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

Eyal Cohen1–3, Péter Szentkuti4, Erzsébet Horváth-Puhó3,4, Hilary K Brown3,5, Sonia M Grandi2, Henrik Toft Sørensen4,6, Joel G Ray2,3,7

1Department of Pediatrics and Edwin S.H. Leong Centre for Healthy Children, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; 2Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada; 3Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; 4Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; 5Department of Health & Society, University of Toronto Scarborough; 6Clinical Excellence Research Center, Stanford University, Stanford, CA, USA; 7St. 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/m² 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/m² in the first pregnancy, to an overweight or obese BMI category of 25+ kg/m² 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 disease14 and mental illness.15 Hypothesized mechanisms of these associations include shared genetic factors,16 a pro-inflammatory state17 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 obesity24 – 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 Registry32 and Civil Registry System33 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,
the Population Education Register. 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/m²), normal weight (18.5 to < 25 kg/m²), overweight (25 to < 30 kg/m²) or obese (≥ 30 kg/m²).

**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/m² at the start of the first pregnancy, which was slightly higher than mothers of an unaffected infant (23.7 [4.4] kg/m²). The mean (SD) time interval between the first and second pregnancies was 36.4 (17.9) and 36.9 (17.6) months, respectively.
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<sup>c</sup>     | 529 (13.1)                                                          | 23,508 (12.0)                                                            |
| Of the first liveborn infant                        |                                                                     |                                                                          |
| Female<sup>d</sup>                                  | 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<sup>e</sup>                             |                                                                     |                                                                          |
| < 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<sup>f</sup>                                  | 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)
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).

### 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                            |                                                                    |                                                                           |
| < 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.

![Figure 2](https://doi.org/10.2147/CLEP.S352889) Interpregnancy weight difference among mothers who delivered 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 ≥ 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.
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. The adjusted weight difference was as follows:

- **Overweight (BMI 25 to <30 kg/m²)**
  - Single-organ Anomaly: 0.24 (0.07 to 0.40)
  - Multi-organ Anomaly: -0.59 (0.02 to 1.16)

- **Normal weight (BMI 18.5 to <25 kg/m²)**
  - Single-organ Anomaly: -0.20 (-0.80 to 0.39)
  - Multi-organ Anomaly: -2.21 (-3.98 to -0.44)

- **Underweight (BMI <18.5 kg/m²)**
  - Single-organ Anomaly: 0.25 (0.07 to 0.43)
  - Multi-organ Anomaly: 0.55 (-0.10 to 1.19)

- **Obesity (BMI ≥30 kg/m²)**
  - Single-organ Anomaly: 0.22 (-0.20 to 0.64)
  - Multi-organ Anomaly: 1.22 (-0.16 to 2.60)

The adjusted weight difference was also analyzed 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 ≥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 3** Interpregnancy weight difference among mothers who delivered an infant with multi-organ 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 ≥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 infant 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.
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. As in the current study, a dose-response relation was noted among the mothers of a more severely affected infant. A similar pattern has also been seen for new-onset maternal myocardial infarction or stroke and psychiatric illness. Other studies have found that mothers of children with chronic conditions have higher rates of all-cause mortality, mental illness and cardiometabolic disease. 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. 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. 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. On the other hand, an infant born with a congenital anomaly, and/or who is ill, is less likely to be breastfed, which in turn may lead to less maternal weight loss postpartum. 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. 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. 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**
This research was supported by the Canadian Institutes of Health Research Grant Numbers FDN-143315 and PJT-180612 (EC). Funding sources had no role in the design, collection analysis or interpretation of data, or in the decision to submit for publication. The authors wish to acknowledge the support of Samantha Quartarone in manuscript preparation and submission.

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

**References**
1. Update on overall prevalence of major birth defects. Atlanta, Georgia; 1978–2005. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/ mm5701a2.htm. Accessed December 7, 2021.
2. EUROCAT. Website database. Available from: https://eu-rdplatform.jrc.ec.europa.eu/eurocat/eurocat-data_en. Accessed December 7, 2021.
3. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. *Adv Exp Med Biol*. 2010;686:349–364. doi:10.1007/978-90-481-9485-8_20
4. Christianson A, Howson CP, Modell CB. *March of Dimes Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children*. White Plains: New York; March of Dimes Foundation; 2006.
5. Ratliffe CE, Harrigan RC, Haley J, Tse A, Olson T. Stress in families with medically fragile children. *Issues Compr Pediatr Nurs*. 2002;25(3):167–188. doi:10.1080/01460860290042558
6. Kuhlthau K, Hill KS, Yucel R, Perrin JM. Financial burden for families of children with special health care needs. *Matern Child Health J*. 2005;9(2):207–218. doi:10.1007/s10995-005-4870-x
7. Raina P, O’Donnell M, Rosenbaum P, et al. The health and well-being of caregivers of children with cerebral palsy. *Pediatrics*. 2005;115(6):e626–636. doi:10.1542/peds.2004-1689
8. Vrijmoet-Wiersma CM, Ottenkamp J, van Roozendaal M, Grootenhuis MA, Koopman HM. A multicentric study of disease-related stress, and perceived vulnerability, in parents of children with congenital cardiac disease. *Cardiol Young*. 2009;19(6):608–614. doi:10.1017/S1047951109991831
9. Cabizuca M, Marques-Portella C, Mendlowicz MV, Coutinho ES, Figueira I. Posttraumatic stress disorder in parents of children with chronic illnesses: a meta-analysis. *Health Psychol*. 2009;28(3):379–388. doi:10.1037/a0014512
10. Brehaut JC, Kohen DE, Garner RE, et al. Health among caregivers of children with health problems: findings from a Canadian population-based study. *Am J Public Health*. 2009;99(7):1254–1262. doi:10.2105/AJPH.2007.129817
11. Thyen U, Terres NM, Yazdgerdi SR, Perrin JM. Impact of long-term care of children assisted by technology on maternal health. *J Dev Behav Pediatr*. 1998;19(4):273–282. doi:10.1097/00004703-199808000-00006
12. Brehaut JC, Kohen DE, Raina P, et al. The health of primary caregivers of children with cerebral palsy: how does it compare with that of other Canadian caregivers? *Pediatrics*. 2004;114(2):e182–191. doi:10.1542/peds.114.2.e182
13. Cohen E, Horvath-Puho E, Ray JG, et al. Association between the birth of an infant with major congenital anomalies and subsequent risk of mortality in their mothers. *JAMA*. 2016;316(23):2515–2524. doi:10.1001/jama.2016.18425
14. Cohen E, Horvath-Puho E, Ray JG, et al. Cardiovascular disease among women who gave birth to an infant with a major congenital anomaly. *JAMA Netw Open*. 2018;1(5):e182320. doi:10.1001/jamanetworkopen.2018.2320
15. Cohn LN, Pechlivanoglou P, Lee Y, et al. Health outcomes of parents of children with chronic illness: a systematic review and meta-analysis. *J Pediatr*. 2019;218:166–177.
16. Sheridan E, Wright J, Small N, et al. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. *Lancet*. 2013;382(9901):1350–1359.
17. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol*. 2002;21(6):531–541. doi:10.1037/0278-6133.21.6.531
45. Han Z, Mulla S, Beyene J, Liao G, McDonald SD; Knowledge Synthesis Group. Maternal underweight and the risk of preterm birth and low birth
44. Sebire NJ, Jolly M, Harris J, Regan L, Robinson S. Is maternal underweight really a risk factor for adverse pregnancy outcome? A population-based
39. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary:
38. Fraser LK, Murtagh FE, Aldridge J, Sheldon T, Gilbody S, Hewitt C. Health of mothers of children with a life-limiting condition: a comparative
37. Rotberg B, Horvath-Puho E, Vigod S, Ray JG, Sorensen HT, Cohen E. Increased maternal new-onset psychiatric disorders after delivering a child
34. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish national patient registry: a review of content, data
32. Knudsen LB, Olsen J. The Danish medical birth registry.
31. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database
30. Gunderson EP, Abrams B. Epidemiology of gestational weight gain and body weight changes after pregnancy.
28. Alwan NA, Grove G, Taylor E, Ziauddeen N. Maternal weight change between successive pregnancies: an opportunity for lifecourse obesity
27. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet. 2006;368
26. Linne Y, Dye L, Barkeling B, Rossner S. Long-term weight development in women: a 15-year follow-up of the effects of pregnancy. Obes Res.
25. Linne Y, Dye L, Barkeling B, Rossner S. Long-term weight development in women: a 15-year follow-up of the effects of pregnancy. Obes Res.
24. Endres LK, Straub H, McKinney C, et al. Postpartum weight retention risk factors and relationship to obesity at 1 year. Obstet Gynecol. 2015;125
23. Cnattingius S, Villamor E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study.
22. Greene GW, Smiciklas-Wright H, Scholl TO, Karp RJ. Postpartum weight change: how much of the weight gained in pregnancy will be lost after
21. Gore SA, Brown DM, West DS. The role of postpartum weight retention in obesity among women: a review of the evidence. Ann Behav Med.
20. Rasmussen KM, Yaktine AL. Weight Gain During Pregnancy: Reexamining the Guidelines. National Academies Press; Washington (DC); 2009.
19. McEwen BS. Neurobiological and systemic effects of chronic stress. Chronic Stress. 2017;1. doi:10.1177/2470547017692328
18. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A. 2004;101(49):17312–17315. doi:10.1073/pnas.0407162101
