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RESEARCH ARTICLE

The impact of birthweight on subsequent phenotype of type 2 diabetes in later life

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Abstract

Aims: It is well established that low birthweight is associated with subsequent risk of type 2 diabetes (T2DM). The aim of our study was to use a large birth cohort linked to a national diabetes registry to investigate how birthweight impacts the phenotype at diagnosis of T2DM and the subsequent rate of glycaemic deterioration.

Methods: We linked the Walker Birth Cohort (48,000 births, 1952–1966, Tayside, Scotland) to the national diabetes registry in Scotland (SCI-Diabetes). Birthweight was adjusted for gestational age. Simple linear regression was performed to assess the impact of the adjusted birthweight on the diabetes phenotype at diagnosis. This was then built up into a multiple regression model to allow for the adjustment of confounding variables. A cox proportional hazards model was then used to evaluate the impact of birthweight on diabetes progression.

Results: Lower birthweights were associated with a 293 day younger age of diagnosis of T2DM per 1 kg reduction in birthweight, $p = 0.005$; and a 1.29 kg/m^2 lower BMI at diagnosis per 1 kg reduction in birthweight, $p < 0.001$. There was no significant association of birthweight on diabetes progression.

Conclusion: For the first time, we have shown that a lower birthweight is associated with younger onset of T2DM, with those with lower birthweight also being slimmer at diagnosis. These results suggest that lower birthweight impacts on T2DM phenotype via reduced beta-cell function rather than insulin resistance.

KEYWORDS

low birth weight, prediction of diabetes, thrifty phenotype, type 2 diabetes

1 | INTRODUCTION

It is well established that there is a link between an individual's birthweight and subsequent risk of developing type 2 diabetes (T2DM) in later life, with lower birthweights consistently associated with an increased risk. For example, a meta-analysis by Mi et al. into the effect of birthweight on subsequent T2DM risk analysed over 108,000 subjects with a known birthweight and T2DM status.[1] Those with low birthweight (<2500 g) were more likely to develop T2DM when compared to those with normal birthweight (2500–4000 g) and those with high birthweight (>4000 g), with an odds ratio (OR) of 1.55 and 1.58, with 95% confidence intervals (CI) of 1.39–1.72 and 1.30–1.93, respectively.[1] In another meta-analysis into the effect of birthweight and T2DM risk, every 1000-gram increase

in birthweight was associated with a reduced risk of developing T2DM (OR 0.79; CI 0.71–0.88).[2,3] This paper also found that those with birthweights below 2500 g were at an increased risk of developing T2DM compared to those with a birthweight over 2500 g (OR 1.45; CI 1.33–1.59).[2] Other studies report a U-shaped relationship with increased risk in those with both low and high birthweight.[4] The two main mechanisms proposed to explain the association between birthweight and subsequent diabetes risk are: Hales and Barker's thrifty phenotype hypothesis and Hattersley and Tooke's foetal insulin hypothesis.[5,6]

As yet there have been no studies reported that investigate how the birthweight affects the subsequent phenotype of T2DM once it has developed or the rate of glycaemic deterioration. As low birthweight is associated with increased diabetes risk by possible genetic or in-utero effects on the beta-cell function we hypothesised that the diabetic phenotype at diagnosis of diabetes would differ in those with low and high birthweight and that this may impact on the subsequent progression of the disease. Therefore, we aimed to investigate if birthweight, particularly low birthweight, has an impact on the phenotype or severity of T2DM once diagnosed.

What's new?

- It has already been shown that a lower birthweight is associated with an increased risk of type 2 diabetes in later life. It is also known that type 2 diabetes can have varying phenotypes with differences in the severity and progression of the disease.
- We have shown that a lower birthweight is associated with younger onset of disease and in patients who are slimmer at the time of diagnosis.
- This is the first such study of these findings and invites further research in this area.

2 | RESEARCH DESIGN AND METHODS

Data were provided by the Health Informatics Centre (HIC) at the University of Dundee. HIC links individual patient data by means of the unique identifier used across NHS Scotland (the Community Health Index (CHI) number).[7]

2.1 | The Walker birth cohort

The Walker cohort contains a record of over 48,000 births from Dundee, Scotland from the years 1952 to 1966 with details of over 75% of the births in Dundee over this time.[8] The creator, James Walker and his colleagues recorded a number of details about the births, including birthweight, gestation, complications and placental weight and later electronically stored this data to allow for follow up data to be collated.[8] Those with birthweight recorded as either above 7500 g or below 250 g, gestational age below 20 weeks or above 50 weeks, were excluded.

Data from the Walker cohort were linked with the following datasets: Demography which provided information on age and sex, the Scottish Care Initiative-Diabetes Collaboration (SCI-Diabetes) which provided information on diabetes type, date of diagnosis, BMI and blood pressure. HbA_{1c}, HDLc, creatinine and ALT measurements were obtained from the laboratory system. Medicines were ascertained from community dispensed prescribing data.

2.2 | Birthweight standardisation

Birthweight was adjusted for gestational age by regressing the birthweight value against the gestational age; from this, we used the standardised residuals as the adjusted birthweight value for analysis. This is the same method used by Hughes et al. when studying the impact of genotype and maternal glucose on birthweights.[9]

2.3 | Covariates

Routinely collected clinical characteristics including BMI, eGFR, HbA_{1c}, HDL, SBP and ALT were taken at the closest time to diagnosis of diabetes. Some variables underwent log transformation to fit them to normal distribution.

2.4 | Study population

The final study population was derived from the Walker cohort. Individuals diagnosed with T2DM; and residents in NHS Tayside and Fife regions from 1 January 1995 in Tayside and 1 January 2010 in Fife to 31 March 2017 (when observations ended) were eligible for the study. A number of subjects were excluded due to incomplete data, not having developed T2DM, or if they were given a diagnosis of diabetes before the introduction of SCI-Diabetes. A flow chart of the study population derivation is presented in Figure 1. In our final cohort, all alive subjects would have been between 51 and 65 years old at the study end point, and the youngest patients who could develop T2DM was 29 years in Tayside and 44 in Fife.

2.5 | Statistical analysis

First, we analysed the characteristics of individuals at diagnosis of diabetes split by birthweight quartile.

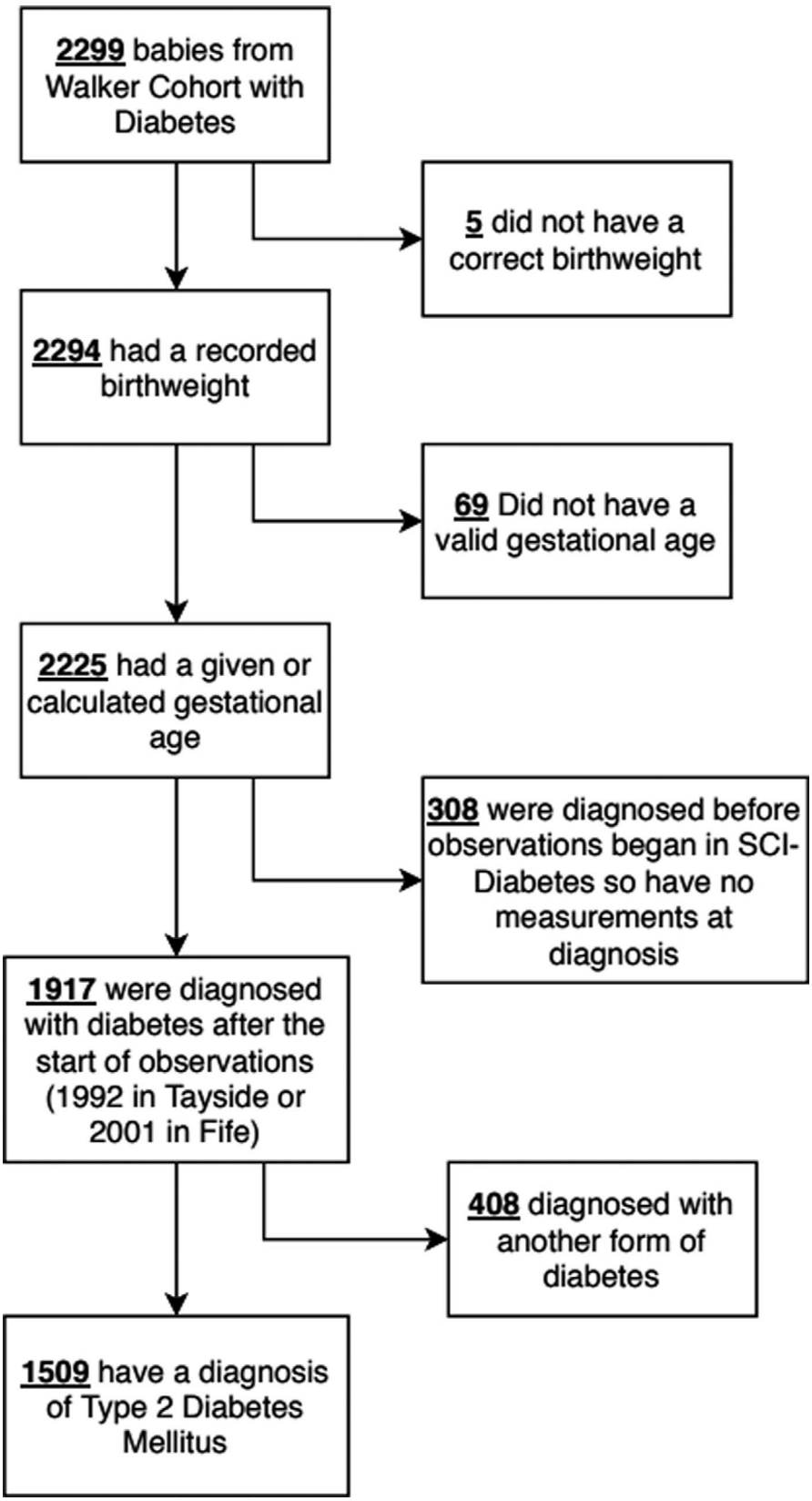

FIGURE 1 Flow chart from original base cohort to final study cohort

We then undertook simple linear regression with the adjusted birthweight as the independent variable and the characteristics at diagnosis as dependent variables. We then adjusted each comparison in a multiple regression model including sex and variables that were univariately associated with birthweight (defined as p-value < 0.2). All regression models were checked for normality of residuals, heteroscedasticity of the residuals and linearity between continuous predictors and outcomes.

To investigate progression to insulin after diagnosis of diabetes, we used a cox proportional hazards model with time to sustain insulin as the event ([6 months or more insulin duration] or clinical requirement for insulin [2 consecutive HbA_{1c} measures >69 mmol/mol (8.5%) whilst on 2 or more non-insulin drugs]), as previously defined.[10] Covariates included in the model were adjusted birthweight, BMI and age at diagnosis as continuous variables and sex. Due to the violation of the proportional hazards assumptions, HbA_{1c} was used as strata in the model with categories of <53, 53–75 and >75 mmol/mol (<7.0, 7.0–9.0 and >9.0%).

All analyses were performed using SAS version 9.3 software with a p-value < 0.05 considered statistically significant.

Ethical approval for this study is approved through the HIC and this study conforms to all recognised standards.

3 | RESULTS

The final study cohort included 1509 subjects with a diagnosis of T2DM and an adjusted birthweight. The baseline clinical characteristics for the final study population are presented in Table 1, split by quartile of adjusted birthweight. Men had a higher mean birthweight of 3.262 kg (95% CI 3.227–3.298 kg), compared to women of 3.151 kg (95% CI 3.115–3.187 kg), $p < 0.001$.

3.1 | Impact of birthweight on diabetes characteristics at the time of diagnosis

The results for the simple linear regression analyses of adjusted birthweight against phenotype at diagnosis are presented in Table 2. Lower birthweights were associated with a 0.8 year (95% CI 0.24–1.37, $p = 0.005$) younger age of diagnosis, a 1.29 kg/m^2 (95% CI 0.58–2.01, $p < 0.0001$) lower BMI at diagnosis and a 0.04 mmol/L (95% CI 0.01–0.06, $p = 0.016$) higher HDL per 1 kg reduction in birthweight.

In the multiple regression models, after adjusting for age, BMI, HDL, log ALT, and sex, the associations between age at diagnosis and birthweight (0.87 [95% CI 0.26–1.4] years, $p = 0.005$) and BMI and birthweight (1.49 [95% CI 0.77–2.2] kg/m^2, $p < 0.0001$) per 1 kg increase in birthweight remained significant.

3.2 | Birthweight and diabetes progression

A secondary aim of this study was to assess if birthweight would have an impact on the time taken from being diagnosed with T2DM to requiring insulin treatment. Overall, 356 (29.1%) individuals progressed to insulin during the study period. The median follow up time was 5.39 years. The event rate within each HbA_{1c} strata was 16%, 33.6%

TABLE 1 Baseline characteristics of our study population by birthweight quartiles[a] with the number of values[b]

	Full study population	1st Quartile (250–2892.5 g)	2nd Quartile (2892.5–3232.41 g)	3rd Quartile (3232.41–3571.5 g)	4th Quartile (3571.5–7500 g)
N	1509	377	379	374	379
Men vs. Women	909:600	207:170	217:162	236:138	249:130
Median age at diagnosis in years (IQR)	51.0 (8.5) $n = 1509$	50.7 (9.0) $n = 377$	50.8 (8.8) $n = 379$	51.2 (8.2) $n = 374$	51.0 (7.8) $n = 379$
Median BMI in Kg/m^2 (IQR)	33.7 (78.9) $n = 1266$	33.5 (9.3) $n = 318$	32.9 (9.2) $n = 311$	33.4 (7.7) $n = 314$	35.2 (8.9) $n = 323$
Median eGFR in ml/min/1.73 m^2 (IQR)	99.4 (28.9) $n = 1457$	99.2 (29.0) $n = 364$	99.6 (28.7) $n = 364$	102.2 (30.0) $n = 360$	97.0 (27.3) $n = 369$
Median HbA_{1c} in mmol/mol [%] (IQR)	57.0 [7.4] (31.0 [5.0]) $n = 1417$	56.0 [7.3] (31.0 [5.0]) $n = 353$	58.0 [7.5] (31.0 [5.0]) $n = 355$	58.0 [7.5] (36.0 [5.4]) $n = 350$	57.0 [7.4] (28.0 [4.7]) $n = 359$
Median ALT in U/L (IQR)	37.0 (27.0) $n = 1367$	36.0 (29.0) $n = 342$	32.0 (25.0) $n = 331$	36.0 (29.0) $n = 339$	39.0 (28.0) $n = 355$
Median HDL in mmol/L (IQR)	(0.4) $n = 1435$	1.1 (0.4) $n = 353$	1.1 (0.4) $n = 362$	1.1 (0.3) $n = 358$	1.1 (0.3) $n = 362$
Median SBP in mmHg (IQR)	136.8 (21.0) $n = 1408$	137.0 (21.0) $n = 351$	136.0 (21.0) $n = 346$	136.0 (23.0) $n = 350$	138.0 (10.0) $n = 361$

[a]Birthweight quartiles supplied in ascending order.

[b]The number of values in each box is denoted by n.

TABLE 2 Results of linear regression analysis with birthweight as a predictor of variables at diagnosis

Variable (units)	Beta[a]	95% CI	R-squared	Observations Used	*p*-value	Adjusted[b] Beta	95% CI	Adjusted[b] *p*-value
Age at diagnosis (Years)	0. 80	0.24–1.37	0.52%	1509	0.005	0.87	0.26–1.4	0.005
BMI (kg/m^2)	1.29	0.58–2.01	0.99%	1266	<0.001	1.49	0.77–2.2	<0.001
eGFR (ml/min/1.73 m^2)	−0.60	−2.85 to 1.65	0.02%	1457	0.602	−1.05	−3.56 to 1.46	0.41
Log of ALT	0.02	−0.001 to 0.04	0.25%	1367	0.062	0.015	−0.01 to 0.039	0.22
HbA_{1c} (mmol/mol) [%]	−0.37 [−0.03]	−2.63 to 1.89 [−0.24 to 0.17]	0.01%	1417	0.748	0.27 [0.03]	−2.31 to 2.84 [−0.20 to 0.26]	0.84
SBP (mm Hg)	0.44	−1.23 to 2.12	0.02%	1408	0.604	−0.70	−2.58 to 1.17	0.46
HDL (mmol/L)	−0.04	−0.06 to −0.01	0.40%	1435	0.016	−0.02	−0.01 to 0.01	0.23

[a]Units for the beta; increase in units of the variable at diagnosis for every 1 kg increase of adjusted birthweight.

[b]Adjusted for age at diagnosis, BMI, Log of ALT, HDL and sex.

and 44.2% for the categories of <53, 53–75 and >75 mmol/mol (<7.0, 7.0–9.0 and >9.0%), respectively.

The results of the Cox proportional hazards model are presented in Table 3. Men had a 33% reduction in the risk of initiating insulin treatment and every 1-year increase in age of diagnosis was associated with a 1.9% reduction in the risk of initiating insulin. However, birthweight was not associated with progression to insulin.

4 | DISCUSSION

In this study, we have shown that low birthweights are associated with the younger onset of T2DM and a lower BMI at diagnosis. The associations between birthweight with the age at diagnosis and the BMI at diagnosis remained after adjustment for confounding variables.

The finding that patients with low birthweight who develop diabetes young have lower BMI suggests that this association is mediated via reduced beta-cell function, as the lower BMI and higher HDL are markers of insulin sensitivity. Ideally, this would be assessed with HOMA or c-peptide measures at diagnosis but unfortunately, these were not available. These results would be consistent with both Barker and Hattersley's hypotheses: an adverse intrauterine environment may result in reduced pancreatic beta-cell mass and subsequent beta-cell deficient diabetes; and/or genetically predisposed β-cell dysfunction would lead to low birthweight and lead to the more severe phenotype of T2DM presenting in younger and slimmer patients. However, studies in the Pima Indians, a native group of Arizona with a very high prevalence of T2DM,[11,12] have shown that birthweight is negatively correlated with insulin resistance, as measured by HOMA, meaning that lower birthweights are associated with higher insulin resistance, which could be driving the increased diabetes risk in this group.[12] This finding has also been reinforced with other studies investigating the Pima Indians.[13]

The lower birthweight association with younger age of diagnosis would be expected to impact diabetes progression. We and others have shown that those diagnosed with T2DM younger have more rapid glycaemic deterioration and greater mortality and morbidity from CV disease.[10,14–18] The fact that we do not see an association of birthweight with the progression of diabetes may reflect a lack of power—the effect on the age of diagnosis is small and the likely impact on the progression would be even smaller. We have reported previously[10,19] that in this model men are less likely to initiate insulin which probably reflects treatment inertia in this group rather than a true biological effect, despite the fact, our endpoint is a composite endpoint that includes those who should have started insulin (HbA_{1c} > 8.5% despite two or more oral agents).[10,19]

TABLE 3 Results of Cox proportional hazards analysis for the time from diagnosis to insulin requirement

Variable (units)	Hazard Ratio	95% CI	*p*-value
Men versus women	0.67	0.53–0.84	<0.001
Age at diagnosis (per 1 year)	0.98	0.96–0.99	0.038
BMI at diagnosis (per 1 kg/m^2)	0.99	0.97–1.00	0.124
Adjusted birthweight (per 1 kg)	1.00	1.00–1.000	0.691
HDL (per 1 mmol/L)	0.84	0.58–1.22	0.849

The main limitations in our study population arise from the fact that due to our data capture collection the Walker participants eligible for our study could only be between age 51 and 65 years old at the end of the observation period, meaning that we do not capture diabetes diagnosed beyond the age of 65. It is possible that the associations we observe for birthweight with diabetes phenotype at diagnosis are not so strong or are absent in those diagnosed after the age of 65. The restricted age window for those with diabetes will also impact our power to see differences in diabetes progression—those diagnosed older progress more slowly[15,20]—so restricting to those diagnosed under 65 years will limit the variance in progression rate. However, for those included in the study the available follow-up time from diagnosis was a median (IQR) of 5.39 years (5.52), 29.1% having an event. We also recognise that our data are left truncated—we can only assess diabetes phenotype at diagnosis in those who are alive and have developed diabetes since SCI-Diabetes data were available however this minimum age is 29 for Tayside and 44 years for Fife, so very few people will have been diagnosed with T2DM or will have died before the observation period. Finally, we should consider that the Walker birth cohort was from 1955–1966. Birthweights have increased since this time, with the mean BW in 1950–1969 being 3.33 kg compared with 3.52 kg in 1990–2008.[21] Given that this increase in birthweight may well reflect the difference in maternal nutrition during pregnancy it is not possible to say that the relationship we observe between BW and diabetes phenotype will be the same for current birth cohorts.

In summary, we have shown, for the first time, that lower birthweight is associated with an earlier onset of T2DM, characterised by a lower BMI and higher HDL consistent with the early onset diabetes being driven by reduced beta-cell function. Further studies, including the measurement of beta-cell function and insulin resistance at diagnosis, are warranted, and genetic studies linking birthweight to the age of diabetes onset will be of value in determining the contribution of foetal genetics to the intrauterine environment to this association.

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CONFLICT OF INTERESTS

All authors declare no conflicts of interest.

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