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# Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2017;357:j2563 <http://dx.doi.org/10.1136/bmj.j2563>

Accepted: 24 May 2017

## ABSTRACT

### OBJECTIVE

To estimate the risks of major congenital malformations in the offspring of mothers who are underweight (body mass index (BMI) <18.5), overweight (BMI 25 to <30), or in obesity classes I (BMI 30 to <35), II (35 to <40), or III (≥40) compared with offspring of normal weight mothers (BMI 18.5 to <25) in early pregnancy.

### DESIGN

Population based cohort study.

### SETTING

Nationwide Swedish registries.

### PARTICIPANTS

1243957 liveborn singleton infants from 2001 to 2014 in Sweden. Data on maternal and pregnancy characteristics were obtained by individual record linkages.

### EXPOSURE

Maternal BMI at the first prenatal visit.

### MAIN OUTCOME MEASURES

Offspring with any major congenital malformation, and subgroups of organ specific malformations diagnosed during the first year of life. Risk ratios were estimated using generalised linear models adjusted for maternal factors, sex of offspring, and birth year.

### RESULTS

A total of 43 550 (3.5%) offspring had any major congenital malformation, and the most common subgroup was for congenital heart defects (n=20 074; 1.6%). Compared with offspring of normal weight mothers (risk of malformations 3.4%), the proportions and adjusted risk ratios of any major congenital malformation among the offspring of mothers with higher BMI were: overweight, 3.5% and 1.05 (95% confidence interval 1.02 to 1.07); obesity class I, 3.8% and 1.12 (1.08 to 1.15), obesity class II, 4.2% and 1.23 (1.17 to 1.30), and obesity class III, 4.7% and 1.37 (1.26 to 1.49). The risks of congenital heart defects, malformations

of the nervous system, and limb defects also progressively increased with BMI from overweight to obesity class III. The largest organ specific relative risks related to maternal overweight and increasing obesity were observed for malformations of the nervous system. Malformations of the genital and digestive systems were also increased in offspring of obese mothers.

### CONCLUSIONS

Risks of any major congenital malformation and several subgroups of organ specific malformations progressively increased with maternal overweight and increasing severity of obesity. For women who are planning pregnancy, efforts should be encouraged to reduce adiposity in those with a BMI above the normal range.

### Introduction

Obesity has reached epidemic proportions globally and is now a major health concern in pregnancy, in both high and low income countries.<sup>1</sup> In particular the prevalence of severe obesity, commonly defined as obesity classes II and III (body mass index (BMI) ≥35) is rapidly increasing.<sup>2-4</sup> In the US, approximately half of the women are overweight or obese at the first antenatal visit,<sup>5</sup> and the high prevalence of obesity class III (BMI ≥40; 10-12%) in women of reproductive age is of concern.<sup>6</sup> In Sweden, the prevalence of early pregnancy obesity (BMI ≥30) increased from 6.0% to 12.9% from 1992 to 2014.<sup>7</sup> Globally, it was recently reported that the number of women aged 18 years and older with a BMI ≥35 doubled from approximately 50 million to 100 million between 2000 and 2010.<sup>8</sup>

Obesity in pregnancy adversely influences both fetal and neonatal outcomes,<sup>9-15</sup> including increased risks of major congenital malformations, which are a common cause of stillbirth<sup>16</sup> and a major cause of infant mortality and long term morbidity.<sup>14 17</sup> A meta-analysis reported that the offspring of obese mothers are at increased risk of a wide range of congenital malformations, including neural tube defects, cardiovascular anomalies, cleft lip and palate, anorectal atresia, and limb reduction anomalies.<sup>18</sup> However, associations between increasing severity of obesity and risks of malformations were not analysed and it is not clear if risks are also increased in the offspring of overweight mothers. Several of the included studies also used non-standard definitions of normal weight, overweight, and obesity.<sup>19-24</sup> Since the prevalence of severe obesity is increasing among women of reproductive age, it is of

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Maternal obesity increases risks of congenital malformations

It is not known if risks are increased in offspring of overweight mothers and if risks increase with increasing severity of obesity

## WHAT THIS STUDY ADDS

Risks of major congenital malformations in offspring progressively increase with maternal overweight and severity of obesity

interest to investigate whether risks of major congenital malformations increase with severity of obesity in mothers.

In this study we included information on 1243 957 live singleton births in Sweden recorded in the medical birth register between 2001 and 2014. We investigated associations between maternal BMI in early pregnancy and risks of any major congenital malformation as well as risks of the most prevalent subgroups of organ specific malformations.

## Methods

### Setting

The study was performed in Sweden, where prenatal and delivery care is publicly funded, and participation in the standardised prenatal care programme is almost 100%. The Swedish medical birth register includes information on close to 100% of all births in Sweden since 1973. Using standardised prenatal, obstetrical, and neonatal records, information is prospectively collected during pregnancy, delivery, and the neonatal period.<sup>25</sup> Individual information on maternal height and weight has been included since 1992.

### Data sources

By using the unique personal identification number assigned to each Swedish resident,<sup>26</sup> we linked data from the medical birth register to the national patient register,<sup>27</sup> cause of death register, education register, and total population register.<sup>28</sup> The national patient register includes diagnoses and dates on visits for hospital based inpatient and outpatient care. Diagnoses are coded according to the Swedish version of the ICD-10 (international classification of diseases, 10th revision). In Sweden, all pregnant women are offered an ultrasound examination at around 18 weeks of gestation. Abortion after 18 until 22 completed weeks must be approved by the National Board of Health and Welfare. Severe birth defects as indication for late abortion are generally approved. In 2015, the rate of abortions in Sweden was 20.9/1000 women (aged 15-44 years; 93% of abortions were performed before 12 weeks of gestation and 83% before nine weeks of gestation).

### Study population

From 1 January 2001 to 31 December 2014, we retrieved information on 1 480 892 deliveries recorded in the Swedish medical birth register. We excluded 42 638 (2.9%) multiple births (since they differ from single births for malformation outcomes<sup>29</sup>) and 4598 (0.3%) stillbirths (where diagnosis and registration of malformations is poor or missing). Of the remaining 1 433 656 live singleton births, 19 863 (1.4%) were excluded owing to lack of valid personal identification numbers (18 929 for the mother and 934 for the infant), as these births could not be linked to other registries. Because we assumed that adiposity is unlikely to cause malformations for which another cause is known, we also excluded 7514 (0.5%) infants with chromosomal aber-

rations, genetic syndromes, malformation syndromes with known causes, and viral infections having a possible association with malformations (see supplementary eMethods).<sup>30</sup> Finally, seven infants did not have data on sex and were therefore excluded. After these exclusions, 1 406 272 singletons remained, of whom 1 243 957 (88.5%) had complete data on all covariates.

Women missing data on BMI were more likely to have missing data on smoking status and family situation (see supplementary eTable 1). Maternal age, level of education, parity, and proportion of women of Nordic origin were similar in women with missing BMI data compared with normal weight women. However, women missing BMI data were more likely to have high education and to be primiparous compared with obese women.

### Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

### Main exposure

We calculated early maternal pregnancy BMI from measured weight and self reported height at the first prenatal visit, which takes place during the first trimester (first 14 weeks of gestation) for 90% of all women.<sup>12</sup> We calculated the median height of each mother using information from all available pregnancies.<sup>31</sup> Data on maternal height and/or weight were missing in 9.6% of live singleton births (see supplementary eTable 1). Based on BMI, we categorised the women as underweight (BMI <18.5), of normal weight (18.5 to <25), overweight (25 to <30), or in obesity class I (30 to <35), obesity class II (35 to <40), or obesity class III ( $\geq 40$ ).<sup>32</sup>

### Covariates

Data on parity, whether the mother cohabited with a partner or not, and self reported smoking were registered at the first prenatal visit. Information on maternal age was obtained at delivery, highest attained education was retrieved from the education register, and mother's country of birth was retrieved from the total population register.

### Outcomes

The main outcome was presence of any major congenital malformations in liveborn infants (from 22 completed gestational weeks), as recorded in either the medical birth register, the national patient register within one year of birth (including inpatient and hospital based outpatient care), or the cause of death register. Major congenital malformations were coded according to the ICD-10 classification and were defined according to the European Surveillance of Congenital

Anomalies classification (EUROCAT; [www.eurocat-network.eu](http://www.eurocat-network.eu); see supplementary eTables 2 and 3 for ICD-10 codes).

We analysed the most common subgroups of major congenital malformations with a prevalence of  $\geq 0.1\%$  as additional outcomes. These included major congenital malformations of the heart, limbs, genital organs, urinary system, digestive system, orofacial clefts, eye, nervous system, and other malformations. In keeping with the EUROCAT definition, patent ductus arteriosus in preterm infants and persistent pulmonary stenosis were not considered as major congenital malformations. Other minor malformations were also excluded in accordance with the EUROCAT classification.

### Statistical analysis

Using generalised linear models with a robust sandwich estimator, we estimated risk ratios and 95% confidence intervals for the outcomes in offspring of underweight mothers (BMI  $<18.5$ ), overweight mothers (25 to  $<30$ ), and mothers in obesity classes I (30 to  $<35$ ), II (35 to  $<40$ ), and III ( $\geq 40$ ) compared with the offspring of normal weight mothers (18.5 to  $<25$ ). To adjust for the possible dependence in outcome introduced by repeated births in the same mother, we constructed models with mother's identification number as a cluster. The outcome was assumed to follow a Poisson distribution. We made adjustments for maternal age, height, parity, early pregnancy smoking status (0, 1-9, or  $\geq 10$  cigarettes daily), educational level, mother's country of birth, family situation (living or not living with a partner), and sex of offspring.

**Subgroup analyses**—sex specific subgroup analyses were performed for any congenital malformations as well as for subgroups of major congenital malformations.

**Sensitivity analyses**—diabetes is a known teratogen<sup>33-35</sup> and may also be in the causal pathway between obesity and major congenital malformations. In sensitivity analyses, we excluded women with pregestational diabetes to investigate whether the associations between

BMI and major congenital malformations were affected. Although gestational diabetes generally develops after the developmentally critical period for malformations, we also performed an analysis where we excluded both women with pregestational diabetes and women with gestational diabetes.

An additional analysis was performed for the association between BMI and the outcome of any chromosomal aberration, genetic syndrome, malformation syndrome with known causes, and viral infection having a possible association with malformations (infants with these conditions were excluded from the study population of the main analyses;  $n=7514$ , of whom 6495 had complete data on all variables).

Data were analysed using SAS (version 9.4). We considered two sided P values  $<0.05$  to be statistically significant. No adjustment was made for multiple comparisons.

## Results

### Major congenital malformations

During the study period a total of 1243957 liveborn singleton infants were included in the cohort, 43550 (3.5%) of whom had any major congenital malformation. Congenital heart defects were the most common malformation subtype (1.6%) followed by malformations of the genital organs (0.5%), limbs (0.4%), urinary system (0.3%), other (0.2%), eye (0.2%), digestive system (0.2%), orofacial clefts (0.1%), and nervous system (0.1%; fig 1).

### BMI and major congenital malformations

The proportions of offspring with any major congenital malformation were 3.4% for underweight mothers, 3.4% for normal weight mothers, 3.5% for overweight mothers, and 3.8% for mothers in obesity class I, 4.2% in obesity class II, and 4.7% in obesity class III (table 1). In unadjusted analyses, risk ratios of any malformation were increased in offspring of overweight mothers, and increased with severity of obesity. A weak U-shaped relation was found between maternal age and risk of any major congenital malformation. Risks of any major congenital malformations were higher in boys than in girls and in offspring of smokers, primiparous women, mothers of low stature, and mothers who were not cohabiting with their partner (table 1). Supplementary eTable 1 provides maternal characteristics by BMI categories.

The adjusted risk ratios of any major congenital malformation increased with maternal overweight and severity of obesity (fig 2). Compared with offspring of normal weight mothers, the adjusted risk ratios for any major congenital malformation increased with maternal BMI: 1.05 (95% confidence interval 1.02 to 1.07) in overweight mothers, 1.12 (1.08 to 1.15) in mothers in obesity class I, 1.23 (1.17 to 1.30) in mothers in obesity class II, and 1.37 (1.26 to 1.49) in mothers in obesity class III (fig 2).

The overall risk of any major congenital malformation was higher in boys (4.1%) than in girls (2.8%). In

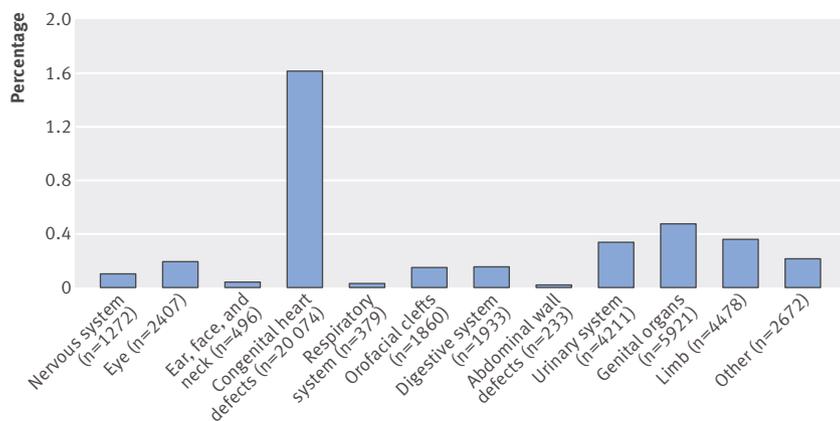


Fig 1 | Prevalence of major congenital malformations in Swedish live singleton births between 2001 and 2014 ( $n=1243957$ )

**Table 1 | Maternal and birth characteristics and major congenital malformations in live singleton births in Sweden**

Characteristics	Total No	No (%)	Unadjusted risk ratio (95% CI)	P value
Total	1 243 957	43 550 (3.5)	-	
Body mass index (kg/m <sup>2</sup> ):				
<18.5	29 864	1020 (3.4)	1.00 (0.94 to 1.07)	<.001
18.5 to <25	756 432	25 713 (3.4)	1.00 (ref)	
25 to <30	311 339	11 050 (3.5)	1.04 (1.02 to 1.07)	
30 to <35	103 085	3903 (3.8)	1.11 (1.08 to 1.15)	
35 to <40	31 883	1335 (4.2)	1.23 (1.17 to 1.30)	
≥40	11 354	529 (4.7)	1.37 (1.26 to 1.49)	
Maternal age (years):				
13-24	178 388	6308 (3.5)	1.02 (0.99 to 1.05)	<.001
25-29	374 411	12 861 (3.4)	1.00 (0.97 to 1.02)	
30-34	433 659	14 964 (3.5)	1.00 (ref)	
≥35	257 499	9417 (3.7)	1.06 (1.03 to 1.09)	
Sex of offspring:				
Girl	604 463	17 107 (2.8)	1.00 (ref)	<.001
Boy	639 494	26 443 (4.1)	1.46 (1.43 to 1.49)	
Maternal height (cm):				
130-154	41 196	1556 (3.8)	1.10 (1.04 to 1.16)	0.006
155-159	126 175	4544 (3.6)	1.05 (1.01 to 1.08)	
160-164	318 994	11 181 (3.5)	1.02 (0.99 to 1.05)	
165-169	362 195	12 457 (3.4)	1.00 (ref)	
170-174	272 951	9523 (3.5)	1.01 (0.99 to 1.04)	
175-200	122 446	4289 (3.5)	1.02 (0.98 to 1.05)	
Smoking status:				
Non-smoker	1 152 475	40 144 (3.5)	1.00 (ref)	<.001
1-9 cigarettes/day	69 323	2531 (3.7)	1.05 (1.01 to 1.09)	
≥10 cigarettes/day	22 159	875 (3.9)	1.13 (1.06 to 1.21)	
Educational level (years):				
<10	108 174	4099 (3.8)	1.00 (ref)	<.001
10-12	478 796	16 854 (3.5)	0.93 (0.90 to 0.96)	
>12	656 987	22 597 (3.4)	0.91 (0.88 to 0.94)	
Parity:				
Primiparous	553 231	20 076 (3.6)	1.07 (1.05 to 1.09)	<.001
Multiparous	690 726	23 474 (3.4)	1.00 (ref)	
Maternal country of birth:				
Nordic*	985 200	34 552 (3.5)	1.00 (ref)	0.47
Non-Nordic	258 757	8998 (3.5)	0.99 (0.97 to 1.01)	
Living with partner:				
Yes	1 172 665	40 812 (3.5)	1.00 (ref)	<.001
No	71 292	2738 (3.8)	1.10 (1.06 to 1.15)	

Supplementary eTable 1 provides data for births to mothers with missing data on body mass index. \*Sweden, Norway, Denmark, Finland, and Iceland.

analyses stratified by sex of offspring, the risk of any malformation in boys of underweight mothers was 4.0%, normal weight mothers was 4.0%, and overweight mothers was 4.3% and in offspring of mothers in obesity classes I, II, and III was 4.5%, 4.9%, and 5.3%, respectively (fig 2). The corresponding risks in girls were 2.8%, 2.8%, 2.8%, 3.0%, 3.4%, and 4.0%. The risk ratios of any malformation increased with maternal severity of obesity in both boys and girls (fig 2).

#### BMI and specific types of major congenital malformations

The adjusted risk ratios of malformations of the nervous system, heart, digestive system, genital organs, limbs, and other malformations all increased with

increasing maternal BMI (P for trend ≤0.03 in all analyses; figs 3 and 4).

The adjusted risk ratios for congenital heart defects by maternal BMI were 1.05 (95% confidence interval 1.01 to 1.08) for overweight mothers, 1.15 (1.09 to 1.20) for mothers in obesity class I, 1.26 (1.16 to 1.37) for mothers in obesity class II, and 1.44 (1.27 to 1.63) for mothers in obesity class III. The largest organ specific increases in risk ratios related to overweight and severity of obesity were observed for malformations of the nervous system. Compared with offspring of normal weight mothers, the adjusted risk ratios for malformations in the nervous system were 1.15 (95% confidence interval 1.00 to 1.31) for overweight mothers, 1.44 (1.20 to 1.73) for mothers in obesity class I, 1.65 (1.23 to 2.21) for mothers in obesity class II, and 1.88 (1.20 to 2.94) for mothers in obesity class III (fig 3).

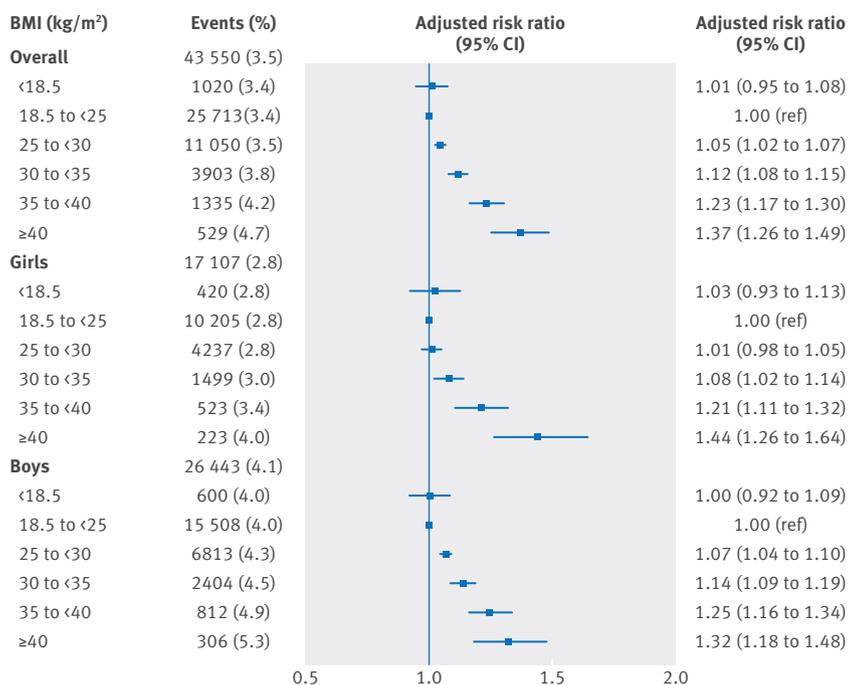
When comparing subgroups of malformations in boys and girls, the largest sex difference (with higher proportions for boys) was noted for genital malformations (boys 0.9% and girls 0.04%) and malformations in the urinary system (boys 0.5% and girls 0.2%; see supplementary eFigure 1). In the sex stratified analyses of malformation subtypes, comparisons were hampered by reduced statistical power in the different BMI categories, especially in girls. The risks of congenital heart defects increased with maternal overweight and severity of obesity for boys, whereas only female offspring of mothers in obesity classes I to III were at increased risks. Maternal BMI was associated with statistically significant increased risks of malformations in the digestive system in boys but not in girls (see supplementary eFigure 2).

Overall, 0.5% of infants who had diagnoses associated with increased risk of malformations were excluded from the main analyses, with a range from 0.5% in the offspring of normal weight mothers to 0.8% in the offspring of mothers in obesity class III. Risks of these malformations also generally increased with maternal overweight and severity of obesity (see supplementary eTable 4).

*Sensitivity analysis: exclusion of women with diabetes*—after exclusion of women with pregestational and gestational diabetes, the associations between BMI and overall major congenital malformations were materially unchanged (see supplementary eTable 5).

#### Discussion

This large population based study found that overall risks of major congenital malformations and risks of several organ specific groups of malformations progressively increase with maternal overweight and severity of obesity. By finding a dose-response relation throughout the spectrum of an above normal body mass index (BMI) and associations between maternal overweight and a range of malformation subgroups, this study substantially expands on previous data, which largely rest on a meta-analysis of pooled studies with varying definitions of obesity and no information on severity of obesity.<sup>18</sup>



**Fig 2 | Major congenital malformations in liveborn singletons by maternal body mass index (BMI) in underweight (BMI <18.5; n=29 864), normal weight (BMI 18.5 to <25; n=756 432), and overweight (BMI 25 to <30; n=311 339) women, and in women in obesity classes I (BMI 30 to <35; n=103 085), II (BMI 35 to <40; n=31 883), and III (BMI ≥40; n=11 354). Adjustment was made for maternal age (13-24, 25-29, 30-34, ≥35 years), height (130-154, 155-159, 160-164, 165-169, 170-174, 175-200 cm), parity (primiparous, multiparous), early pregnancy smoking status (non-smoker, 1-9, ≥10 cigarettes daily), educational level (<10, 10-12, >12 years), maternal country of birth (Nordic (Sweden, Denmark, Finland, Iceland, and Norway), non-Nordic), family situation (living with partner, not living with partner), and sex of offspring**

Congenital heart defects were the most prevalent subtype of organ specific malformation, and risks increased with maternal overweight and increasing obesity in a dose-response pattern. This is consistent with findings from a meta-analysis focused on congenital heart defects, reporting increasing risks with maternal overweight, and with women in obesity class I (BMI 30 to <35) and obesity classes II and III (BMI ≥35).<sup>36</sup>

The largest organ specific risk ratios related to increasing maternal obesity were observed for malformations of the nervous system. Compared with offspring of normal weight mothers, offspring of mothers in obesity class III had an almost doubled risk of major congenital malformations of the nervous system. In line with the present finding, a meta-analysis on maternal BMI and risk of malformations reported a close to two-fold increased risk of neural tube defects in offspring of obese mothers.<sup>18</sup> However, the obesity related risks of malformations in the nervous system must be interpreted with caution as antenatal detection of these malformations might be more difficult in obese women compared with normal weight women.

#### Strengths and limitations of this study

Strengths of the present study include the population based study design, with more than one million

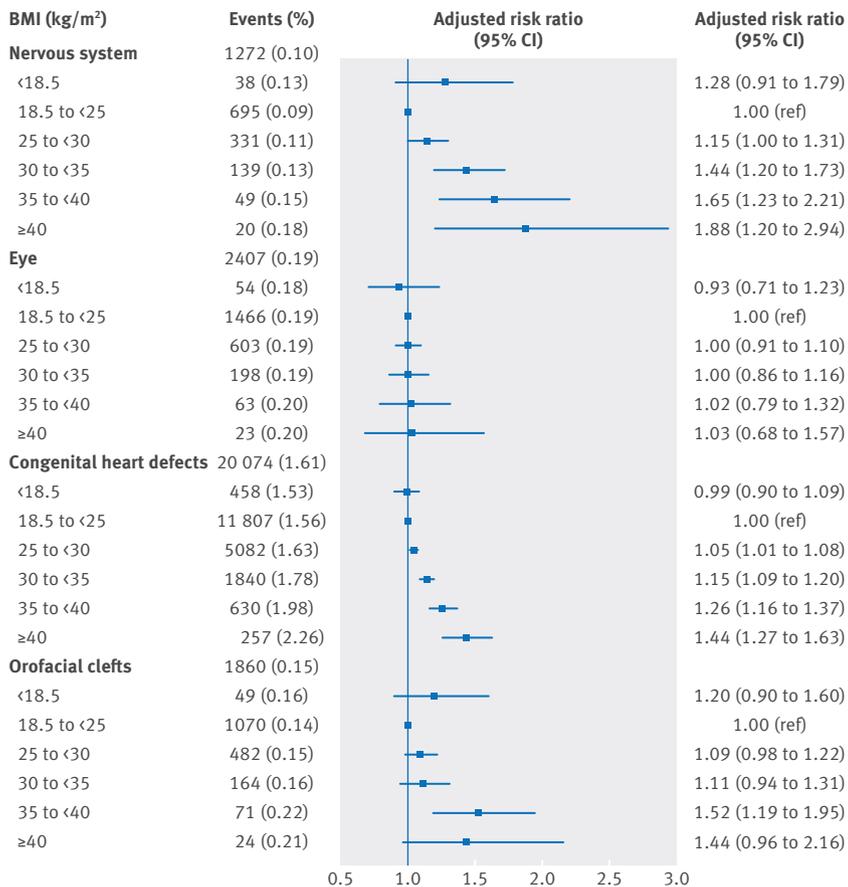
singleton births. The large sample size enabled us to investigate the effects of overweight and severity of obesity on risks of major congenital malformations and several specific malformation subgroups. Data on exposures and outcomes were prospectively collected within the universally accessible Swedish healthcare system. Maternal BMI was calculated based on measured weight, which limits recall bias, but height was self reported. We used standard BMI categories as defined by WHO.<sup>32</sup> Major congenital malformations were classified according to the EUROCAT categorisation. Because we used data from several nationwide registries, we had an opportunity to identify the majority of infants with a diagnosis of a major congenital malformation within the first year of life. Furthermore, we were able to adjust risk estimates for important confounders.

Our study was restricted to live births. Malformations are more common in pregnancies ending in miscarriage or stillbirths, and some prenatally diagnosed malformations may also lead to induced abortions. In particular, most pregnancies complicated by neural tube defects are terminated by induced abortion.<sup>7</sup> The Swedish national registries with patient level data do not include individual data on malformations in pregnancies with miscarriages, stillbirths, and induced abortions. However, aggregated data for Sweden reported on the EUROCAT website for the period 2007-13 show that there were 551 cases of neural tube defects, of which 396 (72%) were classified as termination of pregnancy for fetal anomaly.<sup>37</sup>

Antenatal detection of congenital malformations may be more difficult in obese than in normal weight women.<sup>38</sup> If some malformations in offspring of obese women (notably neural tube defects) were less likely to be diagnosed prenatally and the women underwent an induced abortion, we may have overestimated the risks of malformations in offspring of obese mothers. However, risks may be underestimated if obesity is associated with malformations leading to spontaneous abortion. This hypothesis is supported by findings from studies including information about pregnancy terminations and reporting a doubled risk of neural tube defects and a 50% increased risk of cardiovascular anomalies in pregnancies with obesity.<sup>18</sup> In this study we used BMI as a proxy for adiposity. This is a reasonable assumption given the strong correlation between BMI and fat mass in early pregnancy.<sup>39</sup> We did not have information on the fat distribution, which may be of interest to further explore the association between overweight and severity of obesity and risks of malformations. In addition, we cannot rule out the possibility of residual confounding by unknown or unmeasured factors, such as alcohol use. Power was limited for analyses of less prevalent malformation subgroups by increasing severity of maternal obesity.

#### Potential mechanisms

The pathophysiology of malformations is multifactorial, with interactions between genetic and environmental



**Fig 3 | Major congenital malformations in nervous system, eye, heart, and oral clefts in liveborn singletons by maternal body mass index (BMI) in underweight (BMI <18.5; n=29 864), normal weight (BMI 18.5 to <25; n=756 432), and overweight (BMI 25 to <30; n=311 339) women, and in women in obesity classes I (BMI 30 to <35; n=103 085), II (BMI 35 to <40; n=31 883), and III (BMI ≥40; n=11 354). Adjustment was made for maternal age (13-24, 25-29, 30-34, ≥35 years), height (130-154, 155-159, 160-164, 165-169, 170-174, 175-200 cm), parity (primiparous, multiparous), early pregnancy smoking status (non-smoker, 1-9, ≥10 cigarettes daily), educational level (<10, 10-12, >12 years), maternal country of birth (Nordic (Sweden, Denmark, Finland, Iceland, and Norway), non-Nordic), family situation (living with partner, not living with partner), and sex of offspring**

factors. Other environmental factors associated with increased risks of malformations include maternal smoking, alcohol use, socioeconomic factors, antiepileptic drugs, deficiency of folic acid and other vitamins, and diabetes.<sup>40-43</sup> In the present study, we excluded malformations with a known cause other than maternal overweight or obesity.

Diabetes and abnormal glucose tolerance are common complications of obesity.<sup>44</sup> There is a statistically significant increase in risks of congenital malformations in offspring of women with pregestational diabetes,<sup>45</sup> and risks increase with degree of maternal hyperglycaemia.<sup>46</sup> Experimental studies suggest that hyperglycaemia induces oxidative stress and increased production of free radical species, which may have a teratogenic effect.<sup>47</sup> However, in a recent meta-analysis of maternal BMI and risks of malformations, inclusion of mothers with diabetes had limited impact on the effect size.<sup>18</sup> Furthermore,

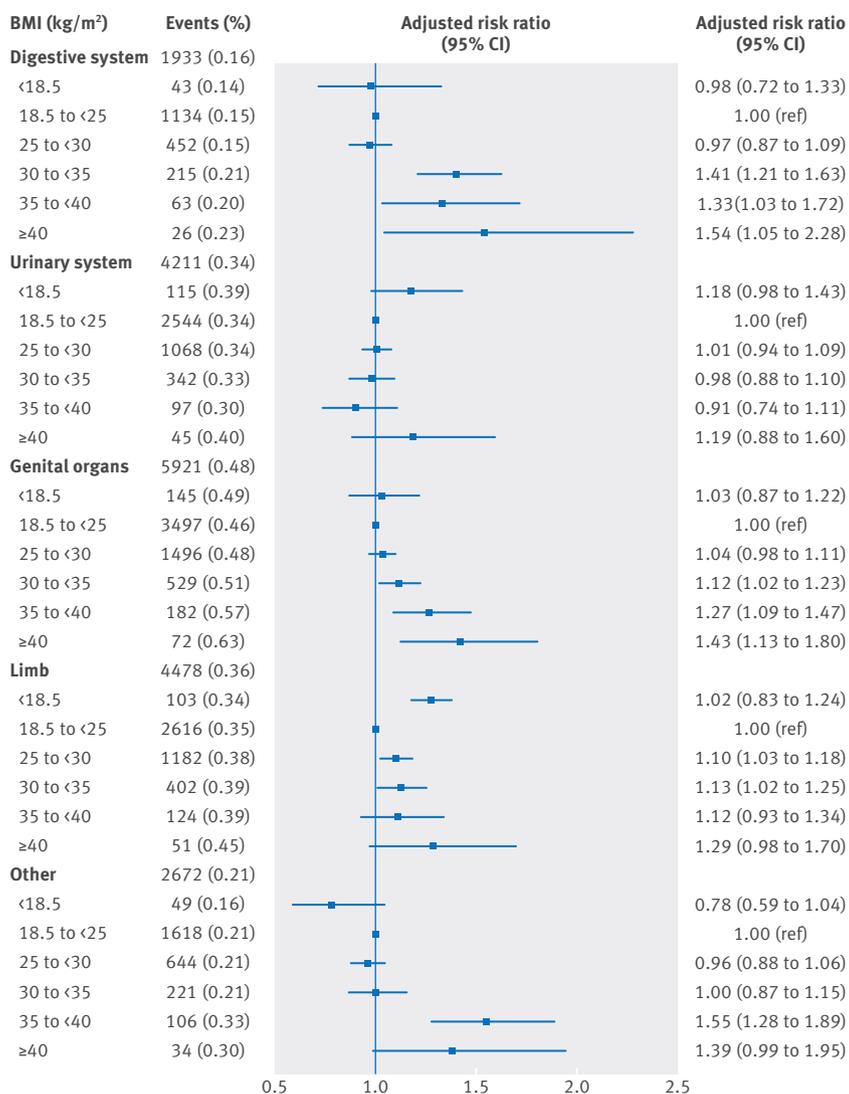
risks of malformations are reported to remain increased in obese women after excluding women with diabetes,<sup>48</sup> and when adjusting for abnormal glucose tolerance in women with glucose values below the threshold of diabetes.<sup>49</sup> This is in line with our findings of essentially unchanged risks of malformations after exclusion of mothers with diabetes. The possible teratogenic role of other metabolic derangements associated with obesity, such as insulin resistance, hyperlipidemia, and inflammation, is unclear. The adipose tissue is an active metabolic and endocrine organ,<sup>50</sup> distributed subcutaneously and in the visceral compartment. Visceral obesity in pregnancy is associated with a state of inflammation, vascular dysfunction, and abnormal placental metabolism,<sup>51</sup> which may adversely influence organogenesis and fetal development.

We found higher risks of several subtypes of malformations in boys than in girls. In particular, risks of genital malformations were markedly higher in boys. One might speculate that this difference may be partly attributed to the clinically more available evaluation of genital structures in boys compared with girls. Data from experimental studies show higher growth rate and substantially higher glucose consumption in males at the embryonal stage, even before sexual differentiation.<sup>52,53</sup> Furthermore, male preimplantation embryos are more vulnerable to heat stress induced production of radical oxygen species than female preimplantation embryos.<sup>54</sup> One might hypothesize that male embryos are more prone than female embryos to respond with enhanced oxygen radical production to different environmental insults, which in turn could contribute to their increased risk of malformations.

Folic acid supplementation has been associated with decreased risks of neural tube defects and congenital heart malformations.<sup>55,56</sup> In the present study we did not have information on folic acid supplementation in early pregnancy. However, folic acid deficiency is common in obesity,<sup>57</sup> and according to a recent national survey from the US, overweight and obese women are less likely to take multivitamins before pregnancy compared with normal weight women.<sup>58</sup> Thus it is possible that the increased risks of neural tube defects and congenital heart defects in offspring of obese mothers may be partly due to folic acid deficiency.

### Conclusion

We found that risks of major congenital malformations in offspring progressively increase with maternal overweight and severity of obesity. This underlines the importance of having a maternal BMI in the normal range before pregnancy. Preventive effects of weight reduction in early pregnancy cannot be expected as organogenesis occurs within the first eight weeks of gestation. Thus, efforts should be made to encourage women of reproductive age to adopt a healthy lifestyle and to obtain a normal body weight before conception.



**Fig 4 | Major congenital malformations in digestive, urinary, and genital systems; limbs; and other malformations anliveborn singletons by maternal body mass index (BMI) in underweight (BMI <18.5; n=29 864), normal weight (BMI 18.5 to <25; n=756 432), and overweight (BMI 25 to <30; n=311 339) women, and in women in obesity classes I (BMI 30 to <35; n=103 085), II (BMI 35 to <40; n=31 883), and III (BMI ≥40; n=11 354). Adjustment was made for maternal age (13-24, 25-29, 30-34, ≥35 years), height (130-154, 155-159, 160-164, 165-169, 170-174, 175-200 cm), parity (primiparous, multiparous), early pregnancy smoking status (non-smoker, 1-9, ≥10 cigarettes daily), educational level (<10, 10-12, >12 years), maternal country of birth (Nordic (Sweden, Denmark, Finland, Iceland, and Norway), non-Nordic), family situation (living with partner, not living with partner), and sex of offspring**

**Contributors:** MN and JS had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. SC, MN, BP, MP, OS, and EV conceived and designed the study. All authors acquired, analysed, and interpreted the data and critically revised the manuscript for important intellectual content. SC, MN, and MP drafted the manuscript. MN and JS carried out the statistical analysis. SC, MN, and OS obtained funding and provided administrative, technical, or material support. MN and JS are the guarantors.

**Funding:** Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number R01DK105948. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funders were not involved in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript. This

study was also funded by the Swedish Research Council for Health, Working Life and Welfare (grant No 2014-0073) and an unrestricted grant from Karolinska Institutet (distinguished professor award to SC). MP was supported by Stockholm County Council (clinical post-doctoral position). OS was supported by the Swedish Research Council (grant No 2013-2429). BP was supported by the Danish Medical Research Council. MN was supported by the Swedish Research Council (grant No 2013-3770) and the National Institutes of Health (award No R01DK105948).

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. MN reports being a member of the scientific advisory board for Itrium (<\$5000 (£3876; €4430)/year).

**Ethical approval:** This study was approved by the regional research ethics committee in Stockholm, Sweden (No 2012/1813-31/4).

**Data sharing:** No additional data available.

**Transparency** The lead author (MP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary web appendix: eTables 1-5 and eFigures 1 and 2