ORIGINAL RESEARCH

Interpregnancy Weight Change Among Mothers of a Child with a Major Congenital Anomaly: A Danish Nationwide Cohort Study

Eyal Cohen[1-3], Péter Szentkúti[4], Erzsébet Horváth-Puhó [4], Hilary K Brown [3,5], Sonia M Grandi[2], Henrik Toft Sørensen [4,6], Joel G Ray[2,3,7]

[1]Department of Pediatrics and Edwin S.H. Leong Centre for Healthy Children, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; [2]Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada; [3]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [4]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [5]Department of Health & Society, University of Toronto Scarborough; [6]Clinical Excellence Research Center, Stanford University, Stanford, CA, USA; [7]St.Michael's Hospital Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence: Eyal Cohen, Department of Pediatrics and Edwin S.H. Leong Centre for Healthy Children, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada, Tel +1 416-813-7654, Email eyal.cohen@sickkids.ca

Background: The mother of an infant with a major congenital anomaly is at a higher risk of premature cardiometabolic disease, possibly from chronic caregiver stress and distraction from self-care, including maintaining a healthy lifestyle and body weight.

Objective: To compare the interpregnancy weight gain in women whose first infant had a major congenital anomaly vs those without an affected child.

Methods: Multivariable linear regression compared women whose infant had an anomaly vs those whose infant did not, adjusting for interpregnancy time interval, demographics, smoking and health status at the first pregnancy.

Results: Of the 199,536 women who had two consecutive singleton births, 4035 (2.0%) had a child with an anomaly at the first birth. The mean (SD) maternal BMI at the start of the first pregnancy was 24.1 (4.7) and 23.7 (4.4) kg/m^2 in women with, and without, an anomaly-affected newborn. By the start of the second pregnancy, 3 years later, they had gained a mean (SD) of 2.2 (5.5) and 1.8 (5.2) kg, respectively – an adjusted absolute higher gain of 0.26 kg (95% CI 0.10 to 0.42) in women with an anomaly-affected first-born infant compared to those with an unaffected pregnancy. The adjusted interpregnancy weight gain difference was greatest in women whose first-born infant had a multi-organ anomaly at 0.59 kg (95% CI 0.02 to 1.16). The adjusted odds ratio of moving from a normal BMI category of 18.5–24.9 kg/m^2 in the first pregnancy, to an overweight or obese BMI category of 25+ kg/m^2 in the second, was 1.18 (95% CI 1.06 to 1.32) comparing mothers with vs without an anomaly-affected child in the first pregnancy.

Conclusion: Mothers of an infant with a major congenital anomaly have a modestly higher interpregnancy weight gain and tend to climb to a higher BMI category. The long-term implications of this greater weight trajectory require further study.

Keywords: weight gain, congenital anomaly, inter-pregnancy, body mass index

Introduction

Major congenital anomalies, such as congenital heart defects, affect 2–5% of all births.[1–3] A child with major anomaly often has chronic health conditions requiring intensive intervention in infancy, and many may face lifelong health challenges.[4] Their mothers often bear substantial caregiving burden, related to frequent child healthcare visits and hospitalizations, use of assistive technologies, need to assist with activities of daily living, as well as increased financial burden.[5–7]

A mother who cares for a child with a chronic illness often experiences protracted stress,[5,8,9] and poor self-reported health.[7,10–12] Women whose child has a major congenital anomaly have a higher mortality risk,[13] and are more likely to have chronic medical conditions, including cardiometabolic disease[14] and mental illness.[15] Hypothesized mechanisms of these associations include shared genetic factors,[16] a pro-inflammatory state[17] and/or advanced cell aging.[18] Competing

caregiving demands may also impact a mother's ability to focus on a healthy lifestyle, in terms of healthy eating and physical activity, potentially leading to other maladaptive health behaviors.[19]

Pregnancy is a time in a woman's life when she will likely experience weight gain, with modest weight retention thereafter.[20] At the start of her second pregnancy, 41–73% of women are at a higher weight than that prior to the first pregnancy,[21–23] with an average weight gain of 3.4 kg.[24] *Interpregnancy weight gain* is an important forecaster of a woman's lifelong weight trajectory - weight at one year postpartum is a strong predictor of developing obesity[24] – more so than the weight gained during the index pregnancy.[25] A higher periconceptional weight strongly contributes to having an adverse cardiometabolic profile,[26] heightening the risk of adverse maternal and perinatal outcomes,[27] including preeclampsia, gestational diabetes mellitus, stillbirth and preterm birth.[23,28] While some risk factors have been identified with postpartum weight retention,[21,29,30] little is known about the tendency for interpregnancy weight gain in women whose child was born with a major congenital anomaly.

The current study compared the interpregnancy weight gain in women whose first infant had a major congenital anomaly vs those without an affected child, including those whose infant had a multi- or single-organ anomaly.

Methods

Cohort

This population-based cohort study was completed in all of Denmark, where there is universal publicly-funded health coverage for all residents. A unique identification number is assigned to each resident, permitting accurate linkage of health and demographic information across all national registries (Table S1).[31] The Danish Medical Birth Registry[32] and Civil Registry System[33] were used to identify primigravid women who had two consecutive singleton births during the study period of January 1, 2004 to December 31, 2017, and in which the first liveborn infant survived to hospital. The cohort was limited to singleton second pregnancies so that the two groups would be comparable in terms of what we might expect their weight to be at the first antenatal visit. Excluded were women without a recorded early pregnancy weight in a first and second pregnancy. Extreme outliers [(<1st percentile of interpregnancy weight loss (≥13 kg weight loss) or >99th percentile for interpregnancy weight gain (≥21 kg weight gain)] were removed as well.

Exposure

The primary exposure was the birth of a child with a major congenital anomaly, ascertained using the Danish National Patient Registry,[34] via diagnostic codes mapped to the International Classification of Diseases, Tenth Revision (ICD-10) up to the end of the first year of life (Table S2). A major congenital anomaly was defined according to the European Surveillance of Congenital Anomalies Classification System, with minor adaptations for use with Danish data.[3] Also excluded were mothers whose first-born child had a minor congenital anomaly, such as a mild skeletal (eg, rib hypoplasia) or craniofacial (eg, plagiocephaly) anomaly.

A secondary study exposure was a first-born infant with a single-organ or multi-organ (2 or more) congenital anomaly.

Outcome

The main outcome was the absolute difference (in kg) in the first maternal weight of pregnancy between the second minus first pregnancy. First maternal weight of pregnancy was defined as that measured at the first antenatal visit, as recorded in the Danish Medical Birth Registry.

Covariates

Demographic data, including maternal age, were captured at the estimated date of conception in the first pregnancy, obtained from the Civil Registration Registry. Interpregnancy time interval was denoted by the number of days between the estimated date of conception of the first pregnancy and the estimated date of conception of the second pregnancy, using the Danish Medical Birth Registry. Socioeconomic characteristics collected included income quintile, obtained from the Income Statistics Register;[35] immigration status, from the Civil Registration System; and education level, from

the Population Education Register.[36] Health status variables, collected from the Danish National Patient Registry, Danish Medical Birth Registry, the Danish Psychiatric Central Research Registry, and the Danish National Prescription Registry, included a history of pre-pregnancy diabetes mellitus, chronic hypertension and a mental health condition. Pregnancy health measures collected in the first pregnancy included gestational diabetes mellitus, pregnancy-induced hypertension (gestational hypertension or preeclampsia/eclampsia) and smoking status. Infant measures at birth included sex, birth weight, gestational age and Apgar score, all from the Medical Birth Registry.

Statistical Analysis

Multivariable linear regression was used to estimate the absolute percent difference in inter-pregnancy weight gain between women whose first-pregnancy infant had a major congenital anomaly vs women whose infant did not (the referent). As the interpregnancy weight gain data were normally distributed, mathematical transformation was not indicated. Given that a woman with a child with a major congenital anomaly may delay planning of her next pregnancy, interpregnancy time interval was included in all unadjusted models, a priori. Adjusted analyses also included maternal age, immigrant status, income quintile, marital status, smoking status in the first pregnancy, gestational diabetes, chronic hypertension, preeclampsia/eclampsia and mental health conditions. Analyses were then further stratified based a woman's BMI in the first pregnancy, categorized as underweight (< 18.5 kg/m^2), normal weight (18.5 to < 25 kg/m^2), overweight (25 to < 30 kg/m^2) or obese (≥ 30 kg/m^2).

Additional Analyses

In addition to modelling the exposure variable by having an infant with a single-organ or multi organ congenital anomaly (vs no anomaly), an additional analysis considered the cumulative number of days that the first-born infant was hospitalized between its birth up to the estimated date of conception of the second pregnancy, categorized as 0–6, 7–30 or > 30 cumulative number of days. In order to explore interpregnancy weight gain based on clinical thresholds of BMI categories, a second additional analysis was conducted using logistic regression with the same covariates as all previous models to assess the odds of a woman in a normal BMI category in the first pregnancy moving to an overweight or obese status in the second pregnancy by exposure status.

A woman who undergoes a second pregnancy may differ from one who does not. Specifically, selection bias may arise due to dropout after a first pregnancy, as in the case of an intercurrent maternal death or illness, preventing a second pregnancy. Accordingly, we created a supplemental table, with standardized differences to contrast the first-pregnancy characteristics of women who did, or did not, have a second birth during the study period. Furthermore, a dropout analysis assessed the odds of any Danish woman with a first singleton live birth in the study period achieving a second pregnancy, comparing those whose first-born infant did vs did not have a major anomaly. Logistic regression generated odds ratio (OR), including the same covariates as in all prior models, with the exception of interpregnancy interval.

All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). The study was approved by the Research Ethics Board of The Hospital for Sick Children (1000053060) and reported to the Danish Data Protection Agency, which oversees the confidentiality of individual-level information in Danish registries.

Results

The final cohort comprised 199,536 first-time mothers, of whom 4035 (2.0%) had an infant with a major congenital anomaly (Figure 1). Among the latter, 308 (7.6%) had multi-organ anomalies.

Minimal differences were seen between mothers with and without a first birth affected by a major anomaly, in terms of sociodemographic characteristics; however, the rates of pre-pregnancy diabetes mellitus, chronic hypertension, gestational diabetes and gestational hypertension were higher among the former (Table 1). Infants with a major anomaly had a greater cumulative number of days in hospital between their birth and their mother achieving her second pregnancy (Table 1).

Women whose infant had a major congenital anomaly had a mean (SD) BMI of 24.1 (4.7) kg/m^2 at the start of the first pregnancy, which was slightly higher than mothers of an unaffected infant (23.7 [4.4] kg/m^2). The mean (SD) time interval between the first and second pregnancies was 36.4 (17.9) and 36.9 (17.6) months, respectively.
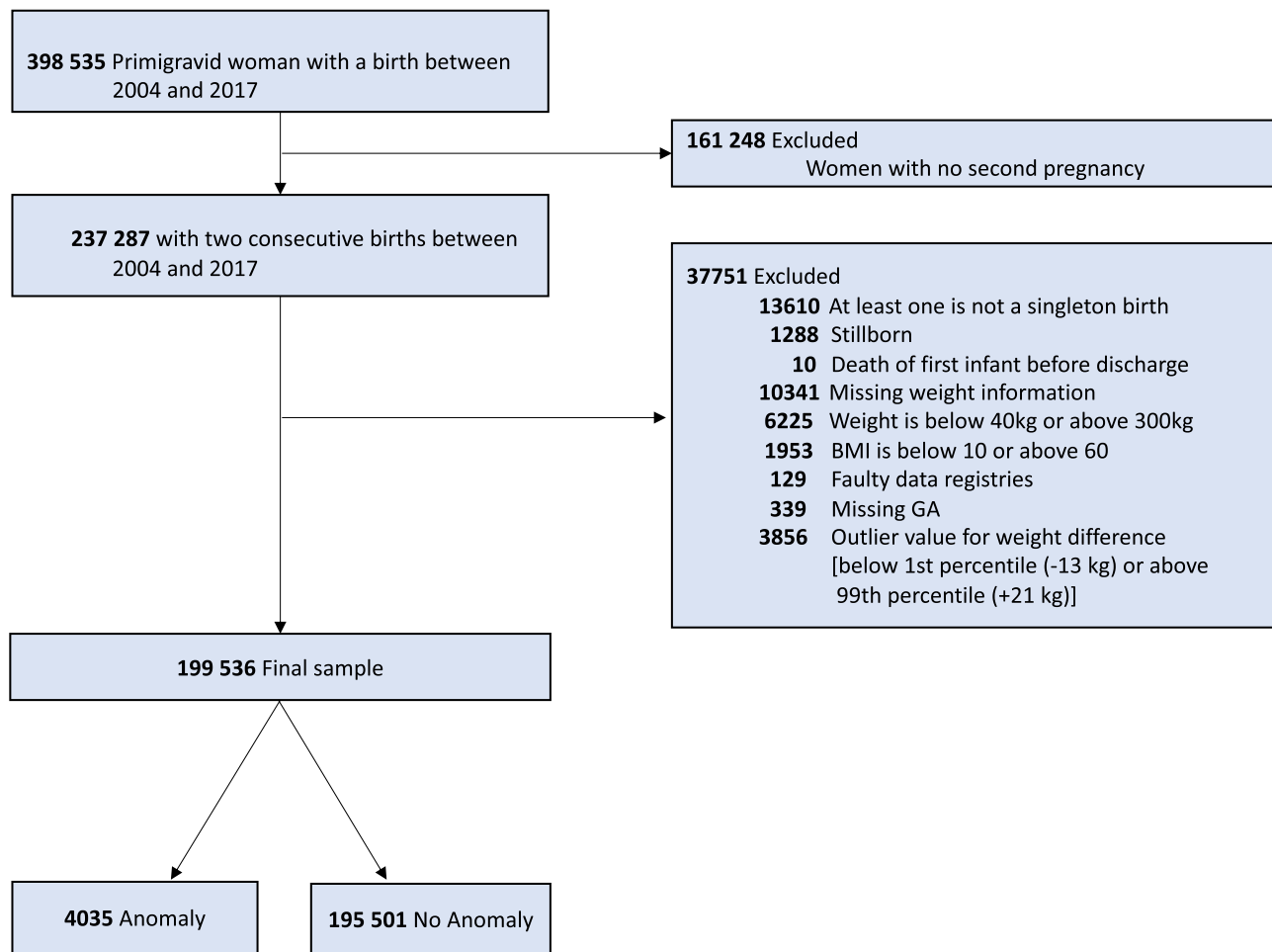
Figure 1 Flow diagram of cohort derivation.

By the start of the second pregnancy, mothers of an infant with a major anomaly had gained a mean (SD) of 3.2 (8.0) kg (a 4.7% relative weight gain), in contrast to a mean (SD) weight gain of 2.8 (7.6) kg (a 4.2% relative weight gain) in mothers of an unaffected infant. In unadjusted models (adjusting just for interpregnancy interval), a mother whose infant had a congenital anomaly gained a net of 0.30 kg (95% CI 0.14 to 0.46) more weight by start of her second pregnancy than the mother of an unaffected infant. After adjusting for study covariates, the mother of an affected infant gaining 0.26 kg (95% CI 0.10 to 0.42) more weight than the mother of an unaffected infant – a relative difference of 14.2% (95% CI 5.5 to 23.0) (Figure 2). This observation was especially evident among the majority of women in the normal weight category at the start of their first pregnancy (adjusted weight difference: 0.27 kg, 95% CI 0.09 to 0.44). In contrast, among the small proportion of women who were underweight in the first pregnancy, the trend was in the opposite direction, albeit with a wide confidence interval (net difference of −0.41 kg, 95% CI −0.98 to 0.16) (Figure 2).

Relative to women with an unaffected first pregnancy, the interpregnancy weight gain difference was greatest in women whose first-born infant had a multi-organ major anomaly (0.59 kg, 95% CI 0.02 to 1.16), followed by those whose infant had a single-organ major anomaly (0.24 kg, 95% CI 0.07 to 0.40) (Figure 3). Exceptionally, mothers of an infant with multi-organ anomalies, and who were underweight in their first pregnancy, had a net weight difference of −2.21 kg (95% CI −3.98 to −0.44) by their second pregnancy (Figure 3).

Relative to women whose first infant was both unaffected by a major congenital anomaly and had the least cumulative number of days in hospital after the index birth discharge date, there was a rising net increase in interpregnancy weight

Table 1 Characteristics of the Mothers and Their First- and Second-Born Infants. All Data are Presented as a Number (%) Unless Otherwise Indicated

Characteristic	First Born Infant Affected by a Major Congenital Anomaly (N = 4035)	First Born Infant Not Affected by a Major Congenital Anomaly (N = 195,501)
Of the mother in the first pregnancy		
Mean (SD) age at delivery, years	27.6 (4.4)	27.7 (4.2)
Mean (SD) weight at the first antenatal visit, kg	68 (14.4)	66.9 (13.4)
Mean (SD) BMI at the first antenatal visit, kg/m^2	24.1 (4.7)	23.7 (4.4)
BMI category, kg/m^2		
Underweight: < 18.5	178 (4.4)	9117 (4.7)
Normal 18.5 to < 25	2450 (60.7)	124,342 (63.6)
Overweight: 25 to < 30	931 (23.1)	42,853 (21.9)
Obese: ≥ 30	476 (11.8)	19,189 (9.8)
Immigrant	470 (11.6)	21,674 (11.1)
Educational level[a]		
Basic education	826 (20.5)	35,007 (17.9)
High school	1643 (40.7)	81,358 (41.6)
Higher education	1255 (31.1)	65,111 (33.3)
Income quintile[b]		
1 (lowest)	774 (19.2)	35,623 (18.2)
2	628 (15.6)	31,705 (16.2)
3	700 (17.3)	32,348 (16.5)
4	841 (20.8)	40,472 (20.7)
5 (highest)	939 (23.3)	48,868 (25.0)
Marital status		
Married/registered partnership	1083 (26.8)	51,347 (26.3)
Divorced	78 (1.9)	3489 (1.8)
Widow	–	91 (0.0)
Not married or unknown	2874 (71.2)	140,574 (71.9)
Medical history		
Pre-pregnancy diabetes mellitus	34 (0.8)	997 (0.5)
Gestational diabetes mellitus	103 (2.6)	3890 (2.0)
Chronic hypertension	24 (0.6)	546 (0.3)
Gestational hypertension	294 (7.3)	10,881 (5.6)
Depression	40 (1.0)	1779 (0.9)

(*Continued*)

Table 1 (Continued).

Characteristic	First Born Infant Affected by a Major Congenital Anomaly (N = 4035)	First Born Infant Not Affected by a Major Congenital Anomaly (N = 195,501)
Smoking at the first antenatal visit[c]	529 (13.1)	23,508 (12.0)
Of the first liveborn infant		
Female[d]	1487 (36.9)	94,998 (48.6)
Year of birth		
2004–2007	1482 (36.7)	74,183 (37.9)
2008–2011	1389 (34.4)	71,031 (36.3)
2012 onward	1164 (28.8)	50,287 (25.7)
Gestational age at birth, weeks		
37–42	3179 (78.8)	172,887 (88.4)
32–36	500 (12.4)	9491 (4.9)
28–31	116 (2.9)	896 (0.5)
23–27	59 (1.5)	392 (0.2)
42+	181 (4.5)	11,835 (6.1)
Birth weight, kg	3.2 (0.8)	3.4 (0.6)
Apgar score[e]		
< 7	139 (3.4)	1531 (0.8)
≥ 7	3840 (95.2)	192,779 (98.6)
Cumulative number of days hospitalized preceding the start of the second pregnancy		
0–6	2166 (53.7)	184,482 (94.4)
7–30	1406 (34.8)	10,247 (5.2)
> 30+	463 (11.5)	772 (0.4)
Died preceding the start of the second pregnancy	35 (0.9)	67 (0.0)
Mean (SD) time interval between estimated date of conception in the first and second pregnancies, months	36.4 (17.9)	36.9 (17.6)
Of the second liveborn infant		
Female[f]	1961 (48.6)	94,950 (48.6)
Gestational age at birth, weeks		
37–42	3735 (92.6)	184,034 (94.1)
32–36	171 (4.2)	5805 (3.0)
28–31	20 (0.5)	553 (0.3)
23–27	10 (0.2)	204 (0.1)
42+	99 (2.5)	4905 (2.5)

(*Continued*)

Table 1 (Continued).

Characteristic	First Born Infant Affected by a Major Congenital Anomaly (N = 4035)	First Born Infant Not Affected by a Major Congenital Anomaly (N = 195,501)
Birth weight, kg	3.5 (0.6)	3.6 (0.5)
Apgar score[g]		
< 7	23 (0.6)	981 (0.5)
≥ 7	3997 (99.1)	193,260 (98.9)
Major congenital anomaly	154 (3.8)	3662 (1.9)

Notes: [a]Education unknown among 311 (7.7%) and 14,025 (7.2%), respectively. [b]Income quintile unknown among 153 (3.8%) and 6485 (3.3%), respectively. [c]Smoking at the first antenatal visit unknown among 96 (2.4%) and 2791 (1.4%), respectively. [d]Sex of the first liveborn infant unknown among 159 (3.9%) and 439 (0.2%), respectively. [e]Apgar score of first liveborn infant unknown among 56 (1.4%) and 1191 (0.6%), respectively. [f]Sex of the second liveborn infant unknown among 8 (0.2%) and 581 (0.3%), respectively. [g]Apgar score of the second liveborn infant unknown among 15 (0.4%) and 1260 (0.6%), respectively.

gain with increased cumulative duration of newborn hospitalization among women with and without infants with anomalies (Figure 4). Mothers whose infant was hospitalized for at least 30 days had the highest absolute net interpregnancy weight gain whether the infant was affected by an anomaly (weight gain 0.76 kg [95% CI 0.29 to 1.22]), or not (weight gain 0.88 kg [95% CI 0.52 to 1.24]).

In the first pregnancy, 60.7% of those with anomalies and 63.6% of those without anomalies had a normal BMI at the first maternal weight of the pregnancy, while in the second pregnancy a normal BMI was observed in 53.9% and 58.0% of these women, respectively (Table S3). The adjusted odds of a woman with a child with an anomaly moving from a normal to an overweight or obese state in the second pregnancy was 1.18 (95% CI 1.06 to 1.32) compared with a woman of an unaffected child.

Women who did not have a second pregnancy were older than those who did (29.5 [5.6] vs 27.7 [4.2] kg), were more likely to be immigrants (21.8% vs 11.1%), and to have comorbidities (21.6% vs 15.8%) (Table S4). In the dropout analysis, the adjusted OR of having a second pregnancy among women whose first infant was affected by a congenital anomaly was 0.87 (95% CI 0.83 to 0.91).
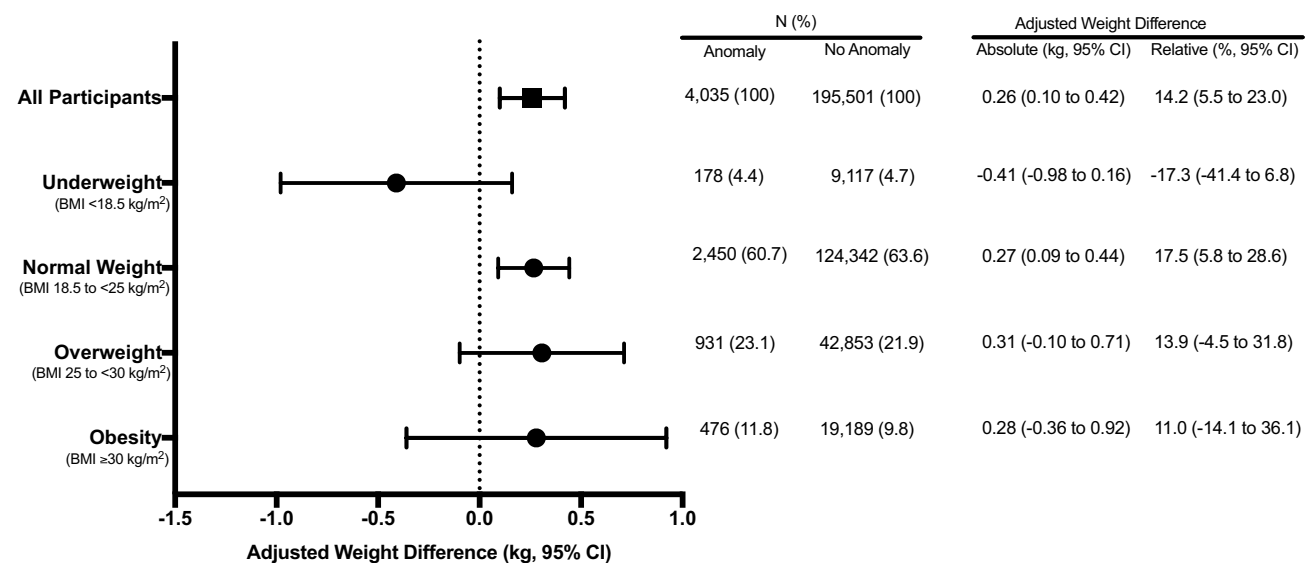

Figure 2 Interpregnancy weight difference among mothers who ielivered an infants with vs without major congenital anomalies. Analyses stratified based on baseline BMI: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5 to <25 kg/m²), overweight (BMI 25 to <30 kg/m²) or obesity (BMI 3 30 kg/m²). Models adjusted for interpregnancy interval, maternal age, immigrant status, income, marital status, smoking status at the first pregnancy, gestational diabetes, chronic hypertension, preeclampsia/eclampsia and depression.
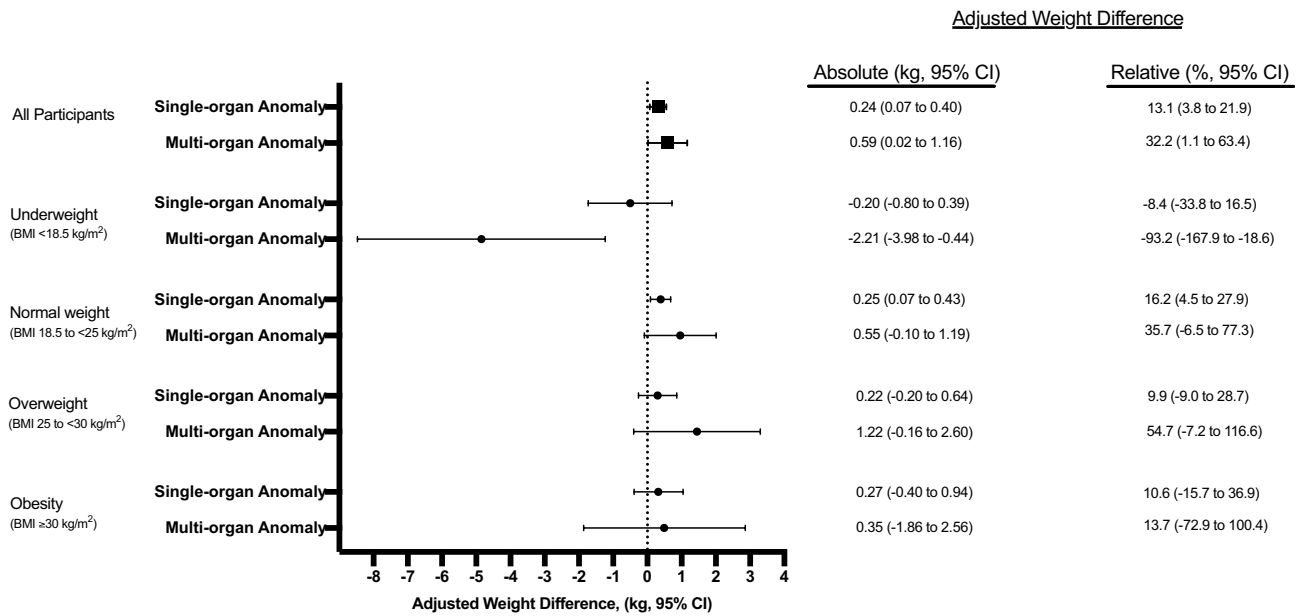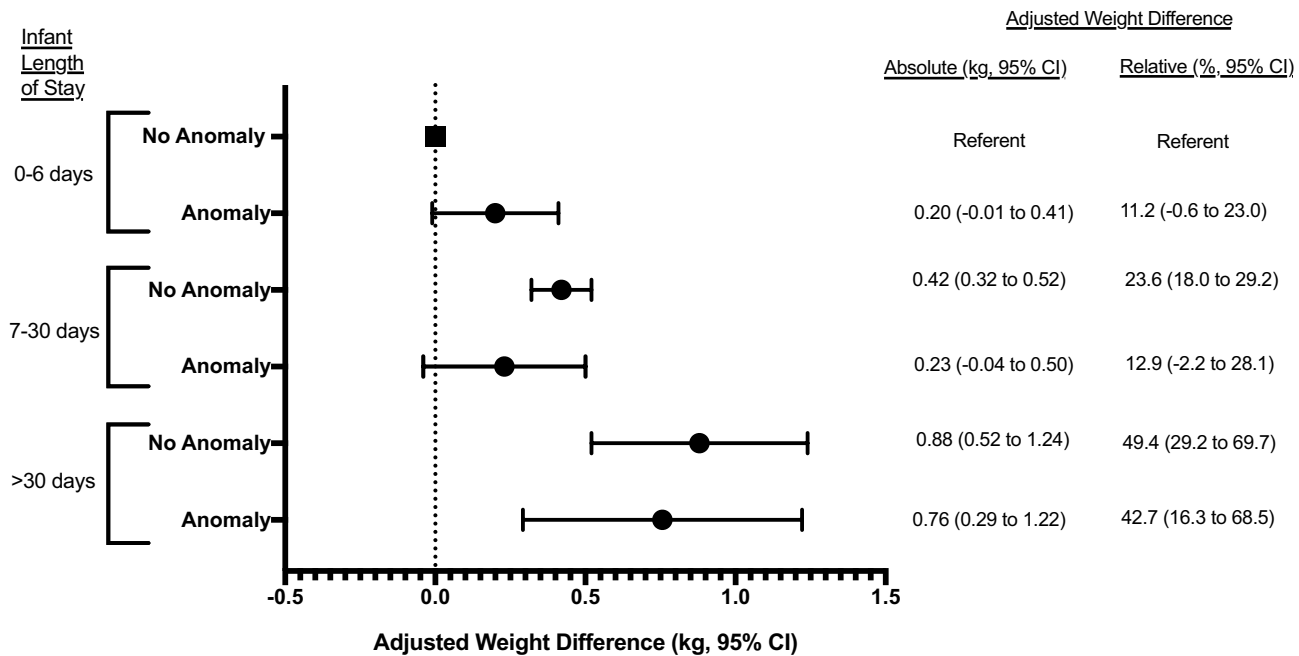
Adjusted Weight Difference

Absolute (kg, 95% CI) Relative (%, 95% CI)

Figure 3 Interpregnancy weight difference among mothers who delivered an infant with multiorgan or single-organ major congenital anomalies vs without major congenital anomalies. Analyses stratified based on baseline BMI: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5 to <25 kg/m²), overweight (BMI 25 to < 30 kg/m²) or obesity (BMI ³ 30 kg/m²). Models adjusted for interpregnancy interval, maternal age, immigrant status, income, marital status, smoking status at the first pregnancy, gestational diabetes, chronic hypertension, preeclampsia/eclampsia and depression.

Figure 4 Interpregnancy weight difference among mothers who delivered an infants with and without major congenital anomalies with varying total infant days of hospitalizations in the interpregnancy interval. Models adjusted for interpregnancy interval, maternal age, immigrant status, income, marital status, smoking status at the first pregnancy, gestational diabetes, chronic hypertension, preeclampsia/eclampsia and depression. Referent group = infants born without major congenital anomalies with total hospitalizations of 0–6 days.

Discussion

In this population-based cohort study of early pregnancy weight change between a first and second pregnancy, a small increased interpregnancy weight gain was observed among a mother whose infant had a congenital anomaly at birth, beyond their pre-existing higher BMI. This effect was more pronounced among those who infant had multi-organ

anomalies and/or prolonged duration in hospital between the first and second pregnancy. Only the much smaller proportion of underweight mothers were more likely to lose weight if her child was born with a major congenital anomaly. Women of infants with anomalies were more likely to cross from normal to overweight or obese weight status than unaffected women status. Since the absolute weight gain difference by exposure status was not large, the clinical importance of the findings is uncertain, and warrants correlation with long-term measures of insulin resistance, blood pressure, and other clinical endpoints.

This is the first study of interpregnancy weight gain among mothers of an infant with a medical or developmental challenge. Our prior work showed that women whose infant had a major congenital anomaly were 22% more likely to experience premature mortality, and 26% more likely to die from a cardiovascular cause.[13] As in the current study, a dose-response relation was noted among the mothers of a more severely affected infant.[13] A similar pattern has also been seen for new-onset maternal myocardial infarction or stroke[14] and psychiatric illness.[37] Other studies have found that mothers of children with chronic conditions have higher rates of all-cause mortality, mental illness and cardiometa-bolic disease.[15,38] Taken together, it appears that the mother of a child with a chronic condition, such as a congenital anomaly, may be at higher risk of interpregnancy weight gain and BMI category reclassification. However, as the degree of weight gain was relatively modest, it may not sufficiently explain the greater risk of cardiometabolic dysfunction seen in women with an anomaly-affected child.[13–15] Even so, the interval between pregnancies was only 36 months, so cumulative weight differences may not yet have been fully appreciated in that short time period, especially since the requirements of caring for an affected child may persist over many years.

We observed a greater effect in the presence of more than one anomaly, or a greater number of child-days in hospital, supporting the hypothesis that the experience of caregiving may play a meaningful role in interpregnancy weight gain. Chronic stress may impact health behaviours, such as smoking, diet and exercise, which may lead to weight gain and/or an adverse cardiometabolic profile.[39] An alternative explanation is that factors that predispose to having a child with a congenital malformation also predispose to greater maternal weight gain – whether genetic and/or environmental in nature.[40] On the other hand, an infant born with a congenital anomaly,[41] and/or who is ill,[42] is less likely to be breastfed, which in turn may lead to less maternal weight loss postpartum.[43] Unfortunately, we did not have reliable estimates of breastfeeding practices to adjust for, or explore, this particular factor. It is noteworthy that we found a greater net weight loss among the small number of underweight mothers of an infant with a major anomaly. Underweight pregnant women are at increased risk of anaemia and preterm birth.[44,45] Hence, by their second pregnancy, such women would seemingly be at even higher risk of adverse perinatal outcomes – something worthy of future exploration.

As a study strength, we used population-level registries with minimal missing data, which minimizes selection bias and provides validated health measures within the Danish registry databases.[31,46,47] Even so, a small proportion of mothers could not be linked to an infant birth. Women who went on to have a second pregnancy differed from those who did not. Likewise, those who had an infant with a congenital anomaly in the first pregnancy had a greater likelihood of study dropout, suggesting a small, but potentially important selection bias. As a diagnosis of a major congenital anomaly was ascertained from birth up to the first year of life, an infant with a subsequently detected anomaly would not have been included in the exposure group. Imprecise estimates of interpregnancy weight gain may have resulted from missing and/or misclassified weight measures. For example, about 7.8% of potentially eligible women were excluded from the cohort for this reason. Also, we did not know the exact gestational age at which the first antenatal weight was measured in each consecutive pregnancy – something that could have differed between women with and without a major congenital anomaly. We also lacked information about other potential confounders, such as diet and smoking. In addition, as the study took place in a country with universal health care and a robust support system for new mothers, the findings might be more pronounced in a setting where fewer resources are freely available. We chose to study mothers who infant had a major congenital anomaly, as they are generally diagnosed at a fixed time point. Even so, we were not equipped to evaluate the influence of other chronic conditions arising after infancy.

Conclusion

The mother of an infant with a major congenital anomaly has a modestly higher interpregnancy weight gain, and a greater tendency to climb to a higher BMI category. Future research should adopt a longer time horizon, to better

ascertain whether interpregnancy weight gain accelerates over time, and how such weight gain is correlated to a woman's cardiometabolic risk profile.

Abbreviations

SD, standard deviation; CI, confidence interval; BMI, body mass index.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors have no conflicts of interest relevant to this article to disclose.

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