

Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study



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Summary

Background Maternal overweight and obesity are risk factors for stillbirth and infant mortality. Whether temporal changes in maternal weight affect these risks is not clear. We aimed to assess whether change of BMI between first and second pregnancies affects risks of stillbirth and infant mortality in the second-born offspring.

Methods In a Swedish population-based cohort of women who gave birth to their first and second child between Jan 1, 1992, and Dec 31, 2012, we investigated associations between change in maternal body-mass index (BMI) during early pregnancy from first to second pregnancies and risks of stillbirth and neonatal, postneonatal, and infant mortality after the second pregnancy. Relative risks (RRs) for each outcome according to BMI change categories were calculated with binomial regression.

Findings Complete information was available for 456 711 (77.7%) of 587 710 women who had their first and second single births in the study period. Compared with women with a stable BMI (change between -1 kg/m^2 and $<1 \text{ kg/m}^2$) between pregnancies, the adjusted RRs for women who gained at least 4 BMI units between pregnancies were 1.55 (95% CI 1.23–1.96) for stillbirth and 1.29 (1.00–1.67) for infant mortality. Stillbirth risks increased linearly with increased BMI gain. Risks of infant mortality in second pregnancy only increased with BMI gain in women with healthy BMI ($<25 \text{ kg/m}^2$) during first pregnancy; the adjusted RR for healthy weight women who gained 2 to less than 4 BMI units was 1.27 (1.01–1.59) and for those who gained 4 BMI units or more the adjusted RR was 1.60 (1.16–2.22). In overweight women (BMI $\geq 25 \text{ kg/m}^2$), weight loss before pregnancy reduced risk of neonatal mortality.

Interpretation Our findings emphasise the need to prevent weight gain before pregnancy in healthy and overweight women and that weight loss should be promoted in overweight women.

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Introduction

The prevalence of overweight and obesity in childbearing women has reached epidemic proportions, and nowadays more than 50% of women in the USA and more than 30% of women in Sweden are either overweight (body-mass index [BMI] 25 kg/m^2 to $<30 \text{ kg/m}^2$) or obese (BMI $\geq 30 \text{ kg/m}^2$) during early pregnancy.^{1,2} Also, in most low-income and middle-income countries, being overweight is more common than being underweight in young women.³

Maternal overweight and obesity are associated with increased risks of pregnancy complications,⁴ preterm birth,^{1,5} and stillbirth.⁶ Women who gain weight between successive pregnancies increase their risks of pre-eclampsia, gestational diabetes, and preterm birth in the second pregnancy in a dose–response manner.^{7,8} These associations are more pronounced in women who start off with a healthy weight than in women who are overweight or obese in their first pregnancy.⁸ Interpregnancy weight gain also increases the risk of stillbirth.^{8,9}

Results from studies^{6,10,11} of maternal overweight and obesity and risk of infant mortality are less consistent. We reported¹² that the risk of infant mortality increases with maternal overweight and obesity in a linear manner, and that increases in risk are more evident in the

neonatal period than in the postneonatal period. We are unaware of any study investigating whether weight change before pregnancy affects infant mortality risk.

In this Swedish population-based cohort study, we included more than 450 000 women with information on early pregnancy BMI in their first and second pregnancies to investigate whether change of BMI between first and second pregnancies affects risks of stillbirth and infant mortality in the second-born offspring. On the basis of our previous findings that the effect of weight change might differ between healthy and overweight women,⁸ we decided a priori to stratify analyses by women's BMI during their first pregnancy.

Methods

Study design and participants

We did a population-based cohort study of women whose first and second consecutive single births were recorded in the Swedish Medical Birth Register¹³ from Jan 1, 1992, to Dec 31, 2012. We used person-unique national registration numbers to link successive births of each mother and to retrieve information about the women's education and country of birth by individual record linkages between the Swedish Medical Birth Register and the Swedish Education and Total Population Registers.^{14,15} Similarly, we used the infant's

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Research in context

Evidence before the study

We searched PubMed for articles assessing risks of stillbirth and infant mortality in relation to maternal BMI or interpregnancy weight change up to Dec 31, 2014, using the search terms "maternal BMI", "stillbirth", "fetal death", "infant mortality", "interpregnancy weight change", and "risk". Observational studies show that prepregnant or early pregnancy maternal BMI is associated with increased risks of stillbirth and infant mortality. In a meta-analysis of studies published until Jan 23, 2014, the summary relative risk per 5-units difference in maternal BMI was 1.24 (95% CI 1.18–1.30) for stillbirth and 1.18 (1.09–1.28) for infant death. In a large population-based study published after the meta-analysis, early pregnancy maternal BMI of at least 35 was related to a more than doubled risk of infant mortality. Studies examining BMI change before pregnancy offer an opportunity to assess whether change in this exposure affect risk. Two studies have followed this approach in relation to stillbirth, but none with regard to infant mortality. In addition to our previous study, reporting that high interpregnancy weight gain increases stillbirth risk, we found one study

reporting that stillbirth risk increases in women with healthy weight who become overweight and in overweight women who become obese before pregnancy. No study has reported a dose-response association between weight gain and stillbirth risk.

Added value of the study

Our study lends support to the hypothesis that interpregnancy weight gain affects risks of stillbirth and infant mortality. We found a dose-response association between weight gain and stillbirth risk, whereas a similar association between weight gain and infant mortality risk was restricted to offspring of women who were of healthy weight at baseline. In overweight women, weight loss between pregnancies reduced the risk of neonatal mortality. These results were essentially unchanged when multiple imputation techniques were used.

Implications of all available evidence

The present findings provide strong support to advocate that weight gain before pregnancy should be prevented in healthy weight and overweight women and that weight loss should be promoted in overweight women.

person-unique national registration number to retrieve information about age at death of offspring from the National Cause of Death Register.¹⁶

The study was approved by the Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden (number: 2013/2192-32).

Procedures

The Swedish Medical Birth Register prospectively collects data on more than 98% of births in Sweden. Standardised forms for antenatal, obstetric, and neonatal care are used in all antenatal care and delivery units in Sweden, and recorded information is forwarded to the registry after delivery. Information on maternal weight and height has been recorded since 1992.

BMI was defined as weight in kg divided by height in square metres (kg/m^2). Maternal BMI in early pregnancy was calculated from self-reported height and weight measured in light indoor clothes and without shoes at the first antenatal visit, which occurs within the first trimester (the first 14 weeks of gestation) for 90% of pregnant women.¹ BMI was used to categorise women as underweight ($<18.5 \text{ kg}/\text{m}^2$), healthy (18.5 to $<25 \text{ kg}/\text{m}^2$), overweight (25 to $<30 \text{ kg}/\text{m}^2$), or obese ($\geq 30 \text{ kg}/\text{m}^2$).¹⁷ We calculated the interpregnancy change as the difference between BMI in the first and second pregnancies. We categorised the interpregnancy differences as BMI loss of more than 2 units (<-2), BMI loss of 2 to less than 1 unit (-2 to <-1), loss of 1 BMI unit to gain of less than 1 BMI unit (-1 to <1), gain of 1 to less than 2 BMI units (1 to <2), gain of 2 to less than 4 BMI units (2 to <4), and gain of 4 BMI units or more (≥ 4). 1 BMI unit corresponds

to 2.8 kg in women with a height of 167 cm (average height of young women in Sweden).

We also had information about daily smoking during each pregnancy, self-reported at the first antenatal visit and in the third trimester. For each pregnancy, we defined smokers as women who stated that they were daily smokers in early or late pregnancy. Women were categorised across the two pregnancies as non-smokers and non-smokers, smokers and non-smokers, non-smokers and smokers, and smokers and smokers. We calculated interpregnancy interval as the difference between the estimated conception date of the second infant (defined as birth date minus gestational age of the second infant) and the birth date of the first infant. Interpregnancy interval was categorised as less than 12 months, 12 months to less than 24 months, 24 months to less than 36 months, or 36 months or longer. Additionally, we collected information on height (≤ 159 cm, 160–164 cm, 165–169 cm, or ≥ 170 cm), age at second delivery (≤ 24 years, 25–29 years, 30–34 years, or ≥ 35 years), years of completed formal education (9 years, 10–11 years, 12 years, 13–14 years, or ≥ 15 years), women's country of birth (Nordic [eg, Sweden, Denmark, Finland, Iceland, and Norway] vs non-Nordic countries), and year of second delivery (1992–99, 2000–04, 2005–08, or 2009–12).

Outcomes

The Birth Register includes livebirths from 22 completed gestational weeks onward and stillbirths from 28 weeks onward. Stillbirth was therefore defined as a fetal death at 28 completed weeks or later. Infant mortality was defined as death during the first year of life in livebirths

with a gestational age of at least 22 completed weeks. Neonatal mortality was defined as infant deaths within the first 28 days of life and postneonatal mortality was defined as infant deaths after the first 28 days of life. Gestational length was calculated from the expected date of delivery. In Sweden, all pregnant women are offered an ultrasound scan at 17 gestational weeks or earlier, and more than 95% of women accept this offer.¹⁸

Statistical analysis

For each outcome, we compared risk in second pregnancy by categories of the main exposure, BMI change from first to second pregnancies, and covariates. Women who had experienced the outcome in the first pregnancy were excluded from the analyses of each respective outcome in

the second pregnancy. We estimated adjusted relative risks (RRs) with 95% CIs using binomial regression with the log link, a Poisson distribution, and robust estimates of variance. In these regression models, the outcomes are proportions and the link function is a smooth monotone transformation that relates each proportion's covariate values to its probability through a linear predictor.¹⁹ The BMI change category of loss of 1 BMI unit to a gain of less than 1 unit was used as reference. Adjustment covariates included independent predictors of the outcomes or variables related to the exposure that were not on the causal path between interpregnancy weight gain and stillbirth or infant mortality. Because we studied the effect of change in BMI, we controlled for BMI at baseline (ie, BMI in early first pregnancy). Other

	Number of births (%)	Stillbirths*		Infant mortality†		Neonatal mortality†		Postneonatal mortality‡	
		Absolute number	Rate per 1000 births	Absolute number	Rate per 1000 births	Absolute number	Rate per 1000 births	Absolute number	Rate per 1000 births
Total	456711 (100.0%)	1082	2.4	943	2.1	544	1.2	399	0.9
BMI change (kg/m ²)									
<-2	20886 (4.6%)	48	2.3	50	2.4	25	1.2	25	1.2
-2 to <-1	38760 (8.5%)	88	2.3	92	2.4	51	1.3	41	1.1
-1 to <1	209427 (45.9%)	413	2.0	387	1.9	218	1.0	169	0.8
1 to <2	91838 (20.1%)	218	2.4	175	1.9	107	1.2	68	0.7
2 to <4	69856 (15.3%)	215	3.1	161	2.3	99	1.4	62	0.9
≥4	25944 (5.7%)	100	3.9	78	3.0	44	1.7	34	1.3
BMI first pregnancy									
<18.5	14151 (3.1%)	25	1.8	27	1.9	12	0.9	15	1.1
18.5 to <25	315960 (69.2%)	670	2.1	607	1.9	338	1.1	269	0.9
25 to <30	94164 (20.6%)	275	2.9	207	2.2	131	1.4	76	0.8
≥30	32436 (7.1%)	112	3.5	102	3.2	63	2.0	39	1.2
Maternal height (cm)									
≤159	55337 (12.1%)	150	2.7	147	2.7	79	1.4	68	1.2
160-164	116821 (25.6%)	296	2.5	244	2.1	145	1.2	99	0.9
165-169	136228 (29.8%)	317	2.3	247	1.8	136	1.0	111	0.8
≥170	148325 (32.5%)	319	2.2	305	2.1	184	1.2	121	0.8
Maternal age (years)									
≤24	50782 (11.1%)	116	2.3	193	3.8	90	1.8	103	2.0
25-29	150802 (33.0%)	346	2.3	287	1.9	152	1.0	135	0.9
30-34	176869 (38.7%)	406	2.3	316	1.8	202	1.1	114	0.6
≥35	78258 (17.1%)	214	2.8	147	1.9	100	1.3	47	0.6
Smoking in first and second pregnancy									
No and no	401266 (87.9%)	902	2.3	767	1.9	459	1.1	308	0.8
Yes and no	18791 (4.1%)	58	3.1	43	2.3	26	1.4	17	0.9
No and yes	7475 (1.6%)	19	2.6	30	4.0	10	1.3	20	2.7
Yes and yes	29179 (6.4%)	103	3.6	103	3.6	49	1.7	54	1.9
Education (years)									
≤9	32830 (7.2%)	111	3.4	120	3.7	63	1.9	57	1.8
10-11	73267 (16.0%)	220	3.0	191	2.6	110	1.5	81	1.1
12	123366 (27.0%)	285	2.3	237	1.9	136	1.1	101	0.8
13-14	68003 (14.9%)	141	2.1	135	2.0	81	1.2	54	0.8
≥15	159245 (34.9%)	325	2.0	260	1.6	154	1.0	106	0.7

(Table 1 continues on next page)

	Number of births (%)	Stillbirths*		Infant mortality†		Neonatal mortality†		Postneonatal mortality‡	
		Absolute number	Rate per 1000 births	Absolute number	Rate per 1000 births	Absolute number	Rate per 1000 births	Absolute number	Rate per 1000 births
(Continued from previous page)									
Country of birth									
Nordic	397 735 (87.1%)	918	2.3	786	2.0	458	1.2	328	0.8
Non-Nordic	58 976 (12.9%)	164	2.8	157	2.7	86	1.5	71	1.2
Interpregnancy interval (months)									
<12	80 913 (17.7%)	181	2.3	187	2.3	98	1.2	89	1.1
12 to <24	173 328 (38.0%)	373	2.2	345	2.0	197	1.1	148	0.9
24 to <36	99 495 (21.8%)	220	2.2	193	1.9	114	1.1	79	0.8
≥36	102 975 (22.5%)	308	3.0	218	2.1	135	1.3	83	0.8
Year of second birth									
1992–99	110 878 (24.3%)	282	2.6	323	2.9	186	1.7	137	1.2
2000–04	113 138 (24.8%)	292	2.6	212	1.9	136	1.2	76	0.7
2005–08	107 328 (23.5%)	234	2.2	193	1.8	106	1.0	87	0.8
2009–12	125 367 (27.4%)	274	2.2	215	1.7	116	0.9	99	0.8

BMI=body-mass index. *Numbers and stillbirth rates are based on 454 360 second births of infants with a gestational age of 28 completed weeks or more, not preceded by stillbirth in first pregnancy. †Numbers and rates of infant and neonatal mortality are based on 454 246 live second births at 22 completed weeks of gestation or later, not preceded by infant death after first birth. ‡Numbers and rates of postneonatal mortality are based on 453 702 second births at 22 completed weeks of gestation or later, surviving the neonatal period, and not preceded by a postneonatal death after first birth.

Table 1: Maternal characteristics and rates of stillbirths and infant mortality after second birth for women with first and second consecutive single births in Sweden from 1992 to 2012

	Stillbirth†, RR (95% CI)	Infant mortality‡, RR (95% CI)	Neonatal mortality§, RR (95% CI)	Postneonatal mortality¶, RR (95% CI)
<-2	0.96 (0.70–1.30)	1.05 (0.77–1.43)	0.91 (0.59–1.41)	1.24 (0.80–1.92)
-2 to <-1	1.09 (0.87–1.37)	1.21 (0.97–1.53)	1.20 (0.88–1.63)	1.23 (0.87–1.74)
-1 to <-1	1.00	1.00	1.00	1.00
1 to <2	1.15 (0.97–1.35)	1.00 (0.84–1.20)	1.08 (0.85–1.36)	0.90 (0.68–1.19)
2 to <4	1.38 (1.16–1.63)	1.11 (0.92–1.33)	1.20 (0.94–1.53)	0.98 (0.73–1.32)
≥4	1.55 (1.23–1.96)	1.29 (1.00–1.67)	1.29 (0.92–1.81)	1.30 (0.89–1.92)
p _{trend}	<0.0001	0.40	0.13	0.66

RR=relative risk. BMI=body-mass index. *RRs are adjusted for BMI during first pregnancy, maternal height, age at second childbirth, smoking in successive pregnancies, education, country of birth, interpregnancy interval, and year of second childbirth. Women who had experienced the outcome in the first pregnancy were excluded from the analyses of each respective outcome during the second pregnancy. †Analyses include 1082 stillbirths among 454 360 births with a gestational age of at least 28 completed gestational weeks and complete information on covariates. ‡Analyses include 943 infant deaths among 454 246 live second births with a gestational age of at least 22 completed gestational weeks and complete information on covariates. §Analyses include 544 deaths during the neonatal period among 454 246 live second births with a gestational age of at least 22 completed gestational weeks and complete information on covariates. ¶Analyses include 399 deaths among 453 702 second births who survived the neonatal period and had complete information on covariates.

Table 2: Change in BMI between first and second pregnancies and adjusted* relative risks of stillbirth and infant, neonatal, and postneonatal mortality

included covariates were maternal height, age at second childbirth, smoking in successive pregnancies, education, mother’s country of birth, interpregnancy interval, and year of second childbirth. In the adjusted models, covariates were categorised according to table 1. We tested for linear trend by introducing into the models a variable representing the ordinal categories of BMI change as a continuous predictor. We next did stratified analyses according to the women’s BMI in first pregnancy

(<25 kg/m² vs ≥25 kg/m²). Interactions between first pregnancy BMI and interpregnancy BMI change were tested with likelihood ratio tests. Interactions were judged significant at p<0.05.

Because a large proportion of women were excluded from the primary analysis because of missing data on BMI change or covariates and these exclusions might lead to selection bias, we did additional analyses with multiple imputation of missing values in women with non-missing BMI data during first pregnancy. We estimated missing values for BMI change and covariates, including height, interpregnancy interval, education level, country of origin, and smoking, using a Markov Chain Monte Carlo multiple imputation method before their inclusion in the multivariable models.²⁰ Results from ten multiple imputation cycles were combined with the PROC MIANALYZE routine of SAS Software version 9.3.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, writing the report, or the decision to submit the manuscript for publication. The corresponding author had full access to the data, and, with EV, had final responsibility for data integrity and data analysis, and the decision to submit for publication.

Results

Of 587 710 women having their first and second single births between Jan 1, 1992, and Dec 31, 2012, information about early pregnancy weight and height for the first pregnancy was available for 515 252 women (87.7%), and

	Stillbirth† RR (95% CI)		Infant mortality‡ RR (95% CI)		Neonatal mortality‡ RR (95% CI)		Postneonatal mortality‡§ RR (95% CI)	
	BMI <25 (n=328 674¶)	BMI ≥25 (n=125 686¶)	BMI <25 (n=328 523¶)	BMI ≥25 (n=125 723¶)	BMI <25 (n=328 523¶)	BMI ≥25 (n=125 723¶)	BMI <25 (n=328 173¶)	BMI ≥25 (n=125 529¶)
<-2	0.99 (0.59-1.68)	0.87 (0.59-1.29)	1.57 (1.02-2.42)	0.68 (0.45-1.03)	1.62 (0.89-2.96)	0.49 (0.27-0.88)	1.51 (0.81-2.82)	1.06 (0.57-1.97)
-2 to <-1	1.04 (0.77-1.40)	1.10 (0.76-1.59)	1.25 (0.94-1.67)	1.07 (0.73-1.56)	1.23 (0.83-1.85)	1.01 (0.63-1.62)	1.27 (0.84-1.92)	1.19 (0.63-2.24)
-1 to <1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1 to <2	1.18 (0.97-1.43)	1.04 (0.76-1.42)	1.02 (0.83-1.27)	0.91 (0.65-1.26)	1.29 (0.98-1.69)	0.68 (0.44-1.07)	0.73 (0.52-1.04)	1.37 (0.83-2.28)
2 to <4	1.33 (1.08-1.65)	1.36 (1.02-1.81)	1.27 (1.01-1.59)	0.80 (0.57-1.11)	1.42 (1.05-1.93)	0.83 (0.55-1.23)	1.10 (0.78-1.55)	0.74 (0.41-1.32)
≥4	1.49 (1.08-2.06)	1.51 (1.07-2.13)	1.60 (1.16-2.22)	0.90 (0.60-1.34)	1.58 (0.99-2.52)	0.89 (0.55-1.43)	1.61 (1.02-2.55)	0.92 (0.45-1.86)
p _{trend}	0.003	0.004	0.24	0.96	0.11	0.57	0.98	0.41

For the comparison between BMI <25 and BMI ≥25 groups, p_{interaction}=0.96 in stillbirth, p_{interaction}=0.04 in infant mortality, p_{interaction}=0.04 in neonatal mortality, and p_{interaction}=0.08 in postnatal mortality. RR=relative risk. BMI=body-mass index. *RRs are adjusted for BMI during first pregnancy, maternal height, age at second childbirth, smoking in successive pregnancies, education, country of birth, interpregnancy interval, and year of second childbirth. Women who had experienced the outcome after the first pregnancy were excluded from the analyses of respective outcome after the second pregnancy. †Analyses of stillbirths include births with a gestational age of at least 28 completed gestational weeks. ‡Analyses of infant, neonatal, and postneonatal mortality include livebirths with a gestational age of at least 22 gestational weeks. §Analyses of postneonatal mortality include offspring who survived the neonatal period. ¶Denotes the number of observations included in each analysis. The number of stillbirths, infant deaths, neonatal deaths, and postneonatal deaths for women with BMI of less than 25 kg/m² or more than 25 kg/m² in first pregnancy were, respectively, 695 and 387, 634 and 309, 350 and 194, and 284 and 115.

Table 3: Change in BMI between first and second pregnancies and adjusted* relative risks of stillbirth, infant, neonatal, and postneonatal mortality after the second pregnancy according to BMI in the first pregnancy

in the two pregnancies for 471 670 women (80.3%). Of these women, 456 711 also had complete information on included covariates (77.7% of all women). Compared to women with complete information (n=456 711), women who were excluded because of missing data (n=130 999) were slightly older, were more often smokers and of non-Nordic origin, and had longer interpregnancy intervals (appendix). Stillbirths and infant mortality rates were also higher in women excluded from the study than in those included (appendix).

59 646 (13.1%) of 456 711 women reduced their weight by at least 1 BMI unit between successive pregnancies, 209 427 (45.9%) were stable in weight (change in BMI between -1 and <1), and 187 638 (41.1%) increased their weight by at least 1 BMI unit (table 1).

The rate of stillbirth increased with interpregnancy weight gain, and infants of women with high weight gain (≥4 BMI units) had increased infant mortality rates. Compared with second offspring of women with normal weight in first pregnancy, second offspring of women who were overweight or obese had higher stillbirth and infant mortality rates (table 1). Rates of stillbirth and infant mortality were also increased among offspring of short women, smokers, women with low education, and women who were of non-Nordic origin. Offspring of older women (≥35 years) had increased stillbirth rates, while offspring of young women (≤24 years) had increased infant mortality rates.

The risk of stillbirth increased linearly with weight gain between pregnancies (table 2). Compared to women with stable weight (BMI change from -1 to <1 kg/m²), women with high weight gain (≥4 BMI units) had a

>50% increased risk of stillbirth in second pregnancy. High weight gain was also associated with a slightly increased risk of infant mortality. Weight loss between pregnancies did not affect stillbirth or infant mortality risks overall.

We tested for interactions between women's BMI (<25 or ≥25 kg/m²) and weight change in six classes. Risks of stillbirth increased with increasing weight gain in both BMI groups (test for interaction p=0.96; table 3). We reported significant interactions between BMI at first pregnancy and weight change with respect to infant mortality (p=0.04) and neonatal mortality (p=0.04); the interaction was not significant for postneonatal mortality (p=0.08).

In women with healthy weight during first pregnancy (BMI <25 kg/m²), the risk of infant mortality increased with weight gain. The risk of infant mortality was higher in women who gained 2 to less than 4 BMI units (RR 1.27, 95% CI 1.01-1.59) and in those who gained 4 BMI units or more (1.60, 1.16-2.22) than in women of stable weight. In women with healthy weight, the risk of neonatal mortality increased linearly with weight gain, whereas only high weight gain (≥4 BMI units) increased the risk of postneonatal mortality (1.61, 1.02-2.55).

By contrast, in women who were overweight during their first pregnancy, weight gain had no effect on infant mortality risk. Of note, weight loss of more than 2 BMI units was associated with reduced neonatal mortality risk in offspring of overweight women (RR 0.49, 95% CI 0.27-0.88), whereas a similar weight loss in women of healthy weight was associated with increased infant mortality risk (1.57, 1.02-2.42).

See Online for appendix

Information about gestational age at registration was recorded from 1996 onwards. Of 390 826 women with two childbirths between 1996 and 2012, 336 271 women (86.1%) underwent both their first pregnancy visits within the first trimester (within 14 completed weeks of gestation). In supplementary analyses, we analysed the associations of interpregnancy weight change with stillbirth and infant mortality in women who had their weight recorded in the first trimester in both pregnancies. Results were very similar, although statistical power was reduced (appendix). Additional analyses using multiple imputation of missing values on interpregnancy weight gain and covariates resulted in only slight reductions in stillbirth risk for women with high weight gain (appendix).

Discussion

In this population-based cohort study, weight gain from first to second pregnancy was positively related to stillbirth risk in the second-born offspring. The weight-gain-related increase in infant mortality was restricted to offspring of women with healthy weight in their first pregnancy. Weight loss between successive pregnancies reduced the risk of neonatal mortality in offspring of overweight women, but increased infant mortality risk in offspring of women with healthy weight.

Obesity and weight gain are associated with inflammatory upregulation,^{21,22} and inflammation has been proposed as one mechanism for the associations between maternal overweight and obesity and several adverse pregnancy outcomes.²³ For example, inflammation might cause preterm premature rupture of the membranes,²⁴ and in pregnancies with preterm premature rupture of membranes, the risk of infant mortality is increased by six times in offspring of obese mothers.²⁵ Although weight gain is most likely due to fat accrual, it is not possible to establish the pattern of fat deposition related to weight gain. Nevertheless, BMI in adults is highly associated with visceral fat²⁶ and accumulation of visceral fat is related to inflammation.²⁷ Thus, accrual of visceral fat could be on the causal path from weight gain to stillbirth or infant mortality.

Possible pathways by which weight change between pregnancies might affect infant mortality risk include preterm birth, congenital malformations, and birth asphyxia. Maternal overweight and obesity increase risks of preterm birth and congenital malformations,^{1,5,28} which are major determinants of infant mortality.^{12,29} In term infants, maternal overweight and obesity not only increase risks of severe asphyxia-related conditions³⁰ but also risk of infant mortality due to birth asphyxia.¹²

The positive association between interpregnancy weight gain and infant mortality was restricted to offspring of women with healthy weight. These findings are in agreement with our previous study showing higher weight gain-related risks of pregnancy complications in women with normal BMI during their first pregnancy than in

overweight women.⁸ However, underlying mechanisms are elusive. BMI is a good marker of body fat in early pregnancy in women with healthy weight, overweight, and obesity.^{31,32} Women who start off with healthy weight have less fat mass than overweight women; therefore, the same absolute increase in weight should imply a larger relative increase in fat mass in women with healthy weight than in those who are already overweight. Weight loss in overweight and obese women is probably mainly due to a reduction of body fat, and parallels drops in concentrations of inflammatory cytokines that are produced in fat tissue.³³ If illness is more often the underlying cause of weight loss in women with healthy weight than in overweight women, this might in turn explain why the associations with pregnancy and offspring risks differ between the two groups.

In this population-based cohort study, we had sufficient statistical power to show a dose-response association between interpregnancy weight gain and stillbirth risk, both in offspring of women with healthy weight and overweight women. These results extend on previous findings that weight gain between pregnancies increases subsequent stillbirth risk.^{8,9} The mechanisms by which overweight and obesity affect stillbirth risk are poorly understood and might be attributed only in part to overweight-related and obesity-related pregnancy complications, including pregnancy-induced hypertensive diseases or gestational diabetes.³⁴

In our study, the availability of the person-unique Swedish national registration number made it possible to link information from two successive pregnancies. Information on women's BMI was based on recordings of height and weight in early pregnancy, which precludes recall bias. Follow-up was complete because information on stillbirths and infant mortality is available for all births in the Medical Birth Register when combined with information in the Causes of Death Register.

We had the possibility to control for several important confounders, including mother's education, interpregnancy interval, and smoking habits across the two pregnancies. Still, we cannot exclude the possibility of residual confounding by social or time-varying covariates. For example, women with high weight gain might also have a less healthy lifestyle in other aspects, such as a less healthy diet or higher alcohol consumption than women who maintain their weight.

Missing data is another limitation because information on interpregnancy weight change and covariates was only available in 78% of all women. Women excluded in the analysis had higher rates of stillbirth and infant mortality than the women included. The excluded women were also more often smokers and of non-Nordic origin, and had longer interpregnancy intervals. We have previously shown that these characteristics are associated with increased interpregnancy weight gain;⁸ thus, exclusion of those women from the present analyses might have resulted in an under-representation of exposed individuals with high outcome rates. Therefore, the estimates of

association we observed, if anything, could represent an underestimation of the effect of weight gain on these outcomes. When we used multiple imputation techniques, there were only negligible changes in the associations, which indicated that selection bias caused by missing data is not a major concern.

Information on women's BMI was based on measured weight and self-reported height recorded in early pregnancy. As women tend to slightly overestimate their height,³⁵ measurement errors in height might have led us to underestimate women's BMI. However, provided that this reporting bias is similar in first and second pregnancies, a possible effect on interpregnancy differences in BMI should be minor.

Although we included information for more than 450 000 births, range of exposure (eg, differences in interpregnancy weight gain) was restricted, and stillbirth and infant mortality rates were low. Moreover, in analyses of infant mortality, statistical power was further hampered because interactions needed stratification. Low statistical power was also the reason why we refrained from studying associations between weight change and causes of infant death.

Our findings might potentially have substantial public health implications. 15% of the women gained 2 to less than 4 BMI units between pregnancies (corresponding to 6–11 kg in women of average height), and 6% gained at least 4 BMI units. Such weight gains would increase stillbirth risks by 30–50%, irrespective of weight in first pregnancy. The same weight gains would increase risks of infant mortality by 27% and 60%, respectively, in offspring of women with a healthy weight in first pregnancy. Conversely, in overweight women, we found that a weight reduction of more than 2 BMI units (corresponding to at least 6 kg) was related to about a 50% lower risk of neonatal mortality.

Prevention of weight gain and promotion of weight loss in overweight women might reduce stillbirth and infant mortality risks in offspring of parous women. The pathways by which overweight and obesity affect stillbirth and infant mortality risks are to be established.

Contributors

SC and EV conceived and designed the study, analysed the data, and drafted the report.

Declaration of interests

We declare no competing interests.

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Interpregnancy weight gain—a modifiable cause of stillbirth?

In *The Lancet*, Sven Cnattingius and Eduardo Villamor¹ capitalise once more on the extraordinary resource of the Swedish Medical Birth Register to identify risk factors for stillbirth and infant death. In a population-based cohort study of 456 711 women with data on height and early gestational weight, the authors investigated the association between change in body-mass index (BMI) between first and second pregnancies and risks of stillbirth and infant mortality. The authors report an incremental increase in risk of stillbirth with BMI gain between first and second pregnancies (relative risk [RR] 1.38, 95% CI 1.16–1.63 if BMI gain is 2 to <4 kg/m² vs -1 to <1 kg/m²; and RR 1.55, 95% CI 1.23–1.96, if BMI gain is ≥4 kg/m² vs -1 to <1 kg/m²); and a novel finding in women of normal weight during their first pregnancy that even modest increases in BMI by their second pregnancy were associated with increased infant mortality (RR 1.27, 95% CI 1.01–1.59 if BMI gain was 2 to <4 kg/m² vs -1 to <1 kg/m²). Women of healthy weight in their first pregnancy who gained more than 4 BMI units (one BMI unit corresponds to 2.8 kg in an average Swedish woman with a height of 167 cm) had a further increase in infant mortality (RR 1.60, 95% CI 1.16–2.22). Reassuringly, overweight women who lost weight before a second pregnancy had a reduction in neonatal mortality (RR 0.49, 95% CI 0.27–0.88, if BMI decrease was >2 kg/m²).

As described in *The Lancet* Stillbirth Series, stillbirth rates in developed countries are intransigently and tragically high.² Neonatal mortality targets prescribed by the Millennium Development Goals have also not been realised, and improvements in infant mortality have plateaued. Is it possible that interpregnancy weight gain represents a modifiable target to reduce stillbirth and neonatal death substantively?

For women, excessive weight gain in pregnancy and post-partum weight retention are major risk factors for obesity, leading to increasing BMI with successive pregnancies.³ We should ask two questions: is it possible to limit gestational weight gain safely and adequately in pregnant women, and why do some women readily regain their prepregnancy BMI whereas many do not?

Trials of diet or physical activity interventions for optimising pregnancy weight gain have had variable success.⁴ Most studies have been underpowered to

address clinically relevant outcomes and few have assessed whether reductions in gestational weight gain affect BMI in future pregnancy.^{5,6} In the LIMIT study⁷ (n=2212), the largest trial of lifestyle intervention in overweight and obese women so far, there was no effect on pregnancy weight gain, although macrosomia was reduced. In a meta-analysis published before LIMIT, the average reduction in gestational weight gain achieved in trials of lifestyle interventions was 1.42 kg.⁴ In the UPBEAT⁸ (n=1555) and RADIEL⁹ (n=293) trials, which used more intensive and individualised interventions, there was a modest reduction in pregnancy weight gain (roughly 0.5 kg). Even if this weight reduction persisted until the next pregnancy, which is by no means certain, this magnitude of weight change would be too small to translate into a significant reduction in stillbirth or infant death in the next pregnancy, according to Cnattingius and Villamor's data.¹ Present evidence suggests that, while lifestyle interventions to limit gestational gain could have health benefits for mother and baby, the effect on post-partum weight retention might not be sufficient to have a major effect on interpregnancy weight gain and consequently stillbirth and infant death risk.

Why then do some women regain their prepregnancy weight and not others, and is excessive pregnancy weight gain the predominant determinant of post-partum weight retention? Improved knowledge could help develop useful post-partum strategies to prevent

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weight gain between pregnancies. Indeed, attempts have already been made to intervene post partum; a systematic review of 11 studies suggested that post-partum weight loss might be achievable, but many uncertainties remain as to the best strategy.¹⁰

A mother's life post partum can be physically and mentally challenging. Post-partum weight retention has been reported to be more common in ethnic minorities and in women with sleep deprivation and post-partum depression, all of which are risk factors for stillbirth.^{11,12} These and other insights should inform development of better interventions to reduce weight retention after delivery, and might in turn contribute to a reduction in stillbirth and neonatal mortality.

An association between maternal overweight and obesity and infant mortality has been widely reported.¹³ Cnattingius and Villamor's study¹ presents new evidence that moderate interpregnancy weight gain (BMI increase of ≥ 2 kg/m², which is about 6 kg in an average Swedish woman) is also associated with increased infant mortality, but only in infants born to the mothers of healthy weight during their first pregnancy. This finding is unexpected, but the authors suggest that increments in BMI in lean women could reflect a greater accrual of fat mass than in obese women, and therefore a greater risk. This association was limited not just to neonatal death, which might be explained by increased risk of congenital malformations, preterm birth, hypoxic-ischaemic encephalopathy, and neonatal sepsis with high maternal BMI, but also to death after the neonatal period (61% risk increase if BMI gain is ≥ 4 ; RR 1.61, 95% CI 1.02–2.55). Although residual confounding from factors such as social deprivation, smoking, and undetected mental illness might be responsible,¹² this association could have a causal component. A previous report¹⁴ suggested that infants born to overweight mothers have a two-fold increase in risk of sudden infant death syndrome, and women with high BMI are less likely to breastfeed successfully, which is associated with increased risk of postneonatal death.¹⁵

Very importantly, we need effective fiscal and public health strategies to improve the awareness and implementation of the benefits of healthy diets

and physical activity in young people. In turn this improvement would reduce obesity and excessive pregnancy weight gain in pregnant women, mitigate against post-partum weight retention, and potentially reduce stillbirth and infant death.

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