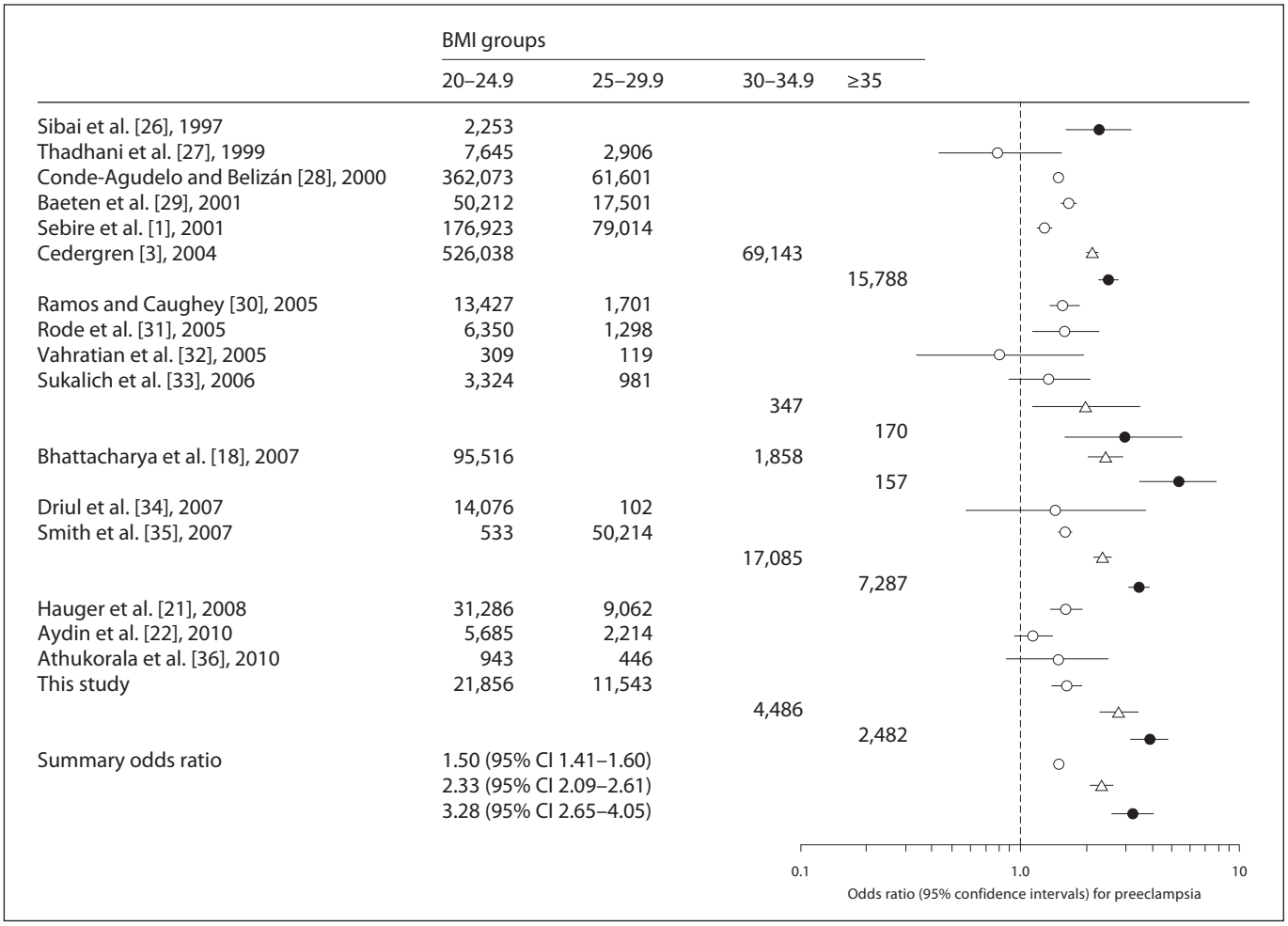


Fig. 4. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of stillbirth according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

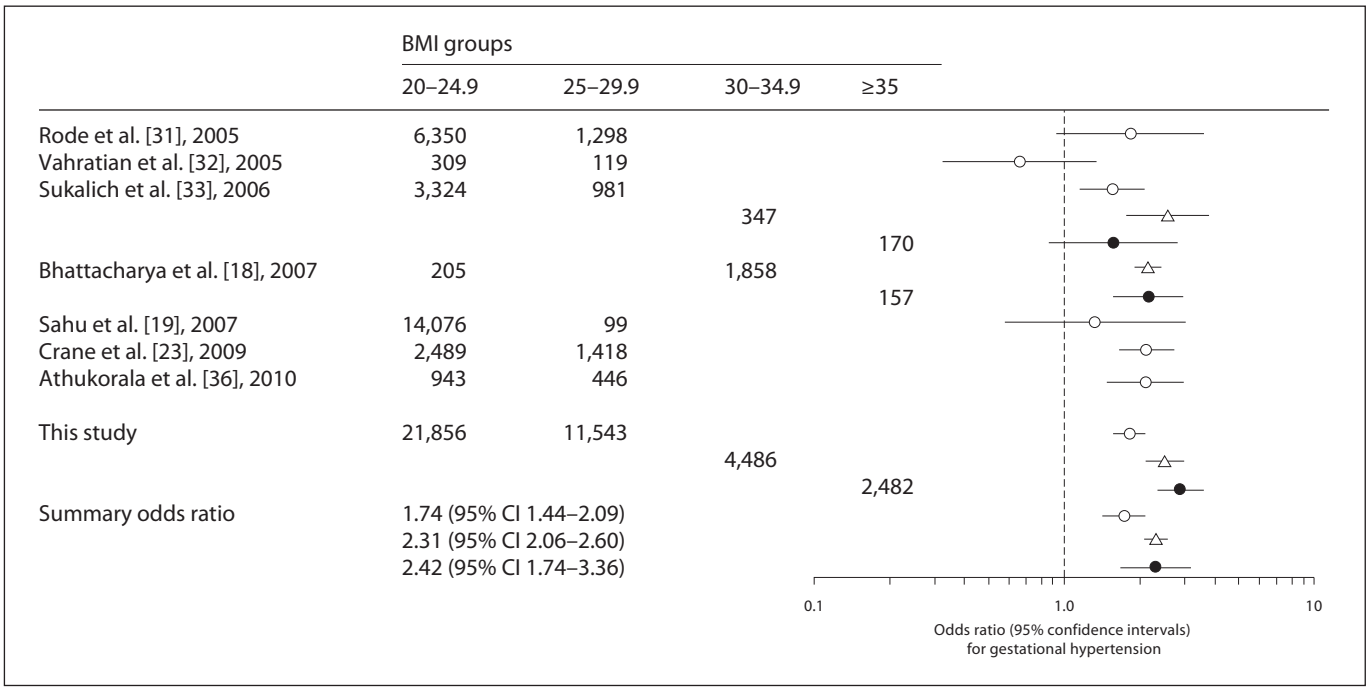
(For figures see page 259.)

Fig. 5. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of preeclampsia according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

Fig. 6. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of gestational hypertension according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).


BMI groups
20–24.9
25–29.9
30–34.9
≥35
Sibai et al. [26], 1997 2,253
Thadhani et al. [27], 1999 7,645 2,906
Conde-Agudelo and Belizán [28], 2000 362,073 61,601
Baeten et al. [29], 2001 50,212 17,501
Sebire et al. [1], 2001 176,923 79,014
Cedergren [3], 2004 526,038 69,143
15,788
Ramos and Caughey [30], 2005 13,427 1,701
Rode et al. [31], 2005 6,350 1,298
Vahratian et al. [32], 2005 309 119
Sukalich et al. [33], 2006 3,324 981
347
170
Bhattacharya et al. [18], 2007 95,516 1,858
157
Driul et al. [34], 2007 14,076 102
Smith et al. [35], 2007 533 50,214
17,085
7,287
Hauger et al. [21], 2008 31,286 9,062
Aydin et al. [22], 2010 5,685 2,214
Athukorala et al. [36], 2010 943 446
This study 21,856 11,543
4,486
2,482
Summary odds ratio 1.50 (95% CI 1.41–1.60)
2.33 (95% CI 2.09–2.61)
3.28 (95% CI 2.65–4.05)
0.1
1.0
10
Odds ratio (95% confidence intervals) for preeclampsia

5


BMI groups
20–24.9
25–29.9
30–34.9
≥35
Rode et al. [31], 2005 6,350 1,298
Vahratian et al. [32], 2005 309 119
Sukalich et al. [33], 2006 3,324 981
347
170
Bhattacharya et al. [18], 2007 205 1,858
157
Sahu et al. [19], 2007 14,076 99
Crane et al. [23], 2009 2,489 1,418
Athukorala et al. [36], 2010 943 446
This study 21,856 11,543
4,486
2,482
Summary odds ratio 1.74 (95% CI 1.44–2.09)
2.31 (95% CI 2.06–2.60)
2.42 (95% CI 1.74–3.36)
0.1
1.0
10
Odds ratio (95% confidence intervals)
for gestational hypertension

6

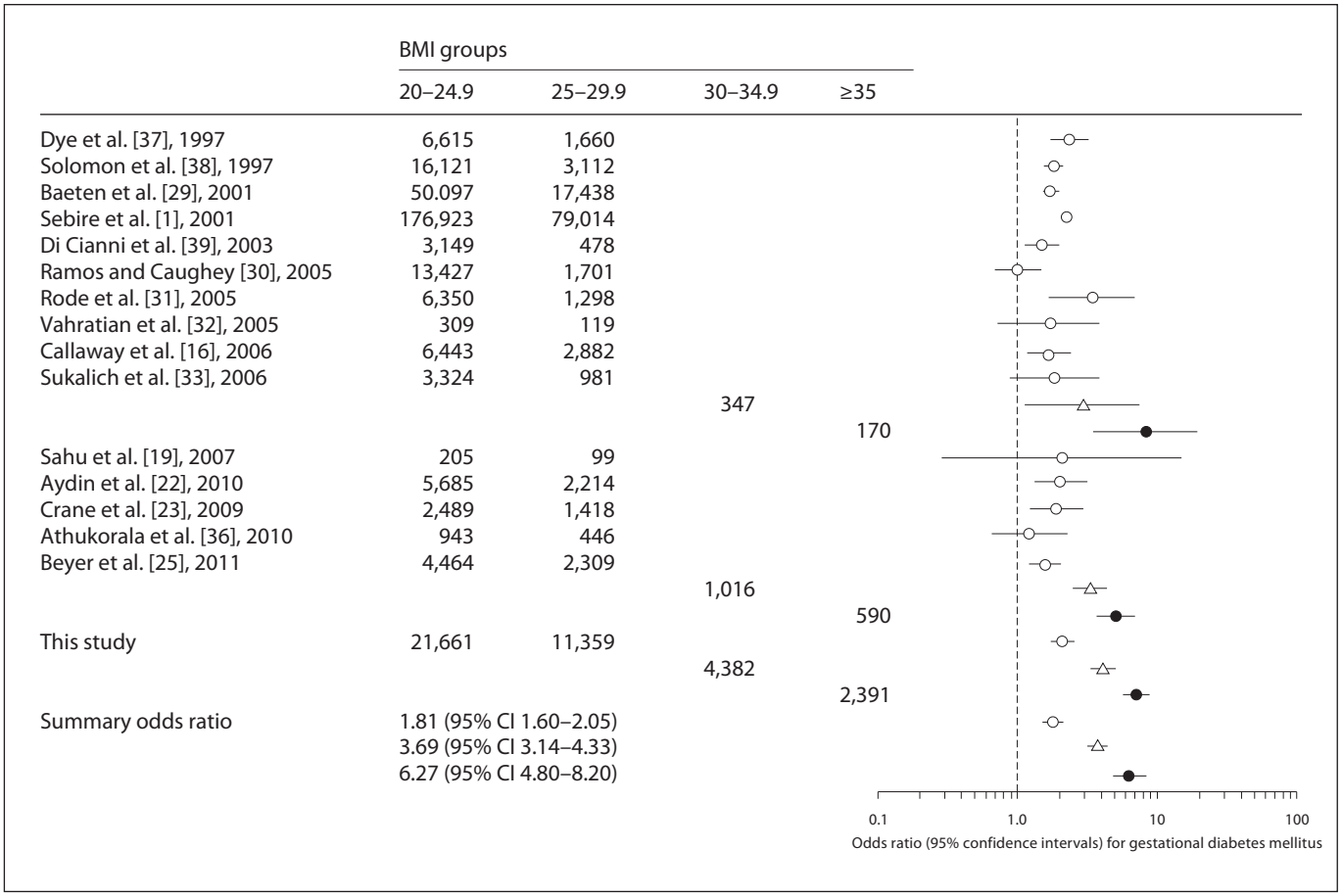


Fig. 7. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of gestational diabetes mellitus according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

glucose intolerance and fetal hypoxia due to impaired placental perfusion in association with PE and extended periods of snoring and apnea-hypoxia events during sleep [51–53]. At present, the only intervention for pregnancies at high risk for stillbirth would be higher frequency of ultrasound scans to monitor fetal growth and well-being with the beneficial consequence that at least some cases of stillbirth could be avoided by timely delivery.

The risks for GDM and delivery of LGA neonates are related to BMI, as well as age, race and history of a previous delivery of a macrosomic neonate. Additionally, at 11–13 weeks' gestation the maternal serum concentration of adiponectin, an adipocytokine released from adipose tissue, is reduced both in pregnancies that subsequently develop GDM and in those that deliver macrosomic neonates [54, 55]. Serum adiponectin level is inversely correlated to maternal BMI and insulin resistance [56, 57]. It is therefore possible that maternal serum adiponectin in early pregnancy may be a biomarker of the common metabolic derangement observed in obesity and GDM causing fetal macrosomia. Screening at 11–13 weeks' gestation by a combination of maternal characteristics, obstetric history and serum adiponectin could identify a high proportion of pregnancies that develop GDM and those that deliver LGA neonates. Future studies will determine whether dietary and pharmacological interventions, with such drugs as metformin, in the high-risk groups can potentially reduce the incidence of GDM and macrosomia with their associated maternal and perinatal complications.

Preterm birth is the leading cause of perinatal death and handicap in children and the vast majority of mortality and morbidity relates to early delivery before 34 weeks

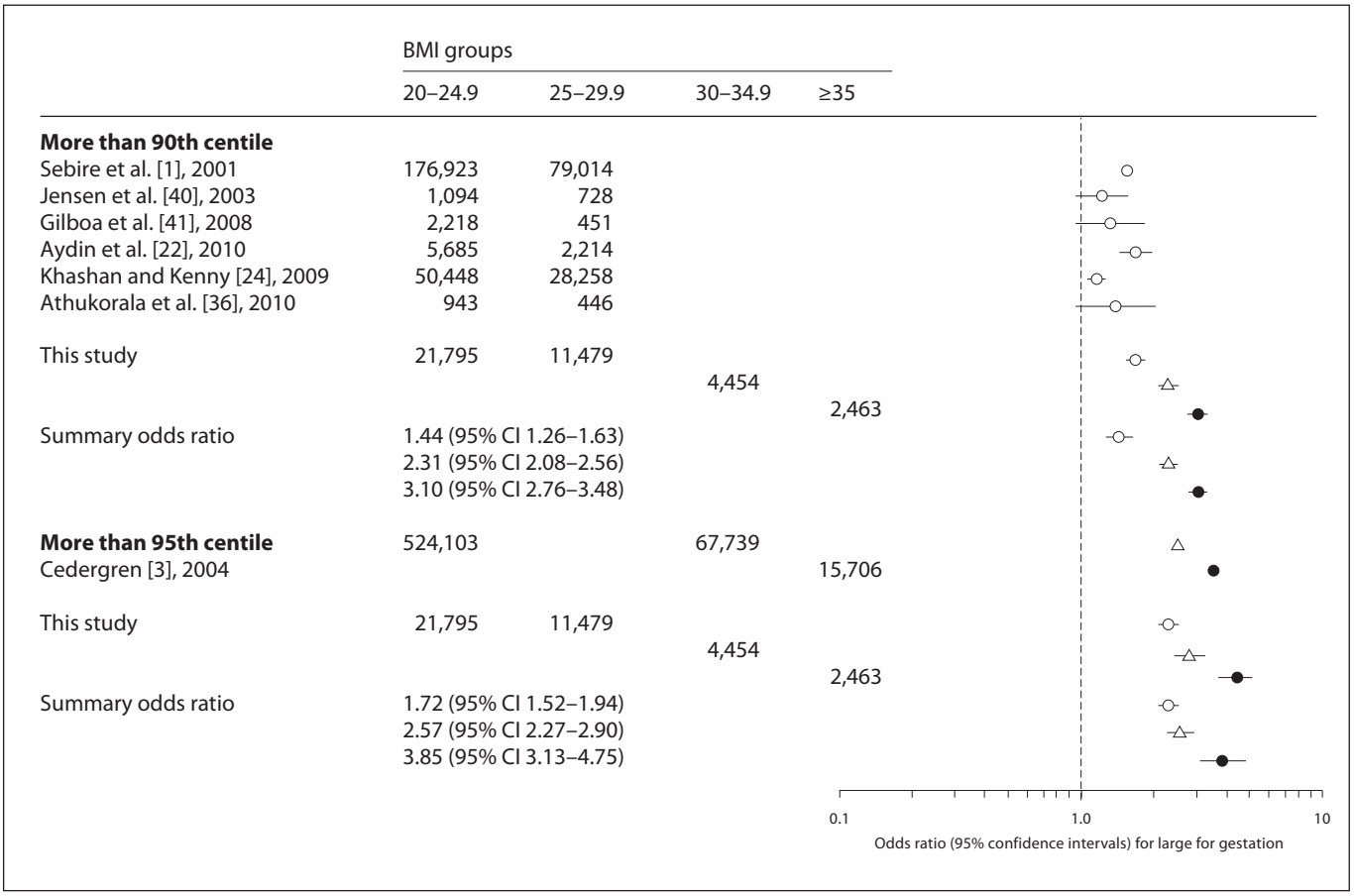


Fig. 8. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of large for gestational age neonates above the 90th and the 95th centile according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

[58, 59]. Delivery before 34 weeks occurs in about 2% of singleton pregnancies and in two thirds of the cases this is due to spontaneous onset of labor or preterm pre-labor rupture of membranes and in the other one third it is iatrogenic, mainly due to PE [60]. Most previous studies reported that obesity is associated with increased risk of preterm delivery, but these studies provided data for total rather than spontaneous delivery [7]. The few studies examining only spontaneous preterm delivery have shown no significant association with maternal BMI.

Obesity is associated with increased risk for cesarean section, and this can be explained by the coincidence of pregnancy complications including PE, GDM and macrosomia as well as possible narrowing of the maternal birth canal by the presence of increased pelvic soft tissue [4, 61–63]. As demonstrated in our study, the rates of both elective and emergency cesarean section increase with maternal BMI by about 6% with each increase of 1 over the mean of 24. Additionally, they are both related to maternal age, race, history of diabetes mellitus and method of delivery in previous pregnancies.

In this study we found that the rate of delivery of SGA neonates decreases with maternal BMI. This is the inevitable consequence of the diagnosis of SGA being defined by birth weight for gestational age at delivery and the association between birth weight and maternal weight [13]. Previous studies in which SGA was defined by birth weight for gestation corrected for maternal characteristics reported that obesity increases the risk of SGA by 50% [64]. Such relative smallness is pathological and a large population-based study reported that in obese women, higher perinatal mortality is associated with higher rates of SGA but only when SGA is defined by customized growth potential [65].

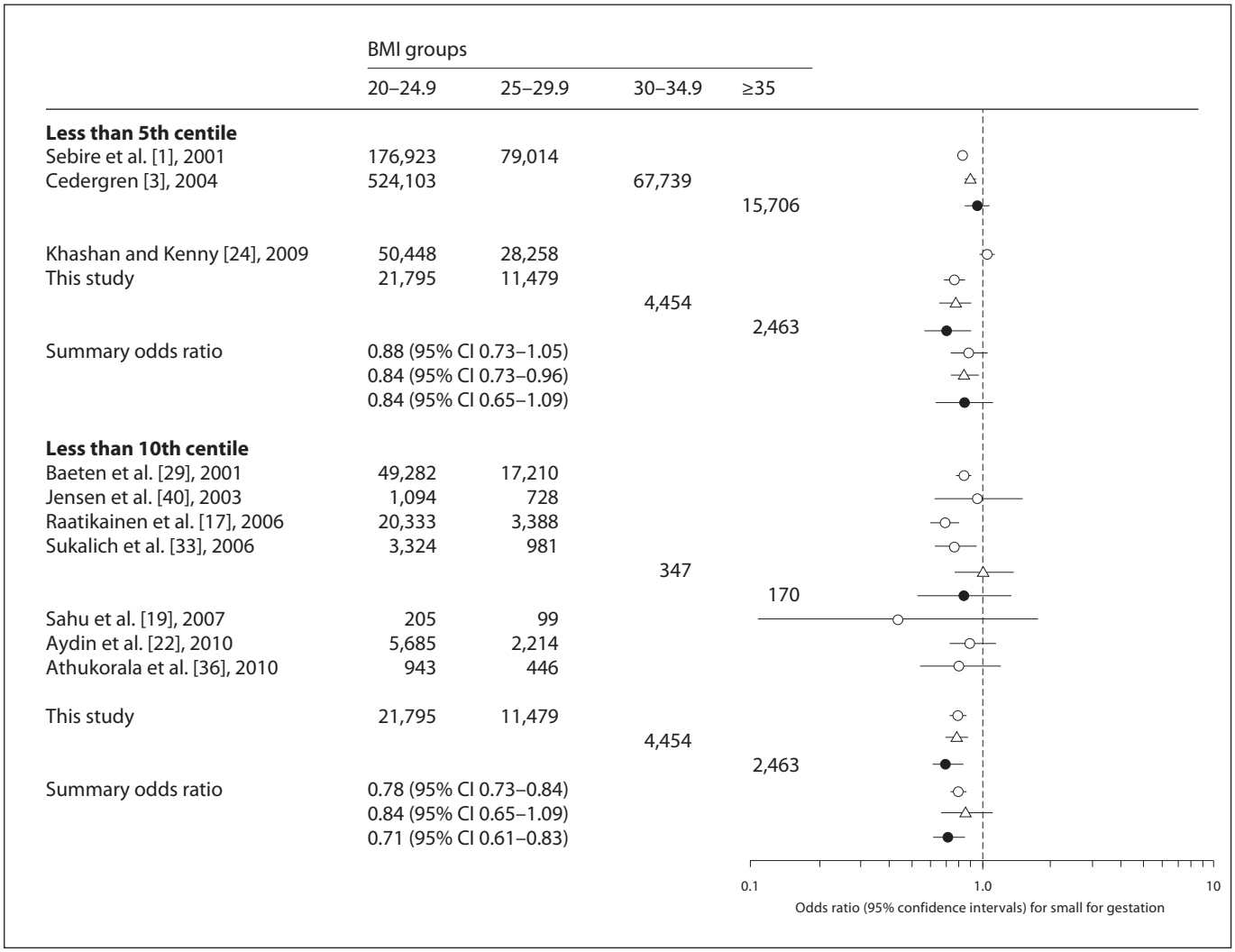
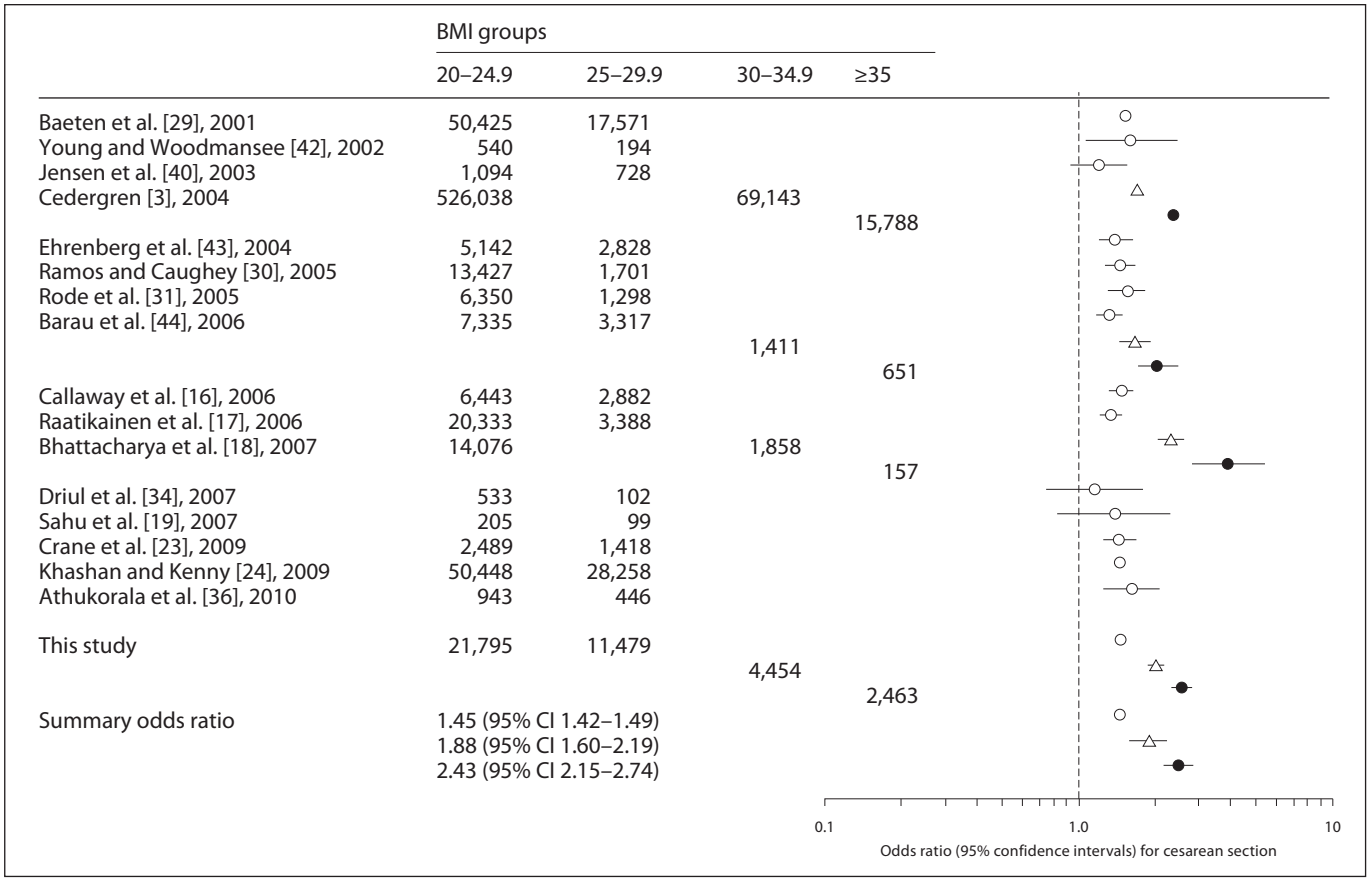


Fig. 9. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of small for gestational age neonates below the 10th and the 5th centile according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

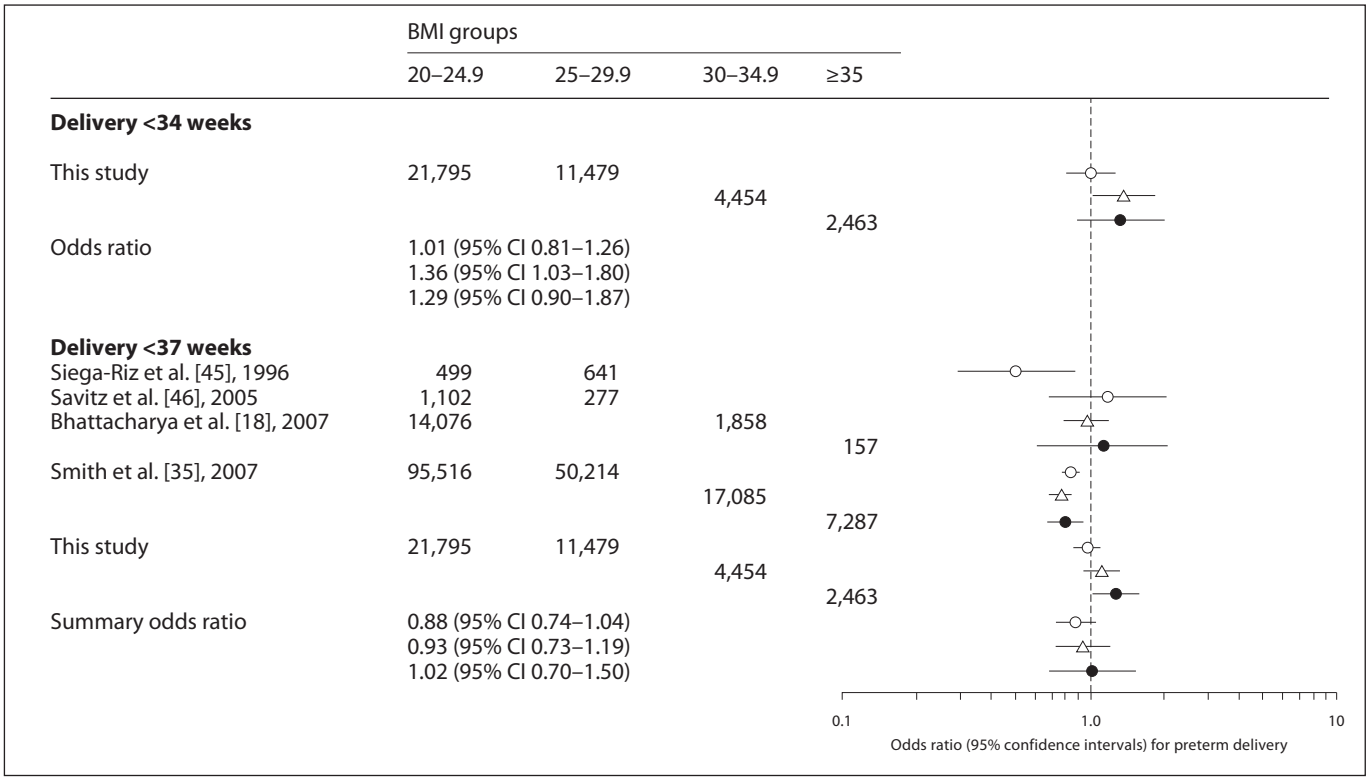
(For figures see page 263.)

Fig. 10. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of cesarean section according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).

Fig. 11. Forrest plot of odds ratios and confidence intervals from previous reports and our study for the risk of spontaneous delivery before 37 weeks and in our study for spontaneous delivery before 34 weeks, according to body mass index (BMI) groups: BMI 25–29.9 (○), BMI 30–34.9 (△), BMI ≥35 (●), compared to the normal BMI group (20–24.9).


BMI groups
20–24.9
25–29.9
30–34.9
≥35
Baeten et al. [29], 2001 50,425 17,571
Young and Woodmansee [42], 2002 540 194
Jensen et al. [40], 2003 1,094 728
Cedergren [3], 2004 526,038 69,143 15,788
Ehrenberg et al. [43], 2004 5,142 2,828
Ramos and Caughey [30], 2005 13,427 1,701
Rode et al. [31], 2005 6,350 1,298
Barau et al. [44], 2006 7,335 3,317 1,411 651
Callaway et al. [16], 2006 6,443 2,882
Raatikainen et al. [17], 2006 20,333 3,388
Bhattacharya et al. [18], 2007 14,076 1,858 157
Driul et al. [34], 2007 533 102
Sahu et al. [19], 2007 205 99
Crane et al. [23], 2009 2,489 1,418
Khashan and Kenny [24], 2009 50,448 28,258
Athukorala et al. [36], 2010 943 446
This study 21,795 11,479 4,454 2,463
Summary odds ratio
1.45 (95% CI 1.42–1.49)
1.88 (95% CI 1.60–2.19)
2.43 (95% CI 2.15–2.74)
0.1
1.0
10
Odds ratio (95% confidence intervals) for cesarean section

10


BMI groups
20–24.9
25–29.9
30–34.9
≥35
Delivery <34 weeks
This study 21,795 11,479 4,454 2,463
Odds ratio
1.01 (95% CI 0.81–1.26)
1.36 (95% CI 1.03–1.80)
1.29 (95% CI 0.90–1.87)
Delivery <37 weeks
Siega-Riz et al. [45], 1996 499 641
Savitz et al. [46], 2005 1,102 277
Bhattacharya et al. [18], 2007 14,076 1,858 157
Smith et al. [35], 2007 95,516 50,214 17,085 7,287
This study 21,795 11,479 4,454 2,463
Summary odds ratio
0.88 (95% CI 0.74–1.04)
0.93 (95% CI 0.73–1.19)
1.02 (95% CI 0.70–1.50)
0.1
1.0
10
Odds ratio (95% confidence intervals) for preterm delivery

11

In conclusion, maternal BMI at 11–13 weeks can be combined with other maternal characteristics and obstetric history to estimate patient-specific risks for many pregnancy complications, including miscarriage and stillbirth, PE, GH, GDM, delivery of LGA neonates and cesarean section.

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