Original research

Maternal obesity, pregnancy weight gain, and birth weight and risk of colorectal cancer

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ABSTRACT

Objective Colorectal cancer (CRC) is a leading cause of cancer-related death worldwide. Obesity is a well-established risk factor for CRC, and fetal or developmental origins of obesity may underlie its effect on cancer in adulthood. We examined associations of maternal obesity, pregnancy weight gain, and birth weight and CRC in adult offspring.

Design The Child Health and Development Studies is a prospective cohort of women receiving prenatal care between 1959 and 1966 in Oakland, California (N=18 751 live births among 14 507 mothers). Clinical information was abstracted from mothers' medical records 6 months prior to pregnancy through delivery. Diagnoses of CRC in adult (age ≥18 years) offspring were ascertained through 2019 by linkage with the California Cancer Registry. We used Cox proportional hazards models to estimate adjusted HR (aHR); we examined effect measure modification using single-referent models to estimate the relative excess risk due to interaction (RERI).

Results 68 offspring were diagnosed with CRC over 738 048 person-years of follow-up, and half (48.5%) were diagnosed younger than age 50 years. Maternal obesity (≥30 kg/m^2) increased the risk of CRC in offspring (aHR 2.51, 95% CI 1.05 to 6.02). Total weight gain modified the association of rate of early weight gain (RERI −4.37, 95% CI −9.49 to 0.76), suggesting discordant growth from early to late pregnancy increases risk. There was an elevated association with birth weight (≥4000 g: aHR 1.95, 95% CI 0.8 to 4.38).

Conclusion Our results suggest that in utero events are important risk factors for CRC and may contribute to increasing incidence rates in younger adults.

Significance of this study

What is already known on this subject?

- Obesity is a well-established risk factor of colorectal cancer (CRC), and several studies suggest fetal or developmental origins of obesity may underlie its effect on cancer in adulthood.

What are the new findings?

- In a population-based cohort of more than 18 000 mother–child dyads, maternal obesity increased the risk of CRC in adult offspring.
- Trajectories of pregnancy weight gain, which may be markers of fetal growth and development, similarly increased risk.

How might it impact on clinical practice in the foreseeable future?

- Given increasing population prevalence of maternal obesity and pregnancy weight gain, the burden of CRC is likely to continue increasing in the future.

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality worldwide.[1] Incidence and mortality rates have evolved strikingly over the past several decades. For example, in many high-income countries, incidence and mortality rates have declined or stabilised in older adults but nearly doubled in younger adults.[2] Low-income and middle-income countries have experienced rapid increases in incidence and mortality rates across all ages.[1] As a result of these temporal trends, by 2030, the global burden of CRC is expected to increase by 60% to more than 2.2 million new diagnoses and 1.1 million deaths.[1]

Obesity is a well-established risk factor of CRC,[3–5] and several studies suggest fetal or developmental origins of obesity may underlie its effect on cancer in adulthood.[6 7] The concept that the intrauterine environment plays a major role in establishing a growth and health trajectory that extends over the life course of offspring is well supported by epidemiological and experimental studies.[8–14] For example, maternal obesity predisposes infants to obesogenic growth patterns that persist across the life course[14 15]; pregnancy weight gain may have lasting effects on risks of obesity in offspring[9 12 13 16–19]; and birth size is consistently associated with measures of obesity in later life.[20 21] These factors are also independently associated with chronic diseases in adulthood, including cardiovascular disease and diabetes.[22 23]

We examined associations of maternal obesity, pregnancy weight gain, and birth weight and CRC in adult offspring of the Child Health and Developments Studies (CHDS), a population-based cohort of more than 18 000 mother–child dyads receiving prenatal care in the Kaiser Foundation Health Plan (Oakland, California, USA) and followed for 60 years. We hypothesised that these factors may be markers of fetal growth and development and that increase the risk of CRC in adulthood.

MATERIALS AND METHODS

Study population

Established in 1959, the CHDS recruited nearly all (98%) pregnant women receiving prenatal care from the Kaiser Foundation Health Plan (Oakland, California, USA) between June 1959 and September 1966, with deliveries through June 1967 (N=18 751 live births excluding neonatal deaths among 14 507 mothers). At enrolment, mothers reported demographic and health-related information during in-person interviews. Clinical information, including prenatal visits, diagnosed conditions and prescribed medications, was abstracted from mothers' medical records beginning 6 months prior to pregnancy through labour and delivery. Additional details of the CHDS and methodology are available elsewhere.[24–26]

We monitor CHDS participants by annual linkage to the California Department of Motor Vehicles, California Department of Vital Statistics and California Cancer Registry. Mothers and their families are matched to these sources using an accumulated name and address history, routinely identifying more than 80% of families.

Primary outcome

We ascertained incident diagnoses of CRC in adult (age ≥18 years) offspring through 2019 by linkage with the California Cancer Registry (International Classification of Disease in Oncology, third edition, codes C18.0–1, C19.9, C20.9). The California Cancer Registry is one of the largest cancer registries in the USA and meets the highest quality data standards set by the National Program of Cancer Registries and US Centers for Disease Control and Prevention.[27 28] We used a rigorous protocol to verify cases, comparing fixed (eg, birth date, sex, race) and changeable (eg, address) identifiers by manual review.

Exposures

Maternal body mass index

We used height and weight reported by mothers during in-person interviews at enrolment or recorded at the first prenatal visit to measure body mass index (BMI, kg/m^2). Weight was adjusted to compensate for variation in the timing of measurement by regressing weight on gestational age using the locally weighted scatterplot smoothing technique.[29] Adjusted weight was then imputed as the fitted mean weight at day 104 of gestation (median value for day of interview) plus the residual from the regression procedure.[30–32] We categorised BMI as underweight (<18.5 kg/m^2) or healthy (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30 kg/m^2).

Pregnancy weight gain

Using weight recorded at prenatal visits, we measured pregnancy weight gain as (1) rate of early weight gain, or pounds gained per week through 32 weeks' gestation; and (2) total weight gain, or the difference between the last predelivery weight and weight recorded at the first prenatal visit. Last predelivery weight was measured at a mean 272 days' gestation (IQR 265–282 days). We used these two measures of pregnancy weight gain based on evidence that the timing of weight gain has different consequences for fetal growth and development.[33–36]

Birth weight

At the time of delivery, birth weight was measured using standardised scales maintained by CHDS research staff. We categorised birth weight using definitions of the US Centers for Disease Control and Prevention and WHO: low (<2000 g), average (2000–3999 g) and high (≥4000 g or macrosomia). In sensitivity analyses, we used birth weight-for-gestation z-scores, calculated by subtracting individual birth weight from the mean for each gestational week and dividing the difference by the SD of the mean.[30] We examined z-scores continuously and at or above the 90th percentile.

Other covariates

Other covariates included race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, other), age at pregnancy, parity at pregnancy (primiparous, multiparous), maternal education (less than high school, high school or trade school, some college or more), total family income (above or below the median, adjusted for 1960 dollars) and gestational age (<37 weeks, ≥37 weeks). Gestational age was calculated by subtracting the date of the last menstrual period from the date of delivery (range 20–42 weeks). We also measured family history of CRC, defined as a mother or father ever diagnosed with CRC, by linking maternal and paternal records to the California Cancer Registry.

Statistical analysis

We used Cox proportional hazards models to estimate HRs and their 95% CIs for associations of maternal BMI, pregnancy weight gain, and birth weight and CRC in offspring. To account for the correlation between observations from siblings (n=4244), we used robust sandwich estimators. Follow-up time was accrued from date of birth through date of CRC diagnosis, date of death or date of last contact (range 6 months to 58.5 years). Because participants are regularly monitored for residence and vital status, we used year of last contact from all sources to create date of last contact. We assessed the proportional hazards assumption in all models by visually examining plots of the survival function versus survival time, as well as log(−log(survival)) versus log(-survival time). The assumption was not violated in any model.

We explored non-linear relationships between pregnancy weight gain, including rate of early weight gain and total weight gain, and CRC in offspring using restricted cubic splines, with three knots at the 10th, 50th and 90th percentiles.[37] The relationship did not deviate from linearity, and model fit was similar when pregnancy weight gain was modelled as a continuous measure versus restricted cubic spline (assessed via Akaike information criterion).[38] Therefore, we modelled rate of early weight gain and total weight gain as continuous measures, and to facilitate interpretation, we report HRs and their 95% CIs at the median of each quartile of the rate of early weight gain (0.40, 0.71, 0.93 and 1.25 pounds/week) and total weight gain (12, 18, 23 and 29 pounds).

We used a theory-based causal model[39] (figure 1) to guide selection of potential confounders and to identify a minimally sufficient adjustment set for each model.[40] Adjustment sets included race/ethnicity (maternal BMI); race/ethnicity, gestational age and maternal BMI (rate of early weight gain); race/ethnicity, gestational age, maternal BMI and rate of early weight gain (total weight gain); and race/ethnicity, gestational age, maternal BMI, rate of early weight gain and total weight gain (birth weight).

We examined modification of high rate of early weight gain (quartile 4 vs quartile 1) by total weight gain (below vs at or above median) on both additive and multiplicative scales. First, we used single-referent models to estimate the relative excess risk due to interaction (RERI) and corresponding 95% CI.[41] Second, we compared nested models with and without a high rate of early weight gain*total weight gain product term using a

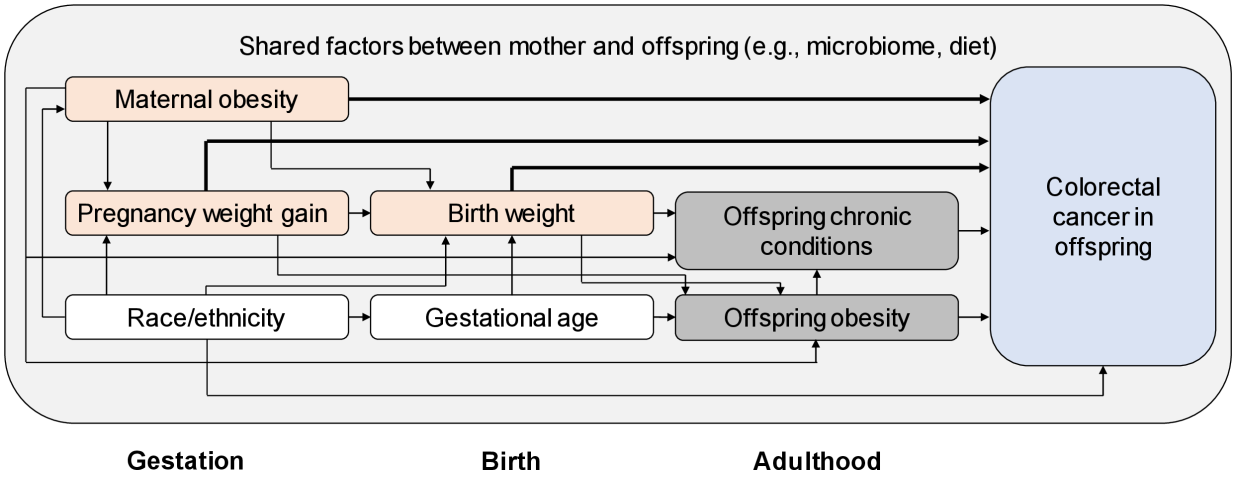

Figure 1 Theory-based causal model illustrating the relationships among maternal body mass index, pregnancy weight gain, birth weight and colorectal cancer in adult offspring. Bold lines illustrate the associations modelled in this study; shading denotes the following: orange, independent variable; blue, dependent variable; white, measured covariate; grey, unmeasured covariate.

likelihood ratio test. We also estimated stratum-specific HRs to evaluate heterogeneity on a multiplicative scale.

Sensitivity analyses

Missingness ranged from 0.0% (birth weight) to 15.6% (rate of early weight gain). In a sensitivity analysis, we used multiple imputation by fully conditional specification[42] to estimate associations of maternal BMI, pregnancy weight gain, and birth weight and CRC in offspring. Fully conditional specification relaxes assumptions of joint multivariate normality and linearity and is well suited for imputation of both categorical and continuous variables. Results in the imputed dataset did not materially differ from the complete case analysis and are reported in online supplemental table 1.

About 5%–10% of CRC is due to underlying genetic predisposition (eg, Lynch syndrome), and the proportion is increased in persons diagnosed at a younger age.[43] We conducted an additional sensitivity analysis to estimate associations of maternal BMI, pregnancy weight gain, and birth weight and CRC in offspring with no family history of CRC (n=17 686).

Quantitative bias analysis

Associations of maternal BMI, pregnancy weight gain, and birth weight and CRC in offspring may be confounded by shared factors between mother and offspring (eg, diet, microbiome), which were not measured in the CHDS. We conducted a probabilistic bias analysis[44 45] to model error from unmeasured confounding. Additional detail is provided in the online supplemental file.

Patient and public involvement

The CHDS routinely engages its own cohort members in community-based participatory research. We meet quarterly with our Participant Advisory Council (PAC), a racially and sex diverse representation of the cohort, to develop research questions, resolve ethical issues related to study participation, design innovative recruitment methods and improve dissemination of findings. At the beginning of this study, we met with PAC members to provide an overview of CRC and to discuss study concepts, rationale and approach; they asked questions and offered feedback. Future meetings will be scheduled for presenting and interpreting ongoing results, and for discussing plans to optimise communication of findings to the larger cohort. Results will be disseminated through the CHDS website, social media platforms and email newsletter.

All analyses were conducted in SAS V.9.4 (SAS Institute).

RESULTS

Table 1 shows the characteristics of 18 751 offspring. Most (48.2%) were born in the early 1960s. About one-third were racial/ethnic minorities (23.5% black, 3.3% Hispanic, 3.9% Asian, 2.9% other), and half (52.1%) were in families with an annual income less than the median.

Over 738 048 person-years of follow-up, 68 offspring were diagnosed with CRC (table 2). Offspring were diagnosed in 1986–2017, between ages 18 and 56 years, and about half (48.5%) were diagnosed before age 50 years. The majority were diagnosed with regional (44.1%) or distant (25.0%) stage disease and with tumours in the distal colon (42.4%) or rectum (28.8%). Nearly 20% had a family history of CRC.

Table 3 illustrates the relationships among maternal BMI, pregnancy weight gain and birth weight. For example, a higher proportion of obese (16.2%) mothers had offspring weighing ≥4000 g at birth compared with underweight/healthy weight (7.4%) and overweight (11.0%) mothers. The rate of early weight gain and total weight gain also differed by maternal BMI. Adjusted HRs from main effects models estimating associations of maternal BMI, pregnancy weight gain, and birth weight and CRC in offspring are reported in table 4.

Maternal overweight (aHR 2.12, 95% CI 1.18 to 3.82) and obesity (aHR 2.51, 95% CI 1.05 to 6.02) were associated with CRC in offspring compared with maternal underweight/healthy weight (table 4). Incidence rates of CRC were 16.2 per 100 000 (95% CI 6.5 to 33.5), 14.8 (95% CI 8.8 to 23.5) and 6.7 per 100 000 (95% CI 4.6 to 9.5) in offspring of obese, overweight and underweight/healthy weight mothers, respectively.

The rate of early weight gain was not associated with CRC in offspring (aHR 1.17, 95% CI 0.71 to 1.95; table 4), although the association was elevated in the highest quartile (1.25 pounds per week: aHR 1.22, 95% CI 0.64 to 2.31). Total weight gain was associated with CRC in offspring (aHR 1.03, 95% CI 0.99 to 1.08). For example, risk was increased at the median of the third and fourth quartiles: 23 (aHR 2.09, 95% CI 0.77 to 5.65) and 29 (aHR 2.54, 95% CI 0.72 to 8.88) pounds, respectively.

Table 1 Characteristics of 18 751 offspring* in the Child Health and Development Studies, 1959–1967

	Male (n=9582)	Female (n=9169)	Total (N=18 751)
	n (%)	n (%)	n (%)
Offspring characteristics			
Year of birth			
1959–1961	2887 (30.1)	2716 (29.6)	5603 (29.9)
1962–1964	4636 (48.4)	4409 (48.1)	9045 (48.2)
1965–1967	2059 (21.5)	2044 (22.3)	4103 (21.9)
Race/ethnicity			
Non-Hispanic white	6266 (66.4)	5999 (66.4)	12 265 (66.4)
Non-Hispanic black	2224 (23.6)	2108 (23.3)	4332 (23.5)
Hispanic	305 (3.2)	308 (3.4)	613 (3.3)
Asian	375 (4.0)	344 (3.8)	719 (3.9)
Other	262 (2.8)	281 (3.1)	543 (2.9)
Missing	*150*	*129*	*279*
Gestational age			
<37 weeks	794 (8.4)	666 (7.4)	1460 (7.9)
≥37 weeks	8622 (91.6)	8371 (92.6)	16 993 (92.1)
Missing	*166*	*132*	*298*
Maternal characteristics†			
Maternal age at pregnancy (years)			
<20	830 (8.8)	847 (9.3)	1677 (9.0)
20–24	2863 (30.2)	2785 (30.7)	5648 (30.4)
25–29	2748 (29.0)	2632 (29.0)	5380 (29.0)
30–34	1721 (18.1)	1595 (17.6)	3316 (17.9)
35–39	1003 (10.6)	921 (10.1)	1924 (10.4)
≥40	326 (3.4)	306 (3.4)	632 (3.4)
Missing	*91*	*83*	*174*
Parity			
Primiparous	2940 (30.9)	2825 (31.0)	5765 (31.0)
Multiparous	6567 (69.1)	6285 (69.0)	12 852 (69.0)
Missing	*75*	*59*	*134*
Maternal education			
Less than high school	1458 (17.9)	1441 (18.4)	2899 (18.1)
High school or trade school	3132 (38.4)	3071 (39.1)	6203 (38.8)
Some college or college degree	3558 (43.7)	3335 (42.5)	6893 (43.1)
Missing	*1434*	*1322*	*2756*
Annual family income‡			
≤Median	3460 (51.4)	3433 (52.8)	6893 (52.1)
>Median	3267 (48.6)	3063 (47.2)	6330 (47.9)
Missing	*2855*	*2673*	*5528*

*Live births excluding neonatal deaths among 14 507 women
†Because mothers may have had more than one live birth during the study period, maternal characteristics are reported at the level of offspring
‡Median income adjusted to 1960 dollars=$6303

Table 2 Characteristics of 68 adult offspring diagnosed with colorectal cancer, by age at diagnosis

	Age 18–49 years (n=33)	Age 50–56 years (n=35)
	n (%)	n (%)
Sex		
Male	14 (42.4)	17 (48.6)
Female	19 (57.6)	18 (51.4)
Year of birth		
1959–1961	10 (30.3)	18 (51.4)
1962–1964	19 (57.6)	14 (40.0)
1965–1967	4 (12.1)	3 (8.6)
Race/ethnicity		
Non-Hispanic white	19 (57.6)	16 (50.0)
Non-Hispanic black	13 (39.4)	6 (18.8)
Hispanic	0 (0.0)	5 (15.6)
Asian	0 (0.0)	3 (9.4)
Other	1 (3.0)	2 (6.3)
Missing	*0*	*3*
Age at diagnosis (years)		
Median (IQR)	44 (40–48)	52 (51–53)
Year of diagnosis		
1980–1989	2 (6.1)	0 (0.0)
1990–1999	3 (9.1)	0 (0.0)
2000–2009	17 (51.5)	0 (0.0)
2010–2016	11 (33.3)	35 (100.0)
Stage at diagnosis		
Local	6 (18.2)	13 (39.4)
Regional	19 (57.6)	11 (33.3)
Distant	8 (24.2)	9 (27.3)
Missing	*0*	*2*
Tumour location		
Proximal colon	7 (21.9)	12 (35.3)
Distal colon	19 (59.4)	9 (26.5)
Rectum	6 (18.8)	13 (38.2)
Missing	*1*	*1*
Family history of CRC†		
No	27 (81.8)	29 (82.9)
Yes	6 (18.2)	6 (17.1)

*Family history of CRC defined as having a mother or a father ever diagnosed with CRC and ascertained by linking maternal and paternal records to the California Cancer Registry
†Stage at diagnosis defined by SEER summary stage and includes local (disease is confined to the large bowel), regional (disease is limited to nearby lymph nodes or other organs) and distant (systemic metastasis)
CRC, colorectal cancer.

There was an elevated association of high (≥4000 g) birth weight (aHR 1.95, 95% CI 0.86 to 4.38) compared with average (2000–3999 g) birth weight (table 4). Results were similar when birth weight was modelled using z-scores (continuous: aHR 1.32, 95% CI 0.99 to 1.78, p value 0.06; ≥90th percentile: aHR 1.46, 95% CI 0.62 to 3.45, p value 0.39).

Associations of maternal BMI, pregnancy weight gain, and birth weight and CRC were similar in the subgroup of offspring with no family history of CRC (online supplemental table 2).

Total weight gain modified the association between high rate of early weight gain (quartile 4 vs quartile 1) and CRC in offspring, and there was evidence of both additive and multiplicative interaction (table 5). Specifically, a high rate of early weight gain was associated with CRC in offspring in the strata of low total weight gain (aHR 4.78, 95% CI 1.45 to 15.74) but had the inverse association in the strata of high total weight gain (aHR 0.41, 95% CI 0.14 to 1.20). We observed a similar pattern of incidence rates by rate of early weight gain and total weight gain (table 5), suggesting discordant growth from early to late pregnancy increased risk.

DISCUSSION

In a population-based cohort of more than 18 000 mother–child dyads, maternal obesity increased risk of CRC in adult offspring. Trajectories of pregnancy weight gain, which may be markers of fetal growth and development, similarly increased risk. Half of cases were diagnosed younger than age 50 years,

Table 3 Pregnancy weight gain and birth weight by maternal body mass index

	Maternal body mass index		
	Underweight/healthy (n=12 223)	Overweight (n=3005)	Obese (n=1023)
Rate of early weight gain*			
Quartile 1	2119 (19.2%)	821 (34.6%)	407 (54.1%)
Quartile 2	2897 (26.2%)	479 (20.2%)	114 (15.2%)
Quartile 3	3079 (27.9%)	493 (20.8%)	106 (14.1%)
Quartile 4	2960 (26.8%)	583 (24.5%)	125 (16.6%)
Missing	*1168*	*629*	*271*
Total weight gain†			
Quartile 1	2204 (18.3%)	816 (27.7%)	447 (44.8%)
Quartile 2	3148 (26.2%)	661 (22.4%)	192 (19.2%)
Quartile 3	3345 (27.8%)	689 (23.4%)	168 (16.8%)
Quartile 4	3339 (27.7%)	779 (26.5%)	191 (19.1%)
Missing	*187*	*60*	*25*
Birth weight			
<2500 g	734 (6.0%)	147 (4.9%)	54 (5.3%)
2500–3999 g	10 586 (86.6%)	2527 (84.1%)	803 (78.5%)
≥4000 g	903 (7.4%)	331 (11.0%)	166 (16.2%)
Maternal race			
Non-Black	9859 (81.2%)	1919 (64.3%)	536 (52.8%)
Black	2287 (18.8%)	1068 (35.8%)	479 (47.2%)
Missing	*77*	*18*	*8*
Gestational age			
<37 weeks	886 (7.3%)	257 (8.6%)	113 (11.1%)
≥37 weeks	11 337 (92.8%)	2748 (91.5%)	910 (89.0%)

A total of 2500 missing maternal body mass index
*Rate of early weight gain (pounds/ week) quartiles: <0.58, 0.58–<0.81, 0.81–<1.05, ≥1.05
†Total weight gain (total pounds) quartiles: <15, 15–<20, 20–<25, ≥25

Table 4 Adjusted HRs for maternal BMI, rate of early pregnancy weight gain, total pregnancy weight gain, and birth weight and colorectal cancer in adult offspring

	Person-years	n	aHR*	95% CI	P value
Maternal BMI					0.02
Underweight/ healthy	477 430	32	1.00		
Overweight	121 235	18	2.12	1.18 to 3.82	
Obese	43 117	7	2.51	1.05 to 6.02	
Rate of early weight gain†	625 752	50	1.17	0.71 to 1.95	0.54
Quartile 1	–	–	1.07	0.87 to 1.31	
Quartile 2	–	–	1.12	0.78 to 1.61	
Quartile 3	–	–	1.16	0.72 to 1.86	
Quartile 4	–	–	1.22	0.65 to 2.31	
Total weight gain†	689 740	60	1.03	0.99 to 1.08	0.15
Quartile 1	–	–	1.47	0.88 to 2.47	
Quartile 2	–	–	1.78	0.82 to 3.88	
Quartile 3	–	–	2.09	0.77 to 5.65	
Quartile 4	–	–	2.54	0.72 to 8.88	
Birth weight					0.17
<2500 g	42 973	3	0.44	0.06 to 3.15	
2500–3999 g	631 307	56	1.00		
≥4000 g	63 768	9	1.95	0.86 to 4.38	

*Adjusted HRs derived from main effects models; maternal BMI adjusted for race/ethnicity; rate of early weight gain adjusted for race/ethnicity, maternal BMI and gestational age; total weight gain adjusted for race/ethnicity, maternal BMI, rate of early weight gain and gestational age; birth weight adjusted for race/ethnicity, maternal BMI, rate of early weight gain and total weight gain
†aHRs and their 95% CIs at the median of each quartile of the rate of early weight gain (0.40, 0.71, 0.93 and 1.25 pounds/ week) and total weight gain (12, 18, 23 and 29 pounds)
aHR, adjusted HR; BMI, body mass index.

and these findings suggest in utero events may contribute to increasing incidence rates of CRC in younger adults.

Maternal obesity more than doubled the risk of CRC in offspring, suggesting the well-established relationship between obesity and CRC[4 46 47] may have origins in periods that begin before birth. This process may occur through fetal programming,[6] the concept that the maternal environment determines the risk of disease in later stages via developmental, genetic and epigenetic changes. For example, nutrients received in utero may lead to persistent adaptations in the structure and function of adipose tissue, appetite regulation and metabolism.[48 49] Excess exposure to insulin and growth hormone in utero may effect insulin sensitivity,[50 51] and high levels of maternal glucose are often accompanied by episodes of fetal hyperinsulinaemia.[52] Epigenetic processes may also play a role[53]; several studies have now identified links between maternal obesity and methylation in placenta, cord blood and child saliva at several genes involved in energy metabolism (eg, *PPARG*).[54–56]

Trajectories of pregnancy weight gain were also associated with CRC in offspring, implicating discordant fetal growth as a possible risk factor. Incidence rates of CRC in offspring were highest when the rate of early weight gain was discordant from total weight gain, and the same pattern held regardless of whether the rate of early weight gain was higher or lower than total weight gain. Like maternal obesity, pregnancy weight gain may increase the risk of obesity in offspring,[9 12 13 16–19] but the modification of rate of early weight gain by total weight gain suggests the timing of weight gain may be most important. Specifically, and independent of maternal obesity, early versus late weight gain may have different consequences for placental and fetal development,[33 35 36] which may translate into different long-term risks of chronic disease and cancer.[34] Weight gain in early pregnancy reflects an increase in maternal fuels (eg, glucose, insulin),[57] whereas weight gain in late pregnancy reflects fetal growth and fluid expansion.[58] The hormonal milieu of mother and fetus also differs substantially in early and late pregnancy.[59] For example, hormone levels in cord blood differ by timing of pregnancy weight gain. Early weight gain is strongly associated with glucose and insulin, whereas weight gain in late pregnancy correlates with hormones related to fetal adiposity.[57]

Another possibility is that the timing of pregnancy weight gain reflects other in utero exposures that increase the risk of CRC in offspring. For example, in the Helsinki Birth Cohort,[60] the risk of CRC in offspring increased as the placental surface became longer and more oval.[61] Placental shape and surface area are determined by events and exposures in very early pregnancy, such as maternal smoking.[62–64] A longer and more oval placental surface may increase the risk of oxidative damage to the fetus[65] during early pregnancy, corresponding to the time when the colon differentiates from the rectum.[66] Collectively, these findings suggest discordant weight gain over the course of pregnancy may contribute to CRC in offspring via two mechanisms: (1) establish obesogenic growth patterns that persist into adulthood; or (2) programme the sensitivity of developing fetal tissue in the GI tract that impacts pathology later in life.

We observed an elevated risk of CRC in offspring associated with birth weight. Birth weight is correlated but not redundant with maternal obesity and pregnancy weight gain and therefore may have an independent association with CRC. European studies linking birth records with cancer registries report no or only modest associations between birth weight and CRC.[61 67–69]

Table 5 Additive and multiplicative interaction between high rate of early pregnancy weight gain (quartile 4 vs quartile 1) and total pregnancy weight gain (at or above vs below median)

Total weight gain*	Rate of early weight gain†	Person- years	n	Incidence rate (95% CI) per 100 000‡	Single-referent aHR§ (95% CI)	Stratified aHR§ (95% CI)
Below median	Q1	127 875	8	6.2 (2.7 to 12.2)	1.00	1.00
	Q4	17 407	4	21.3 (5.8 to 54.7)	4.09 (1.34 to 12.48)	4.78 (1.45 to 15.74)
Above median	Q1	20 602	5	26.2 (8.5 to 61.3)	2.77 (1.19 to 6.45)	1.00
	Q4	137 509	12	8.2 (4.1 to 14.6)	1.49 (0.62 to 3.60)	0.41 (0.14 to 1.20)

Additive interaction evaluated by estimating the relative excess risk due to interaction (RERI −4.37, 95% CI −9.49 to 0.76); multiplicative interaction evaluated by comparing nested models with and without a high rate of early weight gain*total weight gain product term with the likelihood ratio test (p value: 0.01).
*Total weight gain median: 20 pounds
†Rate of early weight gain quartile 1: <0.58 pounds/ week, and quartile 4: ≥1.05 pounds/week
‡Incidence rates and 95% CIs were calculated based on the discrete probability distribution for a binomial parameter
§Adjusted for race/ethnicity, maternal BMI and gestational age
aHR, adjusted HR; BMI, body mass index; Q, quartile.

Only one of these studies reported an association between birth weight and CRC, and in that study, low birth weight increased the risk in men only.[70] Studies relying on self-reported birth weight conflict: some show high birth weight is associated with CRC,[71 72] one shows no association[73] and yet another shows a J-shaped relationship.[74] Finally, Mendelian randomisation studies report no association between birth weight and CRC.[75 76] These prior studies were conducted across multiple generations and countries, and differences in maternal characteristics, such as obesity, in these studies may explain inconsistent results.

Half of offspring diagnosed with CRC in our study were diagnosed younger than age 50 years, and our findings suggest maternal obesity and pregnancy weight gain may contribute to increasing incidence rates of CRC in younger (age <50 years) adults. Incidence rates of early-onset CRC have increased across successive generations,[77] implicating exposures increasingly prevalent in early life—critical periods of growth and development, such as gestation, infancy and childhood.[78] This is consistent with a well-established literature on the consequences of early life exposures for several adult cancers.[79 80] Given population trends in maternal obesity, which has multiplied in prevalence by nearly six since the 1960s,[81–83] we may see a growing burden of early-onset CRC for decades to come. Other factors in early life, including environmental toxins, medications, chronic conditions and microbiome, and that are likely related to maternal obesity, may also contribute to early-onset cancers.[84 85]

A strength of our study is the multigenerational cohort, allowing us to examine associations between maternal characteristics and CRC in offspring in a large, prospective sample over 60 years. Studying exposures in the earliest periods of life is challenging and requires detailed information on both mothers and offspring, collected prospectively over generations, and the ability to systematically ascertain cancer diagnoses. The CHDS is one of the few studies in the USA to prospectively collect health information across multiple generations, avoiding pitfalls of recall bias and measurement error.

There were some limitations of our study. Associations of maternal obesity and pregnancy weight gain and CRC in offspring may be confounded by factors shared between mother and child, such as diet and microbiome, and that were not measured in the CHDS. Similarly, we did not measure BMI of offspring through their adulthood. We addressed unmeasured confounding by conducting a probabilistic bias analysis; for maternal BMI, the median bias–corrected association from all simulations was slightly attenuated but similar to the observed association. These results suggest an unmeasured confounder could only explain the *entire* observed association if the confounder was a strong predictor of CRC and its distribution substantially differed between exposed and unexposed offspring, scenarios that are very unlikely. Several studies[18 19] also suggest associations of maternal obesity and pregnancy weight gain persist in sibling-controlled analyses, supporting results of our bias analysis. Finally, gestational diabetes, likely related to both maternal obesity and pregnancy weight gain, may also contribute to the risk of CRC in offspring. Screening for gestational diabetes was not part of routine clinical practice in the 1950s and 1960s, and very few (<1.0%) mothers enrolled in the CHDS had pre-existing diabetes. This precluded meaningful analyses of its association with CRC; ongoing and future studies of recent birth cohorts may examine gestational diabetes as a risk factor because it can now be ascertained from several sources, including birth certificates.[86]

In summary, our results provide compelling evidence that in utero events are important risk factors of CRC and may contribute to increasing incidence rates in younger adults. There may also be other as yet unknown exposures during gestation and early life that give rise to this disease and warrant further study.

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