RESEARCH ARTICLE

A prospective population-based multicentre study on the impact of maternal body mass index on adverse pregnancy outcomes: Focus on normal weight

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Abstract

Background

Maternal body mass index (BMI) below or above the reference interval (18.5–24.9 kg/m^2) is associated with adverse pregnancy outcomes. Whether BMI exerts an effect within the reference interval is unclear. Therefore, we assessed the association between adverse pregnancy outcomes and BMI, in particular within the reference interval, in a general unselected pregnant population.

Methods

Data was extracted from a prospective population-based multicentre cohort (Risk Estimation for PrEgnancy Complications to provide Tailored care (RESPECT) study) conducted between December 2012 to January 2014. BMI was studied in categories (I: <18.5, II: 18.5–19.9, III: 20.0–22.9, IV: 23.0–24.9, V: 25.0–27.4, VI: 27.5–29.9, VII: >30.0 kg/m^2) and as a continuous variable within the reference interval. Adverse pregnancy outcomes were defined as composite endpoints for maternal, neonatal or any pregnancy complication, and for adverse pregnancy outcomes individually. Linear trends were assessed using linear-by-linear association analysis and (adjusted) relative risks by regression analysis.

Results

The median BMI of the 3671 included women was 23.2 kg/m^2 (IQR 21.1–26.2). Adverse pregnancy outcomes were reported in 1256 (34.2%). Linear associations were observed between BMI categories and all three composite endpoints, and individually for

pregnancy-induced hypertension (PIH), preeclampsia, gestational diabetes mellitus (GDM), large-for-gestational-age (LGA) neonates; but not for small-for-gestational-age neonates and preterm birth. Within the reference interval, BMI was associated with the composite maternal endpoint, PIH, GDM and LGA, with adjusted relative risks of 1.15 (95%CI 1.06–1.26), 1.12 (95%CI 1.00–1.26), 1.31 (95%CI 1.11–1.55) and 1.09 (95%CI 1.01–1.17).

Conclusions

Graded increase in maternal BMI appears to be an indicator of risk for adverse pregnancy outcomes even among women with a BMI within the reference interval. The extent to which BMI directly contributes to the increased risk in this group should be evaluated in order to determine strategies most valuable for promoting safety and long-term health for mothers and their offspring.

Introduction

Normal weight is defined by the World Health Organization (WHO) as a body mass index (BMI) of 18.5 to 25.0 kg/m^2. Maternal BMI below or above this reference interval is associated with various adverse pregnancy outcomes such as gestational diabetes mellitus, hypertensive disorders and large-for-gestational-age neonates [1, 2]. These complications are not only relevant for short-term outcomes, but also pose risks for future pregnancies and predispose to long-term maternal health issues like diabetes mellitus and cardiovascular disease [3, 4]. Maternal BMI in pregnancy may furthermore have long-lasting effects on offspring health and is associated with altered susceptibility to non-communicable diseases later in life [5–11].

The epidemic of overweight and obesity is rapidly increasing as a global health issue across all age categories, including pregnant women. While in some countries obesity levels in women of reproductive age are as high as 19% (United Kingdom) and 32% (United States), there are still countries where the rising problem of high BMI is relatively slow, such as the Netherlands, where most women currently have a BMI within the reference interval (18.5–24.9 kg/m^2) and the obesity rate is 10% [12–14].

Due to the observed associations between unfavourable BMI and adverse outcomes in the obstetric population, risk stratification and subsequent treatment protocols, as well as scientific research are primarily aimed at those cases where BMI exceeds the WHO thresholds. Studies often do not apply the finer BMI categories as advised by the WHO for public health purposes [15–18], masking possible effects of BMI within the reference interval. In the general non-pregnant population it has been shown that for conditions such as diabetes mellitus, metabolic syndrome and cardiovascular disease, risks are already increased in individuals with a BMI within the reference interval [19–23]. Such a continuous relationship has also been suggested for BMI and several adverse pregnancy outcomes [15, 17]. However, prospective studies addressing the association between BMI and adverse pregnancy outcomes primarily focused on the BMI within the reference interval are lacking. Exploring the full extent of the impact of BMI is crucial in order to develop and implement adequate strategies to address BMI-related morbidity. A moderately elevated risk in the majority of the population could contribute to more adverse events than a small group of high-risk individuals [24]. Small changes in the large low-risk group, although maybe not directly noticeable in the individual, may ultimately

result in large health benefits for the entire population and significant effects on healthcare costs, also known as the prevention paradox [25].

Therefore, in this study we prospectively evaluate the association of BMI and adverse pregnancy outcomes in an unselected cohort of pregnant women in the Netherlands. Our main goal was to determine this association in pregnant women falling within the reference interval for BMI.

Materials and methods

Setting and study population

This study was part of the prospective population-based multicentre study the Risk EStimation for PrEgnancy Complications to provide Tailored care (RESPECT) study [26]. The RESPECT study was primarily designed to validate prognostic models for gestational diabetes mellitus and preeclampsia in a regional cohort [26, 27]. Pregnant women were invited to participate by their obstetric health care provider from December 2012 to January 2014 and were included before 14 weeks of gestation. Women were included without specific exclusion criteria to compose a cohort representative of the general obstetric population; all women who were able to provide informed consent in Dutch could participate. Also, recruitment was performed in all type of obstetric care facilities in the central region of the Netherlands (31 independent midwifery practices, five secondary hospitals, and one tertiary care facility). The number of births in our region comprise approximately 20.000 of the annual 170.000 births nationwide.. Participants received routine obstetric care according to Dutch clinical guidelines. For the present study we included singleton pregnancies ≥24 weeks of gestation without chromosomal anomalies. The study was approved by the medical ethics committee of the University Medical Centre Utrecht (protocol number 12-432/C) and all participants provided written informed consent.

Exposure

Maternal prepregnancy BMI was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Both height and prepregnancy weight were collected by self-administered questionnaires in early pregnancy (S1 and S2 Files). We applied the 7-category World Health Organization classification for BMI (I: <18.5, II: 18.5–19.9, III: 20.0–22.9, IV: 23.0–24.9, V: 25.0–27.4, VI: 27.5–29.9 and VII: ≥30.0 kg/m^2) [28, 29]. The additional categories used in the 7-category classification are recommended by the WHO to facilitate international comparisons especially regarding public health research and allowed us to assess the association between adverse pregnancy outcomes and BMI within the reference interval (group II-IV; BMI 18.5–24.9 kg/m^2) [29, 30]. BMI was furthermore considered as a continuous variable.

Co-variates

Data concerning baseline characteristics were collected through a set of standardized questionnaires issued to both participants and their healthcare professionals. Gestational age based on the crown-rump-length measurement at ultrasound examination was recorded by the health care provider in the first trimester, along with random venous glucose (mmol/l), and systolic and diastolic blood pressure (mm Hg). Demographics reported by the subject included smoking (yes/no), ethnicity (white (Western European, other Western)/ non-white (African, Hindustani, Moroccan, Turkish, Middle-Eastern, Asian, other non-Western, mixed), educational level (low/medium/high by the International Standard Classification of Education [31, 32]), method of conception (spontaneous/assisted), family history for diabetes mellitus,

hypertension and cardiovascular disease (positive in case of one or more affected first-degree family members) (S1 and S2 Files).

Outcomes

Pregnancy outcomes were collected postpartum by the health care provider by filling in Case Report Forms. The composite adverse maternal outcome included pregnancy-induced hypertension, preeclampsia, gestational diabetes mellitus (GDM), thromboembolic event, eclampsia, and maternal death. Pregnancy-induced hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured at two consecutive occasions after 20 weeks of gestation in women who previously had a normal blood pressure and preeclampsia if combined with proteinuria (≥300 mg per 24 hours or a protein-creatinine-ratio over 0.30), according to guidelines effective during the study period [33]. GDM was diagnosed with a 75-g oral glucose tolerance test (OGTT) with either a fasting glucose ≥7.0 mmol/l or 2 hour post load ≥7.8 mmol/l (WHO 1999 criteria). According to Dutch guidelines, selective screening is performed in women with predefined risk factors (previous GDM, previous child with birthweight >95th percentile, maternal BMI ≥30.0 kg/m^2, polycystic ovary syndrome or a first degree family member with diabetes) between 24–28 weeks of gestation. Excessive fetal growth, clinical signs or polyhydramnios were reasons to perform an OGTT in both women with or without risk factors.

The composite adverse neonatal outcome included preterm birth, small-for-gestational-age (SGA) or large-for-gestational-age (LGA) infant, admission to a Neonatal Intensive Care Unit, 5 minute Apgar Score (AS) <7, arterial umbilical artery blood pH <7.0 and perinatal mortality (≥24 weeks of gestation until 7 days postpartum). Preterm birth was defined as a gestational age under 37 weeks. This was further subdivided into spontaneous and iatrogenic preterm birth (induction of labour due to maternal or fetal condition). LGA and SGA were defined as a birthweight above the 90th and below the 10th percentile respectively, using the Dutch birthweight reference graphs, adjusted for gestational age, parity and neonatal gender [34].

All women in which at least one of the above stated components of adverse maternal or neonatal outcomes occurred were labelled as positive for the composite adverse pregnancy outcome.

Statistical analysis

Inclusion criteria were applied to the multiple imputed data set with ten imputations, also used in the primary analyses of the RESPECT cohort [26]. Multiple imputation was performed with an imputation model using all exposures, covariates and outcomes to minimize potential bias, because for some participants information was missing and these data were not missing completely at random (S1 Table) [26]. Imputed values were included when calculating descriptive statistics. Analyses were performed on each of the imputed data sets and results were pooled by applying Rubin's rules without any transformation of the estimates.

The rates of adverse pregnancy outcomes per category of the 7-category BMI classification were presented as the number of cases per BMI category divided by the total number of subjects within that BMI category, expressed as a percentage. A linear-by-linear association analysis was conducted to assess whether there was a linear trend between the rates of adverse pregnancy outcomes across the seven ordinal BMI categories.

The association between adverse pregnancy outcomes and BMI were expressed in (adjusted) relative risks with 95% confidence intervals calculated by Cox regression with robust variance with time set as a constant [35, 36]. BMI category III (20.0–22.9 kg/m^2) of the 7-category classification served as the reference category to calculate relative risks per category.

To determine the association between BMI and pregnancy outcomes specifically on BMI within the reference interval, (adjusted) relative risks were calculated with BMI as a continuous variable in a sub-analysis only including subjects with a BMI 18.5–24.9 kg/m^2. Adverse pregnancy outcomes with less than 75 cases were not assessed individually, but incorporated in the composite outcomes.

We selected confounders using the Directed Acyclic Graphs (DAGs) method in a consensus meeting (FH, LW, BBR and MNB). We identified smoking, educational level and maternal age as confounders and relative risks were adjusted for these variables. An overview of the considered confounders, mediators and competing exposures are presented in S1 Fig.

Analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL).

Results

The multiple imputed dataset of the RESPECT cohort comprised of 3738 pregnancies of which 3671 were included for analysis in the present study after exclusion of fetal demise <24 weeks of gestation (n = 27), multiple pregnancies (n = 32) and/or chromosomal anomaly in the neonate (n = 15) (Fig 1).

Characteristics of the study population are presented in Table 1. Overall median prepregnancy BMI was 23.2 (IQR 21.1–26.2) kg/m^2. The number of subjects in BMI category I to VII were 100 (2.7%), 377 (10.3%), 1242 (33.8%), 738 (20.1%), 553 (15.1%), 297 (8.1%), 364 (9.9%), respectively. The median BMI of the obese subjects in category VII was 32.7 kg/m^2 (IQR 31.2–35.4).

Pregnancy outcomes for the cohort are presented in Table 2. Median gestational age at delivery was 40 weeks and 0 days (IQR 39 weeks and 1 days—40 weeks and 5 days) with a
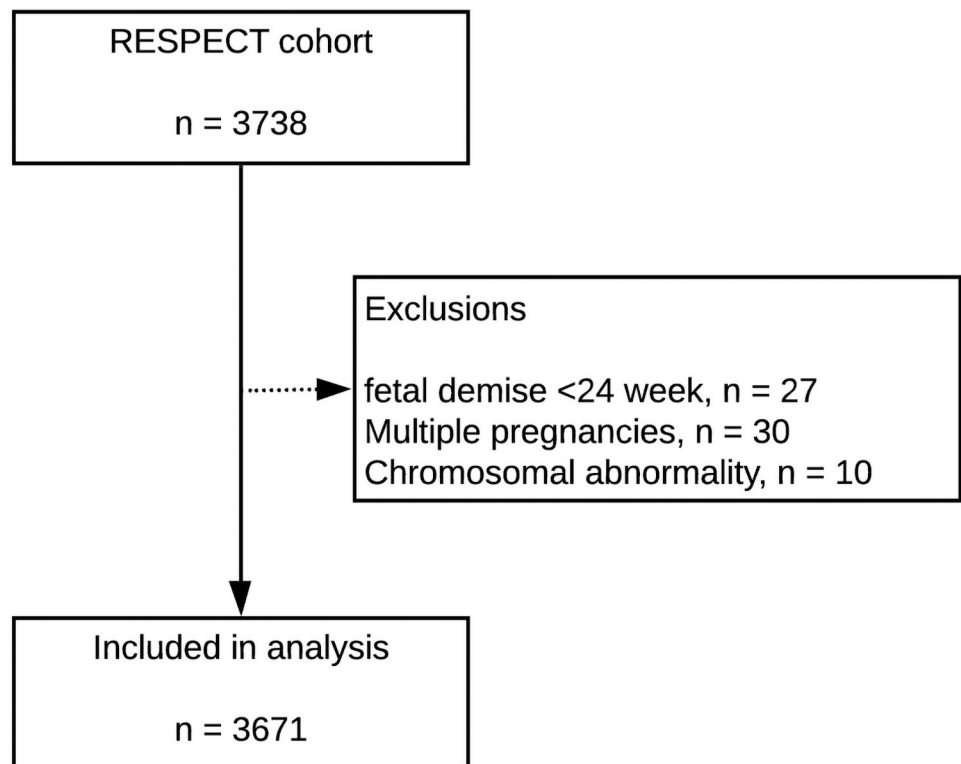

Fig 1. Flowchart of the study population.

Table 1. Characteristics of the study population (n = 3671).

Maternal age (years) [a]		30.8 (4.2) [b]
Prepregnancy body mass index (kg/m^2)		23.2 (21.1–26.2) [b]
Prepregnancy body mass index category–	I. <18.5	100 (2.7)
	II. 18.5–19.9	377 (10.3)
	III. 20.0–22.9	1242 (33.8)
	IV. 23.0–24.9	738 (20.1)
	V. 25.0–27.4	553 (15.1)
	VI. 27.5–29.9	297 (8.1)
	VII. ≥ 30.0	364 (9.9)
Blood pressure (mmHg) [a] –	systolic	115 (12)
	diastolic	67 (8)
Glucose (mmol/L) [a]		4.7 (4.4–5.1) [b]
Ethnicity (white)		3339 (91.0)
Educational level–	low	270 (7.4)
	medium	1256 (34.2)
	high	2145 (58.4)
Parity (nulliparous)		1637 (44.6)
Spontaneous conception		3417 (93.1)
Smoking during pregnancy		284 (7.7)
Comorbidity [c]		126 (3.4)
Chronic hypertension		60 (1.6)
Pre-existent diabetes mellitus		13 (0.4)
Cardiovascular disease		27 (0.7)
Thromboembolic event		14 (0.4)
Other [d]		16 (0.4)
Positive first degree family history of diabetes mellitus		241 (6.6)
Positive first degree family history of hypertension		357 (9.7)
Positive first degree family history of cardiovascular disease		265 (7.2)

Data are number (percentage) unless stated otherwise.

[a] measured at the first prenatal visit.

[b] Data are mean (standard deviation) or median (interquartile range).

[c] Numbers may not add up since women could have more than one comorbidity.

[d] Other comorbidities include kidney disease, antiphospholipid syndrome, and system lupus erythematosus.

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mean neonatal birthweight of 3511 ± 578 grams. Pregnancy-induced hypertension was the most frequent adverse maternal outcome (6.6%), followed by GDM (5.0%) and preeclampsia (2.2%). There were no cases of maternal death. Preterm birth occurred in 176 women (4.9%) of which the majority was spontaneous (3.2%). LGA and SGA were present in 13.2% and 7.3% of neonates born in this cohort, respectively. There were 11 cases (0.3%) of perinatal death.

The rates of the composite and individual adverse outcomes showed an increasing proportion of events per incremental BMI category ($p_{for\ trend}$ = <0.05), except for preterm birth and SGA (Fig 2). Furthermore, no linear trend was found when preterm birth was stratified for iatrogenic and spontaneous preterm birth. The observation that the largest absolute number of adverse events occurred in the group with a BMI within the reference interval (category II to IV) was present in all the assessed composite and individual perinatal outcomes.

Table 2. Pregnancy outcomes in the study population (n = 3671).

General pregnancy outcomes	
Gestational age at delivery (weeks and days)	40w0d (39w1d–40w5d) [a]
Birthweight (grams)	3511 (578) [a]
Neonatal sex (male)	1870 (50.9)
Adverse pregnancy outcome (composite) [b,c]	1256 (34.2)
Adverse maternal outcome (composite) [c]	462 (12.6)
Pregnancy-induced hypertension	243 (6.6)
Preeclampsia	79 (2.2)
Gestational diabetes mellitus	183 (5.0)
Thromboembolic event	7 (0.2)
Eclampsia	2 (0.1)
Maternal death	0 (0.0)
Adverse neonatal outcome (composite) [c]	951 (25.9)
Preterm birth [d]	179 (4.9)
Spontaneous preterm birth	117 (3.2)
Iatrogenic preterm birth	62 (1.7)
Small-for-gestational-age [e]	267 (7.3)
Large-for-gestational-age [f]	484 (13.2)
Neonatal intensive care unit admission	64 (1.7)
Apgar Score <7 after 5 minutes	58 (1.6)
Arterial umbilical cord blood pH < 7.0	38 (1.0)
Perinatal death	11 (0.3)

Data are number (percentage) unless stated otherwise.

[a] Data are mean (standard deviation) or median (interquartile range).

[b] Consisting of all listed components of adverse maternal outcomes (composite) and/or adverse neonatal outcomes (composite).

[c] Numbers may not add up since women could have more than one adverse pregnancy outcome.

[d] Gestational age <37 weeks.

[e] Birthweight <10th percentile.

[f] Birthweight >90th percentile.

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Crude and adjusted relative risks (aRR) for the composite, maternal and neonatal outcomes are shown in Table 3. Compared to reference category III, the aRR for the composite adverse maternal outcome and GDM was significantly increased from category IV onwards, i.e. the highest subgroup within the normal BMI range. The aRR of BMI category IV, V, VI, VII were 1.45 (95%CI 1.06–1.98), 1.99 (95%CI 1.47–2.70), 2.54 (95%CI 1.82–3.55), 3.76 (95%CI 2.83–5.00) for the composite adverse maternal outcome and 2.09 (95%CI 1.22–3.60), 2.52 (95%CI 1.49–4.28), 3.88 (95%CI 2.22–6.79), 6.76 (95%CI 4.19, 10.91) for GDM. A similar graded pattern of increasing aRR per incremental BMI category was found for the composite adverse pregnancy outcome, pregnancy-induced hypertension and LGA, however, with significantly elevated risks only in BMI categories above the reference interval. Although not significant, there was a trend towards higher risk in the highest BMI categories for preeclampsia, whereas the highest risk for SGA was observed in the lowest categories. No pronounced association was found for the composite adverse neonatal outcome and preterm birth.

The association between BMI and pregnancy outcomes in the subpopulation of women with a normal BMI (18.5–24.9 kg/m^2) as a continuous variable is shown in Table 4. BMI was significantly positively associated with the risk for the composite adverse maternal outcome,
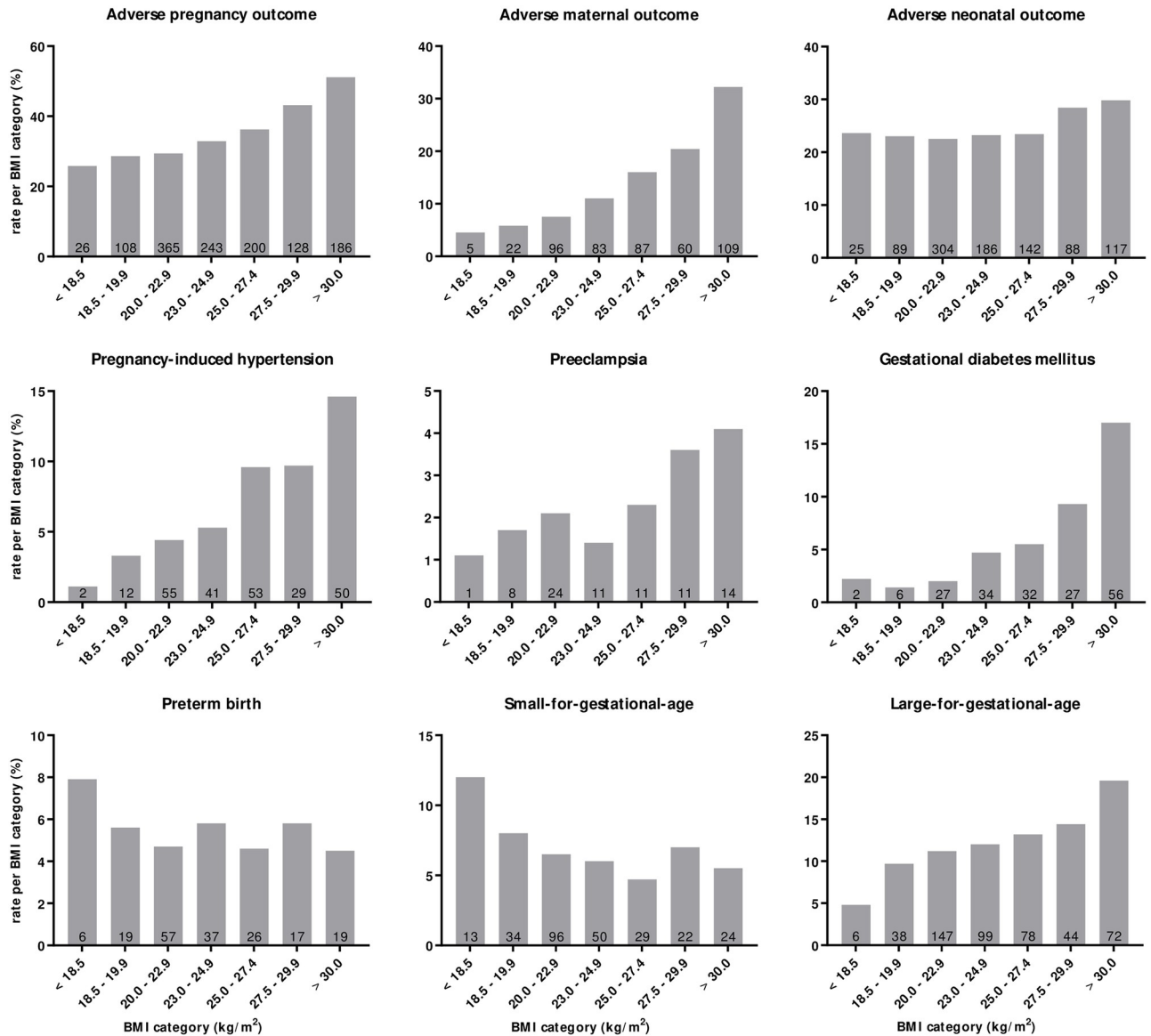
Fig 2. The rate of pregnancy outcomes and number of events per maternal prepregnancy body mass index (BMI) category. The height of the grey bars indicate the rate of pregnancy outcomes per BMI category (the number of events per BMI category divided by the total number of subjects within that BMI category; expressed as a percentage). The number in the grey bars represents the number of events per maternal prepregnancy body mass index (BMI) category. Adverse maternal outcome (composite): pregnancy-induced hypertension, preeclampsia, gestational diabetes mellitus, thromboembolic event, eclampsia, maternal death. Adverse neonatal outcome (composite): preterm birth (gestational age <37 weeks), small-for-gestational-age (<10th birthweight percentile), large-for-gestational-age (>90th birthweight percentile), neonatal intensive care admission, Apgar-score <7 after 5 minutes, pH <7.0 in arterial cord blood, congenital anomalies, perinatal death. Adverse pregnancy outcome (composite): adverse maternal and/or neonatal outcome.

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pregnancy-induced hypertension, GDM and LGA in this group, with adjusted relative risks of respectively 1.15 (95%CI 1.06–1.26), 1.12 (95%CI 1.00–1.26), 1.31 (95%CI 1.11–1.55) and 1.09 (95%CI 1.01–1.17) per BMI-point increment. Trends were observed for the composite adverse pregnancy outcome and SGA with an aRR of respectively 1.04 (95%CI 0.99–1.09)and 0.91 (95%CI 0.83–1.01) per BMI-point increment. For preeclampsia and preterm birth no association with BMI within the reference interval was found.

Table 3. Pregnancy outcomes per maternal prepregnancy BMI category (n = 3671).

COMPOSITE OUTCOMES

BMI category	Adverse pregnancy outcome (n = 1256)				Adverse maternal outcome (n = 462)				Adverse neonatal outcome (n = 951)			
	RR	95%CI	aRR [a]	95%CI	RR	95%CI	aRR [a]	95%CI	RR	95%CI	aRR [a]	95%CI
I. <18.5	0.87	0.55–1.40	1.40	0.53–1.38	0.63	0.23–1.76	0.65	0.23–1.82	1.03	0.64–1.66	0.99	0.62–1.59
II. 18.5–19.9	0.97	0.77–1.22	1.22	0.78–1.23	0.77	0.48–1.24	0.78	0.49–1.25	0.97	0.75–1.25	0.97	0.75–1.26
III. 20.0–22.9		reference		reference		reference		reference		reference		reference
IV. 23.0–24.9	1.12	0.94–1.33	1.33	0.94–1.32	1.47	1.07–2.01	1.45	1.06–1.98	1.03	0.85–1.25	1.02	0.84–1.24
V. 25.0–27.4	1.23	1.03–1.47	1.47	1.02–1.45	2.05	1.52–2.78	1.99	1.47–2.70	1.05	0.85–1.31	1.05	0.84–1.30
VI. 27.5–29.9	1.47	1.19–1.80	1.80	1.17–1.78	2.63	1.88–3.68	2.54	1.82–3.55	1.22	0.95–1.56	1.21	0.94–1.55
VII. ≥30.0	1.74	1.45–2.09	2.09	1.41–2.04	3.89	2.93–5.16	3.76	2.83–5.00	1.31	1.05–1.64	1.28	1.02–1.61

MATERNAL OUTCOMES [b]

BMI category	Pregnancy-induced hypertension (n = 243)				Preeclampsia (n = 79)				Gestational diabetes mellitus (n = 183)			
	RR	95%CI	aRR [a]	95%CI	RR	95%CI	aRR [a]	95%CI	RR	95%CI	aRR [a]	95%CI
I. <18.5	0.35	0.05–2.48	0.37	0.05–2.67	0.53	0.07–3.92	0.50	0.07–3.72	1.02	0.24–4.29	1.08	0.26–4.55
II. 18.5–19.9	0.74	0.40–1.38	0.74	0.39–1.38	1.04	0.44–2.46	1.02	0.43–2.42	0.69	0.26–1.81	0.72	0.27–1.90
III. 20.0–22.9		reference		reference		reference		reference		reference		reference
IV. 23.0–24.9	1.26	0.82–1.93	1.26	0.82–1.94	0.76	0.34–1.68	0.75	0.34–1.67	2.17	1.26–3.73	2.09	1.22–3.60
V. 25.0–27.4	2.14	1.46–3.16	2.13	1.44–3.14	0.99	0.47–2.12	0.96	0.45–2.06	2.70	1.60–4.55	2.52	1.49–4.28
VI. 27.5–29.9	2.22	1.40–3.52	2.20	1.39–3.49	1.90	0.90–4.03	1.82	0.86–3.88	4.17	2.40–7.25	3.88	2.22–6.79
VII. ≥30.0	3.11	2.09–4.61	3.12	2.09–4.67	2.06	1.05–4.04	1.92	0.97–3.80	7.20	4.51–11.51	6.76	4.19–10.91

NEONATAL OUTCOMES [c]

BMI category	Preterm birth (n = 179)				Small-for-gestational-age (n = 267)				Large-for-gestational-age (n = 484)			
	RR	95%CI	aRR [a]	95%CI	RR	95%CI	aRR [a]	95%CI	RR	95%CI	aRR [a]	95%CI
I. <18.5	1.25	0.51–3.07	1.16	0.47–2.86	1.66	0.88–3.16	1.32	0.69–2.54	0.46	0.17–1.23	0.49	0.18–1.32
II. 18.5–19.9	1.08	0.59–1.96	1.08	0.59–1.97	1.16	0.77–1.75	1.18	0.78–1.79	0.84	0.58–1.23	0.84	0.58–1.23
III. 20.0–22.9		reference		reference		reference		reference		reference		reference
IV. 23.0–24.9	1.09	0.70–1.72	1.08	0.68–1.70	0.87	0.59–1.29	0.84	0.57–1.24	1.14	0.86–1.50	1.15	0.87–1.51
V. 25.0–27.4	1.02	0.61–1.70	0.99	0.59–1.66	0.68	0.43–1.07	0.66	0.42–1.04	1.20	0.89–1.60	1.21	0.90–1.63
VI. 27.5–29.9	1.26	0.70–2.25	1.21	0.68–2.16	0.98	0.61–1.58	0.93	0.58–1.50	1.25	0.87–1.80	1.27	0.88–1.84
VII. ≥30.0	1.12	0.64–1.98	1.05	0.60–1.85	0.87	0.53–1.43	0.77	0.46–1.28	1.67	1.24–2.24	1.72	1.28–2.33

[a] aRR was adjusted for age, smoking and educational level.

BMI, prepregnancy body mass index. *RR*, relative risk. *95%CI*, 95% confidence interval. *aRR*, adjusted relative risk.

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Discussion

Principal findings

In this prospective cohort study with a low prevalence of obesity compared with most populations [37, 38], we assessed associations between maternal BMI and several major adverse pregnancy outcomes. Our findings show a graded association between BMI and adverse pregnancy outcomes extending across the BMI range considered 'normal' (18.5–24.9 kg/m^2), mostly driven by maternal complications, and to a lesser extent by neonatal complications. In the sub population of women with a BMI within the reference interval, we observed a significant trend of increased relative risk per single BMI point for the composite adverse maternal outcome, pregnancy-induced hypertension, gestational diabetes mellitus, and for large-for-gestational-age. Although relatively small for the individual, on a population level these effects may be substantial, given the large number of women in the normal BMI group.

Table 4. Associations between maternal prepregnancy BMI as a continuous variable and adverse pregnancy outcomes in a subpopulation of women with a BMI within the reference interval (18.5–24.9 kg/m^2).

Pregnancy outcome	RR	95%CI	aRR	95%CI
Adverse pregnancy outcome (composite)[a]	1.05	1.00–1.10	1.04	0.99–1.09
Adverse maternal outcome (composite)	1.16	1.06–1.26	1.15	1.06–1.26
Pregnancy-induced hypertension	1.11	0.99–1.25	1.12	1.00–1.26
Preeclampsia	0.95	0.79–1.13	0.95	0.80–1.14
Gestational diabetes mellitus	1.35	1.15–1.60	1.31	1.11–1.55
Adverse neonatal outcome (composite)	1.023	0.97–1.07	1.02	0.97–1.07
Preterm birth	0.99	0.89–1.11	0.99	0.88–1.12
Small-for-gestational-age	0.93	0.84–1.02	0.91	0.83–1.01
Large-for-gestational-age	1.08	1.01–1.17	1.09	1.01–1.17

BMI, body mass index; NA, not applicable (no cases). *RR*, relative risk. *95%CI*, 95% confidence interval. *aRR*, adjusted relative risk (adjusted for age, smoking and educational level).

[a] Consisting of all components of adverse maternal outcomes (composite) and/or adverse neonatal outcomes (composite).

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Strengths of the study

The novelty of this study is that the examined population effect on maternal and neonatal morbidity focussed on in-group differences within normal-range BMI. Benefits of our study include a population-based design with an unselected population of pregnant women prospectively recruited in both midwifery practices (low risk) and hospital-based antenatal clinics (medium to high risk). While our study population with a majority of women having a BMI within the reference interval (median prepregnancy BMI 23.2 kg/m^2), reflecting the current situation in Netherlands, was very suitable for the purpose of our study, we believe our findings are likely to be generalizable to many countries or regions worldwide [14, 30, 39]. The application of the recommended finer WHO classification or BMI makes our research internationally comparable [28, 40].

Limitations of the data

Limitations include self-reported prepregnancy weight and height. Although a 2018 meta-analysis has shown that self-reported weight and height among women of reproductive age are representative and can be used in clinical and research settings [41], others have found that self-reporting, as well as categorization, can influence the association between weight and adverse pregnancy outcomes [42, 43]. However, data on first-trimester BMI in our cohort, which was registered by the healthcare professional and therefore not dependent on self-reporting, was strongly correlated with prepregnancy BMI (*r* 0.98; p-value <0.001) and showed a linear relationship through the entire BMI range, including the extremes (S3 File). Also, our analyses on BMI as a continuous variable within the reference interval do not suggest significant misclassification bias. Another limitation is that the study population consists of mostly women of Western European descent with a high educational level. Therefore, our findings need to be interpreted with caution for other populations, and need to be addressed in other more diverse populations. Furthermore, several pregnancy complications that could have been of interest in relation to maternal BMI were not collected in the RESPECT cohort and could therefore not be explored in our study (e.g. post-partum haemorrhage, instrumental vaginal delivery, emergency caesarean section, hyperbilirubinemia, and long-term effects on offspring health).

Interpretation

In clinical practice, continuous measures are often categorized, as clinicians need thresholds to trigger interventions [24]. The same applies to BMI where previous studies mainly used the four WHO categories (underweight, normal weight, overweight, obesity) and, with that, overlooked possible in-group differences. The impact of BMI ≥ 25.0 kg/m^2, i.e. overweight and obesity, on the risk of adverse pregnancy outcomes is unequivocal, as recently summarized in a review of 156 meta-analyses [2]. However, as shown in the 2008 analysis of the HAPO study, many risk factors for adverse pregnancy outcomes, in this case glucose levels, extend well below the clinical thresholds for disease, i.e. gestational diabetes mellitus [44]. In subsequent analyses of the same cohort, similar linear relations were found between maternal BMI and adverse pregnancy outcomes including preeclampsia, neonatal adiposity, fetal hyperinsulinemia and LGA, independent of maternal glycaemia [15]. In a retrospective study analysing data of the Canadian birth registry, data were also suggestive of a (curvi)linear association between BMI between 17 and 50 kg/m^2 and pregnancy complications spanning the full range of BMI, including women classified by the WHO as normal weight [16]. This observation is further supported by data from a Chinese population and a recent individual participant data meta-analysis of 39 cohort studies assessing prepregnancy BMI, and a large British cohort assessing first-trimester BMI [18, 38, 45]. These studies are consistent with our findings of BMI being a strong indicator of risk across the entire population of pregnant women, even in BMI categories not requiring clinical action at an individual level. Our study showed a strong correlation between prepregnancy and first-trimester BMI, and the observed associations of both parameters with adverse outcomes were largely similar (S3 File). This may be explained by the generally limited gestational weight gain in the first trimester.

The mechanisms by which elevated BMI exerts its adverse effects are multifactorial and probably even precede pregnancy itself. Elevated BMI influences metabolic state, including alterations in circulating inflammatory cytokines, hormones and metabolites, which are suggested to negatively affect gamete and embryo quality, early placental function and gene expression [5, 46, 47]. Metabolic changes and altered fetal programming are associated with fetal growth, adiposity and hyperinsulinemia, independent from glycaemic status [15]. Also insulin resistance, dyslipidaemia, chronic inflammation and oxidative stress have all been linked to the development of hypertensive disorders and gestational diabetes mellitus [48, 49]. Additionally, the risk for mechanical complications rises with increasing BMI, resulting in adverse outcomes such as failure to progress, birth injury, increased risk for caesarean section, perioperative difficulties and anaesthesia-related problems [50, 51]. Although it is likely that these mechanisms for BMI-related complications are similar, it is unknown to what extent these mechanisms explain the increased risk in women within the normal BMI range, since the evidence mostly originates from studies in overweight and obese women. Possibly, in addition to BMI, differences in body fat distribution and gestational weight gain may add to the variety observed in women with a normal BMI and their risk for adverse outcomes [52–54].

Population-wide approaches to improve health have been proven beneficial in several lifestyle-dependent conditions in non-pregnant individuals and are increasingly gaining attention. For instance, only modest reduction in mean systolic blood pressure at population level, even in sub populations classified as normotensive, results in lower cardiovascular mortality [55–57]. Also, several countries around the world implemented population-wide initiatives such as taxes on sugar-sweetened drinks and unhealthy energy-dense foods attempting to decrease obesity levels [58–61]. Similar population-wide strategies may also be worth exploring in future studies to reduce BMI-associated perinatal complications. Effects of such interventions might further extent to health improvement in offspring in light of the Developmental

Origins of Health and Disease concept [5], and in the general population by prevention of life-style-dependent conditions. It is important to note that our findings and above proposed health strategies were aimed to respectively explore and counteract the effects of BMI on a population level. Our research should not promote 'fat shaming', nor do we propose strict weight loss regimes for women with a BMI within the reference interval.

In addition, it may also be that the association between normal BMI and negative health outcomes we found in our study is not a direct effect of maternal weight itself, but rather the result of alternative pathways captured by BMI. Previous studies have shown that social determinants of health, such as area of residence, can have profound effects on pregnancy outcomes [62–64]. Such factors, for which BMI may be a potential risk indicator, and their contribution to individual pregnancy health needs further clarification as efforts to reduce their impact would require different approaches than solely weight management.

Conclusion

Findings from our study indicate that the current thresholds for overweight and obesity may not be sufficient to address the full impact of BMI on adverse pregnancy outcomes. Graded increase in BMI appears to be an indicator of risk for pregnancy complications even among women with a BMI within the reference interval. The extent to which BMI directly contributes to the increased risk in this group, that still comprises the majority of women in our population, should be evaluated in order to determine strategies most valuable for promoting safety and long-term health for future generations of mothers and children.

Supporting information

S1 Fig. Directed Acyclic Graph of the relation between body mass index (exposure) and adverse pregnancy outcome (outcome).
(PDF)

S1 Table. Baseline characteristics of patients in the RESPECT cohort, stratified by variables that were available for imputation.
(PDF)

S1 File. RESPECT-study questionnaire—First visit (translated English version).
(PDF)

S2 File. RESPECT-study questionnaire—First visit (original Dutch version).
(PDF)

S3 File. Correlation between prepregnancy and first-trimester body mass index.
(PDF)

S1 Dataset. Minimal anonymized dataset of the RESPECT cohort.
(XLSX)

S1 Checklist.
(DOCX)

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References

1. Lisonkova S, Muraca GM, Potts J, Liauw J, Chan WS, Skoll A, et al. Association Between Prepregnancy Body Mass Index and Severe Maternal Morbidity. JAMA. 2017; 318(18):1777–86. https://doi.org/10.1001/jama.2017.16191 PMID: 29136442

2. Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Mitra A, et al. Obesity and gynaecological and obstetric conditions: umbrella review of the literature. BMJ. 2017; 359:j4511. https://doi.org/10.1136/bmj.j4511 PMID: 29074629

3. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009; 373(9677):1773–9. https://doi.org/10.1016/S0140-6736(09)60731-5 PMID: 19465232

4. Groenhof TKJ, Zoet GA, Franx A, Gansevoort RT, Bots ML, Groen H, et al. Trajectory of Cardiovascular Risk Factors After Hypertensive Disorders of Pregnancy. Hypertension. 2019; 73(1):171–8. https://doi.org/10.1161/HYPERTENSIONAHA.118.11726 PMID: 30571544

5. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, et al. Origins of lifetime health around the time of conception: causes and consequences. Lancet. 2018; 391 (10132):1842–52. https://doi.org/10.1016/S0140-6736(18)30312-X PMID: 29673874

6. Kermack AJ, Van Rijn BB, Houghton FD, Calder PC, Cameron IT, Macklon NS. The 'Developmental Origins' Hypothesis: relevance to the obstetrician and gynecologist. J Dev Orig Health Dis. 2015; 6(5):415–24. https://doi.org/10.1017/S2040174415001324 PMID: 26347389

7. Hochner H, Friedlander Y, Calderon-Margalit R, Meiner V, Sagy Y, Avgil-Tsadok M, et al. Associations of maternal prepregnancy body mass index and gestational weight gain with adult offspring

cardiometabolic risk factors: the Jerusalem Perinatal Family Follow-up Study. Circulation. 2012; 125(11):1381–9. https://doi.org/10.1161/CIRCULATIONAHA.111.070060 PMID: 22344037

8. Gaillard R, Steegers EA, Duijts L, Felix JF, Hofman A, Franco OH, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. Hypertension. 2014; 63(4):683–91. https://doi.org/10.1161/HYPERTENSIONAHA.113.02671 PMID: 24379180

9. Oostvogels AJ, Stronks K, Roseboom TJ, van der Post JA, van Eijsden M, Vrijkotte TG. Maternal pre-pregnancy BMI, offspring's early postnatal growth, and metabolic profile at age 5–6 years: the ABCD Study. J Clin Endocrinol Metab. 2014; 99(10):3845–54. https://doi.org/10.1210/jc.2014-1561 PMID: 24955609

10. Gaillard R, Welten M, Oddy WH, Beilin LJ, Mori TA, Jaddoe VW, et al. Associations of maternal pre-pregnancy body mass index and gestational weight gain with cardio-metabolic risk factors in adolescent offspring: a prospective cohort study. BJOG. 2016; 123(2):207–16. https://doi.org/10.1111/1471-0528.13700 PMID: 26525168

11. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. Circulation. 2009; 119(13):1720–7. https://doi.org/10.1161/CIRCULATIONAHA.108.813436 PMID: 19307476

12. ACOG Practice Bulletin No 156: Obesity in Pregnancy. Obstet Gynecol. 2015; 126(6):e112–26.

13. Denison FC, Aedla NR, Keag O, Hor K, Reynolds RM, Milne A, et al. Care of Women with Obesity in Pregnancy: Green-top Guideline No. 72. BJOG. 2019; 126(3):e62–e106. https://doi.org/10.1111/1471-0528.15386 PMID: 30465332

14. Centraal Bureau voor de Statistiek. Lengte en gewicht van personen, ondergewicht en overgewicht; vanaf 1981 2018 [updated 4-7-2018. https://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=81565ned&D1=0-4&D2=l&D3=6-7&D4=0&D5=0,10,20,30,33-36&HDR=T&STB=G1,G2,G3,G4&VW=T.

15. Hapo Study Cooperative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG. 2010; 117(5):575–84. https://doi.org/10.1111/j.1471-0528.2009.02486.x PMID: 20089115

16. Schummers L, Hutcheon JA, Bodnar LM, Lieberman E, Himes KP. Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. Obstet Gynecol. 2015; 125(1):133–43. https://doi.org/10.1097/AOG.0000000000000591 PMID: 25560115

17. Villamor E, Tedroff K, Peterson M, Johansson S, Neovius M, Petersson G, et al. Association Between Maternal Body Mass Index in Early Pregnancy and Incidence of Cerebral Palsy. JAMA. 2017; 317 (9):925–36. https://doi.org/10.1001/jama.2017.0945 PMID: 28267854

18. Wei YM, Yang HX, Zhu WW, Liu XY, Meng WY, Wang YQ, et al. Risk of adverse pregnancy outcomes stratified for pre-pregnancy body mass index. J Matern Fetal Neonatal Med. 2016; 29(13):2205–9. https://doi.org/10.3109/14767058.2015.1081167 PMID: 26427602

19. Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC. Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. Am J Epidemiol. 2006; 163(11):1042–52. https://doi.org/10.1093/aje/kwj141 PMID: 16611666

20. Rao W, Su Y, Yang G, Ma Y, Liu R, Zhang S, et al. Cross-Sectional Associations between Body Mass Index and Hyperlipidemia among Adults in Northeastern China. Int J Environ Res Public Health. 2016; 13(5). https://doi.org/10.3390/ijerph13050516 PMID: 27213419

21. Hwang LC, Chen CJ, Lin BJ. Obesity and changes in body weight related to 10-year diabetes incidence in women in Taiwan. Asia Pac J Clin Nutr. 2007; 16(4):677–82. PMID: 18042528

22. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. Lancet Diabetes Endocrinol. 2018; 6(12):944–53. https://doi.org/10.1016/S2213-8587(18)30288-2 PMID: 30389323

23. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016; 388(10046):776–86. https://doi.org/10.1016/S0140-6736(16)30175-1 PMID: 27423262

24. Razak F, Davey Smith G, Subramanian SV. The idea of uniform change: is it time to revisit a central tenet of Rose's "Strategy of Preventive Medicine"? Am J Clin Nutr. 2016; 104(6):1497–507. https://doi.org/10.3945/ajcn.115.127357 PMID: 27935518

25. Rose G. Strategy of prevention: lessons from cardiovascular disease. Br Med J (Clin Res Ed). 1981; 282(6279):1847–51. https://doi.org/10.1136/bmj.282.6279.1847 PMID: 6786649

26. Lamain-de Ruiter M, Kwee A, Naaktgeboren CA, de Groot I, Evers IM, Groenendaal F, et al. External validation of prognostic models to predict risk of gestational diabetes mellitus in one Dutch cohort: prospective multicentre cohort study. BMJ. 2016; 354:i4338. https://doi.org/10.1136/bmj.i4338 PMID: 27576867

27. Lamain-de Ruiter M, Kwee A, Naaktgeboren CA, Louhanepessy RD, De Groot I, Evers IM, et al. External validation of prognostic models for preeclampsia in a Dutch multicenter prospective cohort. Hypertens Pregnancy. 2019; 38(2):78–88. https://doi.org/10.1080/10641955.2019.1584210 PMID: 30892981

28. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363(9403):157–63. https://doi.org/10.1016/S0140-6736(03)15268-3 PMID: 14726171

29. World Health Organisation. BMI classification 2004 http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.

30. World Health Organization. Global Health Observatory Data Repository; prevalence of obesity among adults http://apps.who.int/gho/data/node.main.A900A?lang=en.

31. Dutch Ministry of Education Culture and Science. Toedeling Nederlandse onderwijsprogramma's (ISCED) 2012 https://www.trendsinbeeldocw.nl/internationaal/education-at-a-glance-eag/onderwijsbestel-inrichting-en-organisatie-van-scholen/toedeling-nederlandse-onderwijsprogrammas-isced.

32. (Eurostat) Ec. Correspondence between ISCED 2011 and ISCED 1997 levels 2012 https://ec.europa.eu/eurostat/documents/1978984/6037342/Comparability_ISCED_2011_ISCED_1997.pdf.

33. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap 2011 https://www.nvk.nl/Portals/0/richtlijnen/hyperintensieve%20aandoening%20zwangerschap/hyperintensieveaandoeningzwangerschap.pdf.

34. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New Dutch reference curves for birthweight by gestational age. Early Hum Dev. 2009; 85(12):737–44. https://doi.org/10.1016/j.earlhumdev.2009.09.008 PMID: 19914013

35. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003; 3:21. https://doi.org/10.1186/1471-2288-3-21 PMID: 14567763

36. Diaz-Quijano FA. A simple method for estimating relative risk using logistic regression. BMC Med Res Methodol. 2012; 12:14. https://doi.org/10.1186/1471-2288-12-14 PMID: 22335836

37. Scott-Pillai R, Spence D, Cardwell CR, Hunter A, Holmes VA. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004–2011. BJOG. 2013; 120(8):932–9. https://doi.org/10.1111/1471-0528.12193 PMID: 23530609

38. Syngelaki A, Bredaki FE, Vaikousi E, Maiz N, Nicolaides KH. Body mass index at 11–13 weeks' gestation and pregnancy complications. Fetal Diagn Ther. 2011; 30(4):250–65. https://doi.org/10.1159/000328083 PMID: 22067258

39. World Health Organisation. Mean body mass index trends among adults, age-standardized (kg/m2); estimates per country 2016 [updated 27-09-2017. http://apps.who.int/gho/data/node.main.A904?lang=en.

40. Flegal KM, Kit BK, Graubard BI. Body mass index categories in observational studies of weight and risk of death. Am J Epidemiol. 2014; 180(3):288–96. https://doi.org/10.1093/aje/kwu111 PMID: 24893710

41. Seijo M, Minckas N, Cormick G, Comande D, Ciapponi A, BelizAn JM. Comparison of self-reported and directly measured weight and height among women of reproductive age: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2018; 97(4):429–39. https://doi.org/10.1111/aogs.13326 PMID: 29430640

42. Shiely F, Hayes K, Perry IJ, Kelleher CC. Height and weight bias: the influence of time. PLoS One. 2013; 8(1):e54386. https://doi.org/10.1371/journal.pone.0054386 PMID: 23372717

43. Preston SH, Fishman E, Stokes A. Effects of categorization and self-report bias on estimates of the association between obesity and mortality. Ann Epidemiol. 2015; 25(12):907–11 e1–2. https://doi.org/10.1016/j.annepidem.2015.07.012 PMID: 26385831

44. Hapo Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008; 358(19):1991–2002. https://doi.org/10.1056/NEJMoa0707943 PMID: 18463375

45. Santos S, Voerman E, Amiano P, Barros H, Beilin LJ, Bergstrom A, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: An individual participant data meta-analysis of European, North American and Australian cohorts. BJOG. 2019. https://doi.org/10.1111/1471-0528.15661 PMID: 30786138

46. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002; 287(3):356–9. https://doi.org/10.1001/jama.287.3.356 PMID: 11790215

47. Catalano P, deMouzon SH. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. Int J Obes (Lond). 2015; 39(4):642–9.

48. Roberts JM, Bodnar LM, Patrick TE, Powers RW. The Role of Obesity in Preeclampsia. Pregnancy Hypertens. 2011; 1(1):6–16. https://doi.org/10.1016/j.preghy.2010.10.013 PMID: 21532964

49. Fasshauer M, Bluher M, Stumvoll M. Adipokines in gestational diabetes. Lancet Diabetes Endocrinol. 2014; 2(6):488–99. https://doi.org/10.1016/S2213-8587(13)70176-1 PMID: 24731659

50. Biel FM, Marshall NE, Snowden JM. Maternal Body Mass Index and Regional Anaesthesia Use at Term: Prevalence and Complications. Paediatr Perinat Epidemiol. 2017; 31(6):495–505. https://doi.org/10.1111/ppe.12387 PMID: 28833337

51. Pettersen-Dahl A, Murzakanova G, Sandvik L, Laine K. Maternal body mass index as a predictor for delivery method. Acta Obstet Gynecol Scand. 2018; 97(2):212–8. https://doi.org/10.1111/aogs.13265 PMID: 29164597

52. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008; 359(20):2105–20. https://doi.org/10.1056/NEJMoa0801891 PMID: 19005195

53. LifeCycle Project-Maternal Obesity Childhood Outcomes Study Group, Voerman E, Santos S, Inskip H, Amiano P, Barros H, et al. Association of Gestational Weight Gain With Adverse Maternal and Infant Outcomes. JAMA. 2019; 321(17):1702–15. https://doi.org/10.1001/jama.2019.3820 PMID: 31063572

54. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, et al. Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis. JAMA. 2017; 317(21):2207–25. https://doi.org/10.1001/jama.2017.3635 PMID: 28586887

55. Brandt EJ, Myerson R, Perraillon MC, Polonsky TS. Hospital Admissions for Myocardial Infarction and Stroke Before and After the Trans-Fatty Acid Restrictions in New York. JAMA Cardiol. 2017; 2(6):627–34. https://doi.org/10.1001/jamacardio.2017.0491 PMID: 28403435

56. Restrepo BJ, Rieger M. Denmark's Policy on Artificial Trans Fat and Cardiovascular Disease. Am J Prev Med. 2016; 50(1):69–76. https://doi.org/10.1016/j.amepre.2015.06.018 PMID: 26319518

57. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360(9349):1903–13. https://doi.org/10.1016/s0140-6736(02)11911-8 PMID: 12493255

58. Colborne M. Britain's "sugar tax" tackles obesity. CMAJ. 2016; 188(8):E134. https://doi.org/10.1503/cmaj.109-5260 PMID: 27044479

59. Capewell S, Capewell A. An effectiveness hierarchy of preventive interventions: neglected paradigm or self-evident truth? J Public Health (Oxf). 2018; 40(2):350–8. https://doi.org/10.1093/pubmed/fdx055 PMID: 28525612

60. Amies-Cull B, Briggs ADM, Scarborough P. Estimating the potential impact of the UK government's sugar reduction programme on child and adult health: modelling study. BMJ. 2019; 365:l1417. https://doi.org/10.1136/bmj.l1417 PMID: 30996021

61. Barker M, Dombrowski SU, Colbourn T, Fall CHD, Kriznik NM, Lawrence WT, et al. Intervention strategies to improve nutrition and health behaviours before conception. Lancet. 2018; 391(10132):1853–64. https://doi.org/10.1016/S0140-6736(18)30313-1 PMID: 29673875

62. Poeran J, Maas AF, Birnie E, Denktas S, Steegers EA, Bonsel GJ. Social deprivation and adverse perinatal outcomes among Western and non-Western pregnant women in a Dutch urban population. Soc Sci Med. 2013; 83:42–9. https://doi.org/10.1016/j.socscimed.2013.02.008 PMID: 23465203

63. Mahmoodi Z, Karimlou M, Sajjadi H, Dejman M, Vameghi M, Dolatian M. A Communicative Model of Mothers' Lifestyles During Pregnancy with Low Birth Weight Based on Social Determinants of Health: A Path Analysis. Oman Med J. 2017; 32(4):306–14. https://doi.org/10.5001/omj.2017.59 PMID: 28804583

64. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum Reprod Update. 2007; 13(3):209–23. https://doi.org/10.1093/humupd/dml056 PMID: 17208948