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Association of birthweight with diabetes, hypertension, and ischemic heart disease in young adulthood: a retrospective cohort study

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Abstract

Birthweight has been associated with diabetes in a reverse J-shape (highest risk at low birthweight and moderately high risk at high birthweight) and inversely associated with hypertension in adulthood with inconsistent evidence for cardiovascular disease. There is a lack of population-based studies examining the incidence of cardiometabolic outcomes in young adults born with low and high birthweights. To evaluate the association between birthweight and diabetes, hypertension, and ischemic heart disease (IHD) in young adulthood, we conducted a retrospective cohort study of 874,904 singletons born in Ontario, Canada, from 1994 to 2002, identified from population-based health administrative data. Separate Cox regression models examined birthweight in association with diabetes, hypertension, and IHD adjusting for confounders. Among adults 18–26 years, the diabetes incidence rate was 18.15 per 100,000 person-years, hypertension was 15.80 per 100,000 person-years, and IHD was 1.85 per 100,000 person-years. Adjusted hazard ratios (AHR) for the hazard of diabetes with low (<2500g) and high (>4000g), compared with normal (2500–4000g) birthweight, were 1.46 (95% CI 1.28, 1.68) and 1.09 (0.99, 1.21), respectively. AHR for hypertension with low and high birthweight were 1.34 (1.15, 1.56) and 0.86 (0.77, 0.97), respectively. AHR for IHD with low and high birthweight were 1.28 (0.80, 2.05) and 0.97 (0.71, 1.33), respectively. Overall, birthweight was associated with diabetes in young adults in a reverse J-shape and inversely with hypertension. There was insufficient evidence of an association with IHD. Further evidence is needed to understand the causal mechanisms between birthweight and cardiometabolic diseases in young adults.

Introduction

Globally, 15% of all births are low birthweight (<2500g).[1] High birthweight (>4000g) represents 0.5%–20% of births globally and has increased by 15%–25% in the last two decades.[2,3] Birthweight is a strong predictor for neonatal morbidity and mortality in addition to chronic diseases later in life.[4] Several systematic reviews, mostly from small clinical studies or contained cohorts with limited diversity, have examined the association between birthweight and cardiometabolic disease risk later in life.[5–10] Evidence from most of these reviews suggests that low birthweight is associated with higher risk of diabetes and hypertension, while high birthweight is associated with higher risk of diabetes (but to a lesser extent than low birthweight) and lower risk of hypertension.[5–8] The association between birthweight and diabetes as well as hypertension reported in the reviews is consistent with more recent population-based studies.[11,12] Evidence on the association between birthweight and cardiovascular disease (CVD), primarily ischemic heart disease (IHD), is inconsistent with one review finding an inverse association and another finding a reverse J shape association (high risk at low and high birthweight but higher at low birthweight) where both low and high birthweight were associated with CVD risk.[5,10] More recent, larger cohort studies have shown an inverse association between birthweight and CVD.[13,14]

Chronic diseases have been rising in prevalence worldwide and have been recognized as a public health priority.[15] However, there is a lack of population-based studies examining the incidence of cardiometabolic conditions, including diabetes, hypertension, and IHD, in young adults with low and high birthweights. Young adulthood may represent an earlier life stage where opportunities for preventive strategies for cardiometabolic conditions may be applied. Further, it has been suggested that the shape of the association between birthweight and cardiometabolic disease may differ by sex,[5] but more research is needed to understand any potential sex differences. Potential effect modifiers including neighborhood income, caesarean section, maternal history of cardiometabolic conditions, and maternal age may also warrant further investigation. Lastly, pregnancy risk (a composite variable comprised of caesarean section, maternal history of cardiometabolic conditions, and maternal age) may be an important variable to investigate as having one or more of these factors increases maternal and fetal health risks.

The objectives of this study were to evaluate the separate associations between low and high birthweight with diabetes, hypertension, and IHD in young adulthood and to assess whether these associations were modified by sex, neighborhood income and a summary measure of pregnancy risk.

Methods

Study population and design

We conducted a retrospective cohort study of approximately 900,000 singletons born in Ontario, Canada, from 1994 to 2002 using population-based health administrative data from ICES. ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without requiring individual participant consent, for the purpose of health system evaluation and improvement.[16] We used the MOMBABY dataset from ICES, which is derived from hospital discharge abstracts, to identify maternal-newborn records for all hospital births (approximately 98% of births in Ontario).[17,18] We also used ICES data to identify hospitalizations, emergency department visits, outpatient physician visits, and other sociodemographic characteristics. Datasets were linked deterministically using a unique encoded identifier. The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board.

For inclusion in this study, we defined the cohort as singleton live births occurring in Ontario between 1994 and 2002. We investigated births from 1994 because this allowed for two-years lookback time (to 1992 based on data availability) to obtain the history of mother's cardiometabolic conditions. We also excluded 122 young adults missing birthweight and 23 young adults missing maternal age at delivery. Since we were interested in adult-onset diagnoses, for the analysis with diabetes as the outcome, we excluded 6,407 young adults with a diagnosis of diabetes before the age of 18. It is likely that most of the young adults included in this analysis have type 2 diabetes since most diagnoses for type 1 diabetes occur between 10 and 16 years.[19] For the analysis with IHD as the outcome, we excluded 436 young adults with a diagnosis of IHD before the age of 18. Individuals with hypertension were already restricted by ICES to be at least 20 years of age and older due to issues defining hypertension in young people. A flow chart of participant inclusion and exclusion are provided in Supplementary Fig S1.

Ascertainment of birthweight

The primary exposure was birthweight, and it was identified from the MOMBABY dataset. Birthweight was analyzed as a categorical variable with three groups defined *a priori*: low (<2500g), normal (2500g–4000g; used as the reference group), and high (>4000g). We chose to examine categorical variables instead of a continuous birthweight variable because the categorical cut-offs are often used clinically and have been traditionally used in the literature especially since evidence shows a nonlinear association between birthweight and some cardiometabolic outcomes.[5] Further, the specification allows for comparison between our study and others. Birthweight obtained from hospital records (from which MOMBABY is derived) had predictive validity compared to corresponding figures reported by Statistics Canada.[20]

Ascertainment of diabetes, hypertension, and IHD

The study cohort was followed up for the earliest adult-onset diagnosis of diabetes, hypertension or IHD from 2012 to 2020 (age at diagnosis between 18 and 26 years). Diabetes was identified using an ICES-derived cohort called Ontario Diabetes Dataset (ODD) using a validated linked data algorithm. Diabetes was defined using International Classification of Diseases (ICD) codes (ICD-9: 250; ICD-10: E10, E11, E13, E14) from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) to capture hospital admissions and codes from OHIP to capture outpatient physician visits (OHIP: 250).[21,22] Hypertension was identified using an ICES-derived cohort called the Ontario Hypertension Dataset (HYPER) using a validated linked data algorithm which is restricted to individuals aged 20 years and older due to issues defining hypertension in young people. Hypertension was defined using ICD codes (ICD-9: 401–405; ICD-10: I10–I13, I15) from CIHI-DAD and OHIP codes (OHIP: 401–405).[21,23] IHD was identified using ICD codes (ICD-9: 410–414; ICD-10: I20–I25) from CIHI-DAD and National Ambulatory Care Reporting System to capture emergency department visits. IHD was also identified using OHIP codes (OHIP: 410, 412, 413) as previously validated.[24]

Confounding variables

Confounding variables were selected *a priori* guided by previous literature and a directed acyclic graph. The directed acyclic graph is provided in Supplementary Fig S2. We considered maternal, perinatal, young adult, and sociodemographic characteristics hypothesized to be associated with birthweight and the aforementioned diseases, but not on the causal path between them.[7,25,26] The included confounders were maternal characteristics (maternal age, maternal history of IHD, maternal history of stroke, maternal history of diabetes, maternal history of hypertension), perinatal characteristics (gestational diabetes, gestational hypertension, and pre-eclampsia/eclampsia), young adult sex, and neighborhood income quintile (referred to as neighborhood income throughout for brevity). Maternal history of cardiometabolic outcomes excluded the pregnancy period. The operationalization of variables, including the ICD codes where applicable, is provided in Supplementary Table S1.

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Statistical analysis

Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals for the associations between birthweight and incident diabetes, hypertension, and IHD at ages 18-26 years among persons without a prior diagnosis of the condition being examined at the beginning of the age range. Individuals with incident diabetes or IHD diagnosed prior to 18 years were excluded from the study; however, hypertension prior to age 20 could not be defined in the administrative data due to lack of a validated algorithm in the younger age group. Age to diagnosis (or censoring) was used as the Cox model time scale. Cause-specific hazard models were used, where individuals were censored at death, emigration, or the study end date, whichever came first. Unadjusted and adjusted analyses (adjusted for maternal age, maternal history of IHD, maternal history of stroke, maternal history of diabetes, maternal history of hypertension, gestational diabetes, gestational hypertension, pre-eclampsia/eclampsia, young adult sex, and neighborhood income) were conducted. The proportional hazards assumption was assessed through the Supremum Test and was met for the models.[27]

The potential multiplicative interactions between birthweight and sex, neighborhood income, caesarean section, maternal history of cardiometabolic conditions, and maternal age, were examined in association with diabetes, hypertension, and IHD separately. We used a p-value threshold of < 0.05 to indicate evidence of effect modification. Stratified analyses were conducted when evidence of effect modification with birthweight was observed. As it has been suggested that the shape of the association between birthweight and cardiometabolic disease may differ by sex, we included analyses stratified by sex to ascertain potential sex differences. We also conducted analyses stratified by a composite variable called 'pregnancy risk' for ease of interpretation where low-risk pregnancy was defined as having no caesarean section, no maternal history of cardiometabolic conditions, and maternal age < 35 years while. High-risk pregnancy defined as having had one of: c-section, maternal history of cardiometabolic conditions or maternal age ≥ 35 years. Lastly, separate Cox models were constructed to estimate the association between *continuous* birthweight and the hazard of each outcome as well as the cumulative incidence probability of each outcome (with splines).

Data were complete except for neighborhood income which had missingness of 0.42%. Due to the low proportion of missing data, complete case analyses were performed. All analyses were conducted using SAS, version 9.4. Lastly, we conducted sensitivity analysis to evaluate how strong an unmeasured confounder would have to be to explain away the observed associations using the E-value formula $E_{HR} = HR + \sqrt{HR \times (HR - 1)}$.[28]

Results

Table 1 shows maternal, perinatal, young adult, and socio-demographic characteristics by birthweight. In the sample, infants born low birthweight were more likely than infants born normal weight to be female, born by caesarean section, or live in a neighborhood with lower average income and have mothers who were younger, had a history of CVD or hypertension, or gestational diabetes, hypertension, or pre-eclampsia/eclampsia. Infants born high birthweight were more likely than infants born normal weight to be male, born by caesarean section, or live in a neighborhood with higher average income and have mothers who were older, had a history of diabetes, or gestational diabetes or hypertension.

Associations between birthweight and diabetes

Between 18 and 26 years, 3401 people received a diagnosis of diabetes in 18.7 million person-years of follow up, yielding a crude incidence rate of 18.15 per 100,000 person-years. The incidence rates were 29.77 among those born low birthweight, 17.68 among those born normal birthweight, and 17.37 among those born high birthweight (Table 2).

In the adjusted analyses, birthweight was associated with the hazard of diabetes diagnosis in a reverse J-shape manner whereby low birthweight (adjusted HR 1.50, 95% CI 1.30, 1.72) and high birthweight (adjusted HR 1.11, 95% CI 1.00, 1.23) were associated with higher hazard of diabetes, compared with those born normal birthweight. The direction of the associations and overall conclusions were consistent between the adjusted and unadjusted analyses (Table 2). To understand the potential for bias due to unmeasured confounding, we calculated the E-value and for our observed HR of 1.50 between low birthweight and diabetes, the E-value was 2.4 with a lower limit of the 95% CI of 1.9. This suggests that a relatively strong unmeasured confounder would be needed to explain away the observed association. Whereas, for our observed HR of 1.11 for the association between high birthweight and diabetes, the E-value was 1.4 with a lower limit of the 95% CI of 1, suggesting possibly a higher risk for an unmeasured confounder to explain away that observed association. For continuous birthweight, there was a decreased hazard of diabetes diagnosis for every 100g increase in birthweight until 3200g from which point the hazard increased (Supplementary Table S2). For example, at 4000g, for every 100g increase in birthweight, the hazard of diabetes increased by 5%. Fig. 1 shows the adjusted predicted cumulative incidence probability and 95% confidence intervals (fitted by cubic spline) for diabetes across birthweight at age 26 years.

The p-vale for the interaction between pregnancy risk and birthweight was < 0.01. The stratified analyses revealed that among those born to a low-risk pregnancy, low birthweight was associated with greater hazard of diabetes; however, high birthweight was associated with lower hazard of diabetes and appeared protective. When there was high-risk pregnancy, low birthweight and high birthweight were both associated with higher hazard of diabetes (Table 3). When the interaction terms were evaluated separately for the components of the pregnancy risk variable, all components had a p value < 0.05 (stratified analyses are presented in Supplementary Table S3–5). There was insufficient evidence of effect modification by sex ($p = 0.07$) and neighborhood income ($p = 0.30$). Sex stratified results are presented in Supplementary Table S6 and show that for females, low birthweight and high birthweight (to a lesser extent) were associated with greater hazard of diabetes. For males, only low birthweight was associated with greater hazard of diabetes.

Associations between birthweight and hypertension

Between 20 and 26 years, 2983 people received a diagnosis of hypertension in 18.9 million person-years of follow up, yielding a crude incidence rate of 15.80 per 100,000 person-years. The incidence rates were 23.76 among those born low birthweight, 15.75 among those born normal birthweight, and 13.69 among those born high birthweight (Table 2).

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Table 1. Characteristics of study participants by birthweight in Ontario, Canada born between 1994 to 2002

	Mean (SD) or *N* (%)			
Characteristic	Overall *N* = 874,904	Less than 2500g *N* = 38,578 (4%)	Between 2500g and 4000g *N* = 713,032 (82%)	Greater than 4000g *N* = 123,294 (14%)
Maternal				
Age (years)	29.2 (5.4)	29.0 (6.0)	29.1 (5.5)	29.7 (5.2)
History of IHD	1194 (0.14%)	132 (0.34%)	898 (0.13%)	164 (0.13%)
History of stroke	1895 (0.22%)	137 (0.36%)	1505 (0.21%)	253 (0.21%)
History of diabetes	6869 (0.79%)	404 (1.0%)	5011 (0.70%)	1454 (1.2%)
History of hypertension	12,851 (1.5%)	1359 (3.5%)	9714 (1.4%)	1778 (1.4%)
Perinatal				
Gestational diabetes	24,964 (2.9%)	1390 (3.6%)	19,532 (2.7%)	4042 (3.3%)
Gestational hypertension	31,111 (3.6%)	3523 (9.1%)	23,301 (3.3%)	4287 (3.5%)
Pre-eclampsia/eclampsia	24,622 (2.8%)	4426 (12%)	17,376 (2.4%)	2820 (2.3%)
Caesarean section	164786 (19%)	10,413 (27%)	123945 (17%)	30,428 (25%)
High-risk pregnancy[a]	285257 (33%)	16,123 (42%)	221236 (31%)	47,898 (39%)
Young Adult				
IHD	349 (0.04%)	19 (0.05%)	283 (0.04%)	47 (0.04%)
Age (years) of diagnosis	20.9 (2.0)	20.3 (1.9)	20.9 (2.0)	20.6 (1.9)
Diabetes	3401 (0.39%)	235 (0.61%)	2708 (0.38%)	458 (0.37%)
Age (years) of diagnosis	21.0 (1.9)	21.1 (1.9)	21.1 (1.8)	20.9 (1.9)
Hypertension	2983 (0.34%)	189 (0.49%)	2430 (0.34%)	364 (0.30%)
Age (years) of diagnosis	21.5 (1.4)	21.4 (1.4)	21.5 (1.4)	21.5 (1.4)
Sex				
Female	425938 (49%)	19,769 (51%)	359927 (50%)	46,242 (38%)
Male	448966 (51%)	18,809 (49%)	353105 (50%)	77,052 (62%)
Length of follow up (years)	21.6 (3.7)	20.1 (5.7)	21.6 (3.6)	21.6 (3.5)
Sociodemographic				
Neighborhood income quintile[b]				
1	190190 (22%)	10,246 (27%)	156770 (22%)	23,174 (19%)
2	177548 (20%)	8355 (22%)	145478 (20%)	23,715 (19%)
3	177191 (20%)	7601 (20%)	143993 (20%)	25,597 (21%)
4	178093 (20%)	6868 (18%)	144588 (20%)	26,637 (22%)
5	148218 (17%)	5333 (14%)	119586 (17%)	23,299 (19%)
Missing	3664 (0.42%)	175 (0.45%)	2617 (0.37%)	872 (0.71%)

[a]High risk pregnancy defined as having had one of: c-section, maternal history of cardiometabolic conditions or maternal age ≥ 35 years. Low risk pregnancy defined as: no c-section, no maternal history of cardiometabolic conditions, and maternal age < 35 years.
[b]Quintile 1 refers to the lowest neighborhood income quintile and quintile 5 refers to the highest neighborhood income quintile

Table 2. Association between categorical birthweight and hazard of diabetes, hypertension, or IHD attained between 18-26 years in Ontario, Canada from 2012 to 2020

				Hazard Ratio (95% CI)	
Birthweight	Cases	Risk[a]	Rate[b]	Unadjusted	Adjusted[c]
Diabetes					
Less than 2500g	235	613	29.77	1.67 (1.46, 1.90)	1.50 (1.30, 1.72)
2500–4000g	2708	382	17.68	Referent	Referent
Greater than 4000g	458	375	17.37	1.01 (0.91, 1.11)	1.11 (1.00, 1.23)
Overall	3401	391	18.15	–	–
Hypertension					
Less than 2500g	189	490	23.76	1.49 (1.28, 1.73)	1.35 (1.16, 1.57)
2500–4000g	2430	341	15.75	Referent	Referent
Greater than 4000g	364	295	13.69	0.90 (0.80, 1.00)	0.87 (0.78, 0.97)
Overall	2983	341	15.80	–	–
IHD					
Less than 2500g	19	49	2.39	1.29 (0.81, 2.06)	1.27 (0.79, 2.04)
2500–4000g	283	40	1.84	Referent	Referent
Greater than 4000g	47	38	1.77	0.98 (0.72, 1.34)	0.97 (0.71, 1.31)
Overall	349	40	1.85	–	–

[a]Crude cumulative incidence per 100,000 population.
[b]Crude incidence rate per 100,000 person years.
[c]Adjusted for young adult sex, neighborhood income, perinatal characteristics (gestational diabetes, gestational hypertension, pre-eclampsia/eclampsia), and maternal characteristics (maternal: age, IHD, stroke, diabetes, and hypertension).

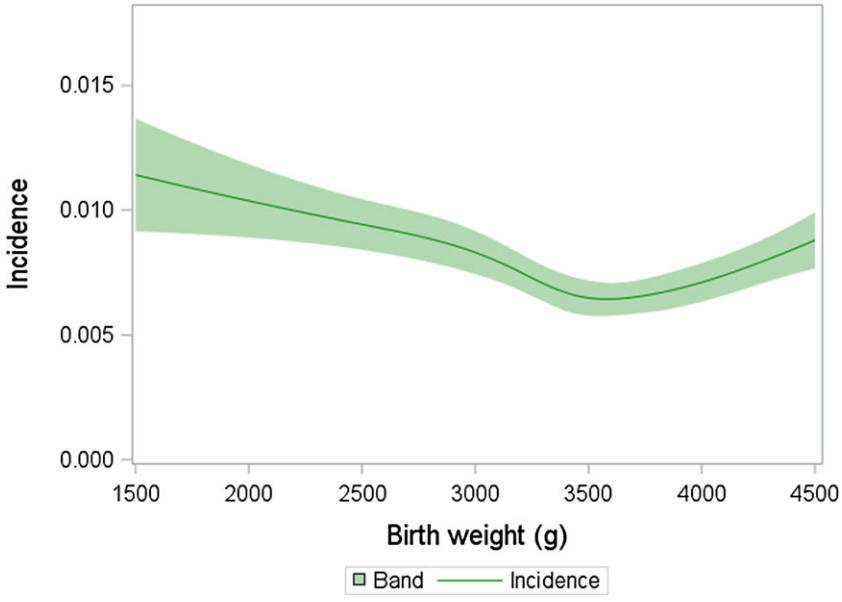

Figure 1. The adjusted predicted cumulative incidence probability and 95% confidence intervals (fitted by cubic spline) for diabetes across birthweight at the attained age of 26 years.

Birthweight was inversely associated with the hazard of hypertension whereby low birthweight (adjusted HR 1.35, 95% CI 1.16, 1.57) was associated with higher hazard of hypertension, compared with those born normal birthweight and high birthweight (adjusted HR 0.87, 95% CI 0.78, 0.97) was associated with lower hazard of hypertension. The direction of the associations and overall conclusions were consistent between the adjusted and unadjusted analyses (Table 2). Further, the E-value was 2.4 with a lower limit of the 95% CI of 1.6, suggesting a relatively strong unmeasured confounder would be needed to explain away the observed association for low birthweight and hypertension. However, for the association between high birthweight and hypertension, the E-value was 1.6 with a lower limit of the 95% CI of 1.2, suggesting greater possibility for bias due to unmeasured confounding. For continuous birthweight, there was a decreased hazard of hypertension diagnosis for every 100g increase in

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Table 3. Association between birthweight and hazard of diabetes attained between 18 and 26 years by pregnancy risk in Ontario, Canada from 2012 to 2020

	Adjusted Hazard Ratio (95% CI)[a]	
Birthweight	Low-risk pregnancy[b]	High-risk pregnancy[c]
Diabetes		
Less than 2500g	1.58 (1.33, 1.89)	1.35 (1.08, 1.69)
2500–4000g	Referent	Referent
Greater than 4000g	0.91 (0.79, 1.05)	1.37 (1.18, 1.59)

[a]Adjusted for young adult sex, neighborhood income, and perinatal characteristics (gestational diabetes, gestational hypertension, and preeclampsia/eclampsia).
[b]Low risk pregnancy defined as: no c-section, no maternal history of cardiometabolic conditions, and maternal age < 35 years.
[c]High-risk pregnancy defined as having had one of: c-section, maternal history of cardiometabolic conditions or maternal age ≥ 35 years.

birthweight from 2500g to 3400g from which point there was no evidence of an association (Supplementary Table S2). For example, at 2500g, for every 100g increase in birthweight, the hazard of hypertension decreased by 3%. Fig. 2 shows the adjusted predicted cumulative incidence probability and 95% confidence intervals (fitted by cubic spline) for hypertension across birthweight at the attained age of 26 years.

There was insufficient evidence of effect modification by pregnancy risk on birthweight ($p = 0.17$). When the interaction terms were evaluated separately for the components of the pregnancy risk variable, all had a p-value > 0.05. The p value was 0.38 for the caesarean section interaction term, 0.09 for maternal history of cardiometabolic conditions, and 0.66 for maternal age. There was insufficient evidence of effect modification by sex ($p = 0.77$) and neighborhood income ($p = 0.22$). Sex stratified results are presented in Supplementary Table S7 but do not show evidence of any differences by sex.

Associations between birthweight and IHD

Between 18 and 26 years, 349 people received a diagnosis of IHD in 18.9 million person-years of follow up, yielding a crude incidence rate of 1.85 per 100,000 person-years. The incidence rates were 2.39 among those born low birthweight, 1.84 among those born normal birthweight, and 1.77 among those born high birthweight (Table 2).

There was insufficient evidence of an association between birthweight and IHD (Table 2, Supplementary Table S2). Figure 3 shows the adjusted predicted cumulative incidence probability and 95% confidence intervals (fitted by cubic spline) for IHD across birthweight at the attained age of 26 years.

There was insufficient evidence of effect modification by pregnancy risk on birthweight ($p = 0.79$). When the interaction terms were evaluated separately for the components of the pregnancy risk variable, all had a p-value > 0.05. The p value was 0.92 for the caesarean section interaction term, 0.37 for maternal history of cardiometabolic conditions and 0.31 for maternal age. There was insufficient evidence of effect modification by sex ($p = 0.28$) and neighborhood income ($p = 0.33$). Sex stratified results are presented in Supplementary Table S8 but do not show evidence of any differences by sex.

Discussion

In this large population-based cohort study, birthweight was associated with the hazard of diabetes in a reverse J-shape manner and inversely associated with the hazard of hypertension in young adulthood. There was insufficient evidence of an association between birthweight and IHD up to 26 years of age. Adjusting for confounders, low birthweight was associated with a 50% increased hazard of new-onset diabetes and 35% increased hazard in hypertension. High birthweight was associated with an 11% increased hazard of new onset diabetes and 13% decreased hazard in hypertension. The association between high birthweight and diabetes was only observed among high-risk pregnancies. Further, sex stratified analyses showed that only females had an increased hazard of diabetes when born with high birthweight.

Our findings are generally consistent with results reported by previous systematic reviews, which investigated the association between birthweight and type 2 diabetes, hypertension, or CVD. Most reviews included studies which featured individuals of all ages[6–8,10] except for two reviews which included studies only investigating adults aged 18 and over.[5,9] Three reviews have found that birthweight was associated with diabetes in a U-shape[7] or reverse J shape.[5,8] Findings by Zhao *et al.* 2018 indicated a reverse J-shape association where low birthweight (OR 1.41; 95% CI 1.26, 1.58) and high birthweight (OR 1.11; 95% CI 1.00, 1.24) to a lesser extent were associated with type 2 diabetes compared to normal birthweight.[8] Knop *et al.* 2018 also found a reverse J shape association between birthweight and diabetes.[5] However, increased odds of diabetes was more evident in those born > 4500g instead of > 4000g.[5] Consistent with our findings, sex stratified analyses revealed that females with high birth weight (> 4500g compared to < 4500g) had a 19% higher odds of type 2 diabetes with no evidence of an association found for males.[5] The review by Mi *et al.* 2017 found that only low birthweight was associated with increased risk of type 2 diabetes.[9] The reason for discrepant findings may have been influenced by differences in how the reference group was defined. Combining low and normal birthweight may partially obscure the association between high birthweight and diabetes risk.

Two reviews found that birthweight was inversely associated with hypertension and estimates were like those observed in our study.[5,6] Mu *et al.* 2012 and Knop *et al.* found low birthweight (< 2500g) compared with birthweight greater than 2500g was associated with increased odds of hypertension (OR 1.21; 95% CI 1.13, 1.30 and 1.30; 95% CI 1.16, 1.46, respectively), and high birthweight (> 4000g) compared with birthweight less than 4000g was associated with decreased odds of hypertension (OR 0.78; 95% CI 0.71, 0.86 and 0.88; 95% CI 0.81, 0.95), respectively.[5,6]

Reviews examining birthweight and CVD have found varying results. Wang *et al.* 2014 found that birthweight was inversely associated with CVD.[10] However, Knop *et al.* 2018 found a reverse J shape association but only if high birthweight was defined as > 4500g with no evidence of an association at > 4000g.[5] Our null findings for IHD may potentially be due to the young age range studied which did not allow for sufficient follow-up into later adulthood for IHD risks to manifest.

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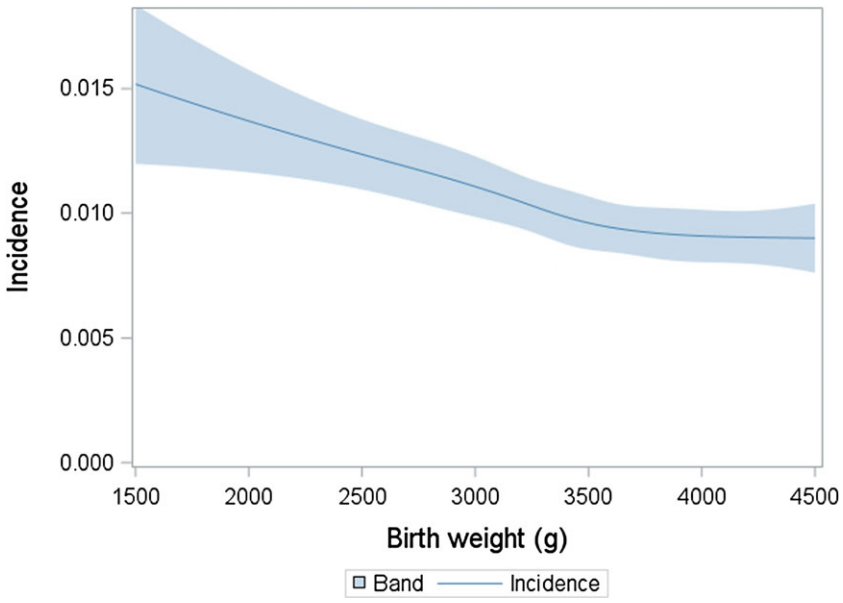

Figure 2. The adjusted predicted cumulative incidence probability and 95% confidence intervals (fitted by cubic spline) for hypertension across birthweight at the attained age of 26 years.

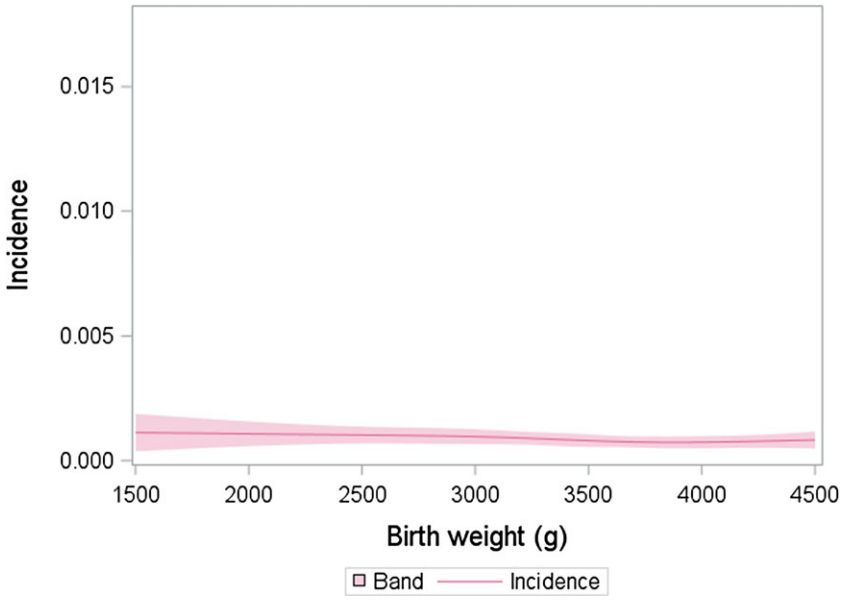

Figure 3. The adjusted predicted cumulative incidence probability and 95% confidence intervals (fitted by cubic spline) for IHD across birthweight at the attained age of 26 years.

Mechanisms

The underlying mechanisms by which birthweight may be related to cardiometabolic risk need further elucidation. Some research has suggested that an adverse intrauterine environment during fetal development could cause changes in utero, influencing the structure and function of important organs.[29] For low birthweight, poor intrauterine growth and/or prematurity could influence the maturation of fetal organs, permanently compromising cardiovascular structure and function, increasing the risk of hypertension later in life.6

Low birthweight has been linked with impaired glucose metabolism and increased insulin resistance, whereby the latter has been suggested to be present as early as before birth.[30,31] These results suggest that the perinatal period may be particularly important for the programming of glucose metabolism and that infants born low birthweight may be more vulnerable to disorders such as type 2 diabetes and CVDs such as IHD later in life.[31] It has been hypothesized that the postnatal environment may also play a role in the association between birthweight and diabetes. Infants born low birthweight are likely subjected to neonatal overfeeding, leading to rapid weight gain, which tracks to adulthood overweight which is a known risk factor for type 2 diabetes.[32] Exposure to maternal hyperglycemia and/or overweight during pregnancy has been hypothesized to partially explain the relation between high birthweight and increased type 2 diabetes risk.[7] Our study also found that the association between high birthweight and diabetes was only among high-risk pregnancies. The high-risk nature of these pregnancies including caesarean section, maternal history of cardiometabolic conditions, and maternal age $\geq$ 35 years may contribute to increasing diabetes risk in infants born high birthweight. The presence of the high-risk pregnancy factors may aggravate pregnancy-related metabolic changes, especially those related to insulin resistance.[33]

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Previous research has demonstrated that females exhibit a diminished sensitivity to insulin compared to their male counterparts across the lifespan, potentially predisposing them to a heightened susceptibility to insulin resistance and increasing the risk of type 2 diabetes.[34] Knop *et al.* additionally posit that high birthweight female infants may be considered an outlier in comparison to their male counterparts, as females typically exhibit a lesser weight and stature than males at the time of birth.[5] This may result is a more pronounced phenotype in girls as opposed to boys.

The prevalence of low birthweight is approximately 15% and although the prevalence of high birthweight is variable, rates have been steadily increasing.[1–3] Even a modestly increased risk of cardiometabolic conditions has major public health implications. Although underlying mechanisms need further elucidation, our findings suggest that persons born low and high birthweight need long-term follow-up for health surveillance and preventive actions to reduce the risk of cardiometabolic conditions.

Strengths and limitations

A strength of this study was the ability to use administrative data, with a large sample size and low amount of missing data to conduct a retrospective cohort study that spanned up to 26 years. This study design minimizes potential selection bias. However, further time to follow participants may be needed to fully understand the influence of birthweight on cardiometabolic outcomes, particularly IHD. In Canada, men are most likely to be diagnosed with IHD between 55 and 64 years while women are between 65 and 74 years of age.[35]

A limitation of this study was that we did not have data on gestational age at birth, which were not systematically recorded until 2002. If data on gestational age had been available, we would have evaluated size for gestational age or gestational age itself as the predictor of interest. As birthweight is a component of gestational age and size for gestational age, the latter two variables may be more meaningful to study, allowing researchers to better elucidate the exposure leading to disease states of interest.[36] We also did not have data on other potentially important confounding variables such as maternal smoking, body mass index, and race or ethnicity. We have conducted sensitivity analyses to evaluate the potential for unmeasured confounding and reported the e-values which ranged from 1.4 to 2.4 depending on the outcome, suggesting our observed associations could possibly be explained by a moderate to strong unmeasured confounding variable.[28] The literature shows considerable variation in cardiometabolic risk and adverse perinatal outcomes including low birthweight by race or ethnicity.[37–43] Race and ethnicity are important variables to identify and measure health inequalities that stem from racism, bias, and discrimination, providing insight for potential clinical and health policies.[44] Another limitation was the lack of data on the indication for caesarean section, which could further elucidate potential pathways leading to cardiometabolic outcomes. Further, our pregnancy risk variable was a summary of three individual variables hypothesized *a priori* to increase risk, but it was not a comprehensive measure of all risk and could be subject to measurement error. Additionally, based on the limitations of provincial billing codes, the ODD cannot distinguish between type 1 and type 2 diabetes. However, it has been estimated that 90% of diabetes cases among Canadian adults are type 2.[45] There were also no existing valid algorithms in Ontario administrative data to define hypertension before age 20. Thus, it is a limitation of our study that we could not exclude prevalent hypertension cases in this analysis. Based on other recent data from another province in Canada, the estimated overall prevalence of pediatric hypertension is < 6%.[46] As our data may include few prevalent cases, our results may slightly overestimate the true impact in early adulthood of hypertension. In this study, we did not consider kidney disease which future studies should evaluate. Lastly, while the follow-up time was 26 years, this may be relatively short in the course of an entire lifespan and further follow-up into middle and older age may reveal stronger associations, with more precise estimates. Alternatively, it is possible that birthweight may more strongly increase risk of young adult cardiometabolic conditions as a review found for hypertension[47] and the risks may wane over time with the development of new risk factors, but we were unable to evaluate older ages. The cumulative incidences of the outcomes studied in our paper are low. However, the incidences are generally consistent with overall prevalence estimates in Canada. Although difficult to directly compare since national estimates are reported based on prevalence and wider age categories, Statistics Canada reported that 1.1% and 2.2% of Canadians aged 18–24 years had diabetes and hypertension, respectively.[48,49] The Public Health Agency of Canada reported that the incidence of IHD was 0.4 for women and 0.6 for men per 1,000 for Canadians aged 20–39 years.[50]

Conclusion

Consistent with previous literature, we found that birthweight was associated with the risk of diabetes in a reverse J-shape manner and inversely associated with risk of hypertension between 18 and 26 years of age in a large population-based cohort. Stratified analyses by pregnancy risk and sex only provided evidence of an association between high birthweight and diabetes among high-risk pregnancies and females, respectively. There was insufficient evidence of an association between birthweight and IHD. Further evidence is needed to understand the association between birthweight and IHD in young adults. Additional research is needed to determine whether reducing modifiable risk factors for low and high birthweight prevent diabetes and hypertension later in life.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174423000417.

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Competing interests. None.

Ethical standards. The use of ICES data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

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