Associations between birth weight and glucose intolerance in adulthood among Greenlandic Inuit

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ABSTRACT

Aims: To examine the association between birth weight and glucose intolerance in adult Greenlandic Inuit.

Methods: We examined 1429 participants aged 18–56 years from two population-based, cross-sectional studies in Greenland with information on birth weight. Oral glucose tolerance tests, anthropometric measures and ultrasound of abdominal tissue were performed. Associations of birth weight with glucose markers were analysed using linear or logistic regressions. Spline analyses were conducted to examine u-shaped associations. Adjustments were done for age, sex, birth place, family history of diabetes, genetic admixture, *TBC1D4* p.Arg684Ter carrier status, BMI and visceral adipose tissue.

Results: The median birthweight was 3300 g and 3.9% had type 2 diabetes, T2DM. Spline analyses indicated overall linear associations. In fully adjusted analyses, an increase in birth weight of 1 kg was associated with a change in fasting plasma glucose of −0.06 mmol/L (95%CI: −0.11, −0.01), 2-h plasma glucose of −0.16 mmol/L (95%CI: −0.35, 0.02), HOMA-IR of −5.45% (95%CI: −10.34, −0.29), insulin sensitivity index of 7.04% (95% CI: 1.88, 12.45) and a trend towards a reduced risk of hyperglycaemia and T2DM, although statistically insignificant.

Conclusions: Birth weight was inversely associated with hepatic and peripheral insulin resistance independently of adult adiposity. Thus, the findings support low birth weight as a contributing factor for glucose intolerance in adult Inuit in Greenland.

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1. Introduction

The indigenous Inuit population in Greenland has undergone rapid social, nutritional and health transitions in the past years, and studies have shown a surprisingly high prevalence of obesity, type 2 diabetes mellitus (T2DM) and some cardiovascular disease (CVD) risk factors [1,2]. A high genetic risk of cardiometabolic disturbances has previously been

documented among Arctic Inuit [3,4]. However, while the interaction between lifestyle changes and genetic factors play a key role in the rising burden of these conditions, the role of early life factors like fetal nutrition in chronic disease development is less clear in the Inuit.

Barker and colleagues showed more than 25 years ago in an analysis of longitudinal cohorts that low birth weight was associated with later risk of impaired glucose tolerance, T2DM and CVD [5–7], whereas both low and high birth weight has been associated with adiposity in adulthood [8,9]. The inverse associations between birth weight and adult cardiometabolic outcome has been reproduced in numerous populations and settings of different geography, ethnicity and background [10,11]. These findings nourished the Thrifty Phenotype Hypothesis, suggesting that during restricted fetal nutrition, permanent metabolic adaptions take place which promotes nutrient storage to ensure survival under suboptimal conditions [11]. Epigenetic modifications and changes in the regulation in cellular aging has been put forward as possible pathways [12] and later research has indicated that the early postnatal environment and influences through the life course e.g. obesogenic environments or rapid nutrition transition settings may modify the effects of fetal life on later disease [13].

In the Greenlandic Inuit, only few studies have investigated the association between fetal nutrition and adult disease risk. We have investigated the association between birth weight and adult adiposity in Greenland and found that higher birth weight was associated with adiposity in adulthood with little indication of a U-shaped relationship. An exception was for adult visceral fat levels which were higher with lower birth weight in men [14]. High visceral fat levels have been associated with insulin resistance and other metabolic disturbances [15], and could therefore play a role in the associations between low birth weight and adult T2DM as reported in other studies. However, there is a lack of knowledge about the relation between birth weight and development of cardiometabolic risk in Greenland and other Inuit populations. Furthermore, Inuit populations may differ on several factors such as maternal nutrition, which may have been high on fat and protein [16], and climatic adaptions, which could have affected birth size and tissue development in fetal life as well as expression of disease later in life [17]. We therefore aimed to investigate the association between birth weight and glycemic status, insulin resistance and T2DM in the adult Inuit population in Greenland.

2.   Methods

2.1.   Study population and design

The study population comprised participants from two population-based surveys, the B99 study and the Inuit Health in Transition Study (IHIT), conducted in Greenland in 1999–2001 and 2005–2010, respectively. The participants in the two surveys were recruited as a random sample of adult Inuit above 18 years in Greenland. All participants were asked to complete a self-administered questionnaire and participate in an interview and a clinical examination. A detailed description of the study methods can be found elsewhere [18,19].

Out of 4221 participants (1304 from B99 and 2917 from IHIT) who underwent clinical examinations, information on birth weight was available for 1523 ethnic Greenlanders. Individuals born before 1950 (n = 6) were excluded because birth weight before this year was not systematically registered and participants with missing values on covariates were excluded (n = 79). Thus, the final study population was 1429 (n = 375 from B99 and 1054 from IHIT).

Written informed consent was obtained from participants before investigation, and the studies were approved by the ethical review committee of Greenland and have been performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

2.2.   Birth weight

Information on birth weight on participants was collected from medical records at hospitals as previously described [14]. The records included birth records, midwife records and outpatient records of participants, and for the latest years, information from the central birth register of Greenland.

2.3.   Glucose homeostasis markers

A venous blood sample was drawn from participants after an overnight fast ($\geq$8 h) without consumption of food or liquids. The participants afterwards received a standard 75-g oral glucose tolerance test with blood samples drawn 2 h after the intake. Plasma glucose was analysed by the hexokinase/G6P-DH method and serum insulin by an AutoDELFIA using fluoro-immunoassay.

Fasting c-peptide was measured in pmol/L in serum and stood for 30–150 min before centrifugation at 20 °C, 3000 rpm for 10 min. After centrifugation, the c-peptide samples were frozen at 20 °C. The content of c-peptide was analysed using Cobas e411, Roche. All measures were analysed in the laboratories at Steno Diabetes Center, Gentofte, Denmark [18,19].

As a measure of insulin resistance-associated beta-cell function, the c-peptide-insulin ratio was calculated as fasting c-peptide (ρmol/L)/fasting insulin (ρmol/L) [20]. Hepatic insulin resistance (HOMA-IR) was calculated as: (fasting insulin (ρmol/L)* fasting plasma glucose (mmol/L))/22.5 [21]. Insulin sensitivity in the peripheral tissues was assessed using the insulin sensitivity index ($ISI_{0,120}$) calculated according to Gutt et al. [22] as follows:

$$ISI_{0,120} = \frac{(75000 + (glucose_{t0min} \times 18 - glucose_{t120min} \times 18) \times 0.19 \times weight_{kg})/120}{(glucose_{t0min} + glucose_{t120min})/2} \Big/ \log\left(\frac{(insulin_{t0min}/6.945) + (insulin_{t120min}/6.945)}{2}\right)$$

T2DM was classified according to criteria defined by the World Health Organisation [23] as fasting plasma glucose ≥ 7.0 mmol/L, 2-h plasma glucose ≥ 11.1 mmol/L or self-reported T2DM. Self-reported diabetes was based on questions "Have you ever been diagnosed with diabetes" or reported glucose-lowering medication. Binary outcomes of fasting hyperglycaemia (fasting plasma glucose ≥ 6.1 mmol/L) and postprandial hyperglycaemia (2-h plasma glucose ≥ 7.8 mmol/L) were created to assess impaired glucose regulation.

2.4. Obesity measurements

Weight and height were measured with the participants wearing underwear and socks. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured midway between the rib cage and the iliac crest on the standing participant.

Abdominal visceral adipose tissue (VAT) was assessed by ultrasonography in the IHIT study [14,18]. The measure was performed by a portable ultrasound scanner (Pie Medical) using a 3.5 MHz transducer. The distances between the posterior edge of the abdominal muscles and the lumbar spine was measured using electronic calipers from three different angles: medial, 10 cm left and 10 cm right lateral. VAT was defined as the depth (cm) from the peritoneum to the lumbar spine.

2.5. Covariates

Information on sex and age was retrieved from the central personal register, while birthplace, ancestry, and family history of diabetes were collected from questionnaires. Birthplace was categorized as either town or village. Family history of diabetes was determined based on whether the participant's parents and/or siblings were diagnosed with diabetes. The variable was dichotomized as yes (any parent or sibling had diabetes) and no.

Blood samples were genotyped and the degree of genetic admixture [24] and the Inuit-specific TBC1D4 p.Arg684Ter variant associated with insulin resistance was determined [3].

2.6. Statistical analyses

Multiple linear regression models were performed with fasting plasma glucose, 2-h plasma glucose, HOMA-IR, $ISI_{0,120}$ and c-peptide-insulin ratio as functions of birth weight (kg) as a continuous variable. Log-transformed variables (HOMA-IR, $ISI_{0,120}$ and c-peptide-insulin ratio) were back-transformed and associations with birth weight were presented as percentwise change.

Selection of confounders was done a priori and presented in four models as follows: model 1 was adjusted for age and sex; model 2 was additionally adjusted for birthplace, family history of diabetes, admixture and TBC1D4 variant; model 3 was additionally adjusted for current BMI and model 4 further adjusted for current VAT. Model 4 was done in a sub-population, since VAT was only measured in IHIT study. We tested for interactions of birth weight with sex, BMI and the TBC1D4 variant in model 3.

To investigate potential non-linear associations with birth weight, we used quadratic splines and plotted the predicted values from the model for a relevant range of birth weight for an average person with the following covariate values (man, 33 years, full Inuit, born in a town, no family history of diabetes, TBC1D4 non-carrier and a BMI of 25 kg/m^2). Different combinations of criteria for prediction were tested. The splines were interpolated with three knots (2.5 kg, 3.5 kg and 4.0 kg) for each outcome measure. Several knots were investigated in the linear regression models, and the knots that resulted in the most obvious change in the quadratic parameter estimates were chosen. All analyses were tested for linearity and total effects by comparing the spline model to a model with linear effect of birth weight using ANOVA.

Multiple logistic regression analyses were conducted to analyse the associations of birth weight with fasting hyperglycaemia, postprandial hyperglycaemia and T2DM. Odds ratios (OR) and 95% CI intervals were calculated. The same adjustments as in the linear regression models were performed.

Participants who showed up non-fasting (n = 144) and/or with self-reported T2DM (n = 5) was excluded from analyses with continuous glucose measures and hyperglycaemia.

For illustrative purpose the logistic regression was repeated with birth weight categorised as low birth weight (<2500 g) and high birth weight (≥4000 g) compared to average (2500–4000 g). In sensitivity analyses we adjusted for waist circumference instead of BMI in model 3. We furthermore tested for study differences by including an interaction between birth weight and study.

All analyses were performed in SAS Statistical Software (version 9.4).

3. Results

The median birth weight was 3350 g (IQR: 3000–3700). Birth weight was in the range 1400–5500 g and 6% (n = 86) had a birth weight under 2500 g. T2DM was present in 3.9% (n = 45) and of these 40 were screen-detected cases. Table 1 shows the population characteristics.

The results from multiple linear regressions are shown in table 2. In models adjusted for sex, age, birthplace, family history of diabetes, admixture, TBC1D4 variant and BMI (model 3), a 1 kg increase in birth weight was associated with a change in fasting plasma glucose of −0.06 mmol/L (95%CI: −0.11, −0.01), in 2-h plasma glucose of −0.16 mmol/L (95% CI: −0.35, 0.02), in HOMA-IR of −5.45% (95%CI: −10.34, −0.29), in $ISI_{0,120}$ of 7.04% (95%CI: 1.88, 12.45) and a change in fasting c-peptide-insulin ratio of −1.71% (95%CI: −5.23, 1.95). Additional adjustment for VAT in a sub-population did not change the estimates significantly (model 4).

Tests for interactions between sex and birth weight were not statistically significant for any of the outcomes; thus, the analyses were conducted for men and women together. Neither did we find an interaction between birth weight and BMI. For the TBC1D4 variant we only found a significant interaction with birth weight for 2-h plasma glucose as outcome (p = 0.014) with a positive association for homozygous carriers (β = 1.23, p = 0.014) compared to a negative for heterozygous (β = −0.3, p = 0.071) and non-carriers (β = −0.17, p = 0.126).

Table 1 – Population characteristics.

	n	Men (n = 606)			Women (n = 823)			Total (n = 1429)		
Age (years)	1429	33.0	(26,	41)	33.0	(26,	40)	33.0	(26,	41)
Birth weight (g)	1429	3400	(3100,	3750)	3300	(2950,	3600)	3350	(3000,	3700)
Birth weight, n (%)	1429									
<2500 g		21	(3.5)		65	(7.9)		86	(6.0)	
2500–4000 g		488	(80.5)		663	(80.6)		1151	(80.6)	
>4000 g		97	(16.0)		95	(11.5)		192	(13.4)	
Birthplace, n (%) born in town	1429	441	(72.8)		607	(73.8)		1048	(73.3)	
BMI (kg/m²)	1429	24.2	(22.0,	27.5)	25.3	(22.3,	29.1)	24.7	(22.3,	29.1)
Waist circumference (cm)	1409	85.7	(79.7,	96.0)	86.5	(78.5,	96.5)	86.0	(78.5,	96.5)
Visceral abdominal fat (cm)	1002	6.6	(5.7,	8.1)	5.9	(5.0,	7.3)	6.2	(5.0,	7.3)
Fasting plasma glucose (mmol/l)	1322	5.5	(5.2,	5.9)	5.3	(5.1,	5.7)	5.4	(5.1,	5.7)
2-h plasma glucose (mmol/l)	1156	4.5	(3.8,	5.4)	5.3	(4.4,	6.3)	4.9	(4.4,	6.3)
Fasting plasma insulin (pmol/l)	1319	34.0	(23.0,	52.0)	44.0	(31.0,	63.0)	40.0	(31.0,	63.0)
2-h plasma insulin (pmol/l)	1157	45.0	(26.0,	112.0)	141.0	(75.0,	243.0)	97.0	(75.0,	243.0)
Fasting c-peptide (pmol/l)	1319	440.0	(327.0,	610.5)	537.0	(397.0,	729.0)	499.0	(397.0,	729.0)
ISI $_{(0,120)}$	1156	72.2	(46.0,	99.1)	44.5	(34.7,	60.9)	52.0	(34.7,	60.9)
HOMA-IR	1318	1.2	(0.8,	1.9)	1.5	(1.0,	2.3)	1.4	(1.0,	2.3)
Fasting hyperglycaemia, n (%)	1322	95	(17.2)		64	(8.3)		159	(12.0)	
Postprandial hyperglycaemia, n (%)	1156	26	(5.3)		49	(7.3)		75	(6.5)	
Type 2 diabetes, n (%)[*]	1163	24	(4.9)		21	(3.1)		45	(3.9)	
Family history of diabetes, n (%)	1429	48	(7.9)		82	(10.0)		130	(9.1)	
TBC1D4 variant, n (%)	1,429									
Non-carrier		390	(64.4)		557	(67.7)		947	(66.3)	
Heterozygous carrier		188	(31.0)		241	(29.3)		429	(30.0)	
Homozygous carrier		28	(4.6)		25	(3.0)		53	(3.7)	

Data are medians (interquartile range) or n (%).
[*] T2DM including self-reported and screen-detected diabetes.

The spline analyses illustrated in Fig. 1 showed some deviations from linearity; however, numerical tests showed that none of the associations performed better than the linear effects.

The OR's for hyperglycaemia and T2DM are shown in Table 3. After adjustment for confounders (model 3), an increase in birth weight of 1 kg was associated with a reduced fasting hyperglycaemia (OR: 0.68, 95%CI: 0.47, 0.97), postprandial hyperglycaemia (OR: 0.95, 95%CI: 0.59, 1.54) or T2DM (OR: 0.70, 95%CI: 0.39, 1.25) although the last two were statistically insignificant. When repeating the analyses for birth weight categorised as low and high birth weight vs. average. The OR for T2DM was 2.26 (95%CI: 0.60, 8.52) for low birth weight (<2500 g) as compared to average birth weight (2500–4000 g), and 1.56 (95%CI: 0.59, 4.12) for high birth weight (≥4000 g). Including waist circumference instead of BMI in model 3 in the linear and logistic regression analyses showed similar estimates (results not shown).

In addition, we tested for differences by cohort. The population characteristics separated by cohort (Supplementary Table 1) show differences in some of the values (age, birth weight, birth place, waist circumference, 2-h plasma glucose, 2-h insulin and c-peptide). However, tests for interactions between birth weight and cohort were not significant, and no substantial differences were found in the regression analyses when adjusted for cohort.

4. Discussion

In this study we found that higher levels of birth weight were associated with lower levels of fasting glucose and lower hepatic and peripheral insulin resistance. Although the estimates were small and mainly significant after adjustment for current body size, both as BMI and visceral adipose tissue, these findings indicate that lower birth weight may affect adult glucose markers in a Greenland Inuit population. Our results correspond to the well-documented associations between low birth weight and increased adult cardiometabolic risk and disease [6,7], but have not previously been reported in Greenland or other Inuit populations. Many adult Inuit populations undergo nutritional transition and experience a high prevalence of obesity, T2DM and CVD [1,2], and based on the findings in the current study it is possible that programming effects of fetal undernutrition contributes to this pattern.

We also investigated associations between birth weight and T2DM but did not find clear evidence that T2DM was associated with birth weight on a continuous range. Many studies on fetal growth and adult T2DM and CVD risk assess the risk of low birth weight using <2500 g as the cut-off point. When we analysed the association between low birth weight and T2DM we did not find significant associations but there was a consistent trend in all models. One reason for the lack of a significant effect on T2DM could be that, the prevalence of T2DM in this sub-population was small (3.9%) compared to that found in the source population (Inuit Health in Transition study) of 9% [2]. The population included in the present study is relatively young since birth weight information only was registered systematically after 1950. Consequently, the power to detect statistically significant associations with T2DM and other glucose markers was limited in these analyses.

Our results of an overall inverse association between birth weight and glucose markers are consistent with many former

Table 2 – Regression coefficients (95%CI) of glucose homeostasis markers per kg increase in birth weight.

	n	Model 1	Model 2	Model 3	n	Model 4
Fasting plasma glucose (mmol/L)	1257	-0.03 (-0.09, 0.02)	-0.02 (-0.08, 0.03)	-0.06 (-0.11, -0.01)	966	-0.08 (-0.14, -0.02)
2-h plasma glucose (mmol/L)	1113	-0.1 (-0.29, 0.09)	-0.09 (-0.27, 0.09)	-0.16 (-0.35, 0.02)	956	-0.17 (-0.37, 0.03)
HOMA-IR (% change)	1254	4.06 (-2.47, 11.03)	2.44 (-3.99, 9.31)	-5.45 (-10.34, -0.29)	966	-6.32 (-11.86, -0.43)
ISI (% change)	1113	2.25 (-3.02, 7.80)	3.32 (-1.94, 8.85)	7.04 (1.88, 12.45)	956	6.88 (1.24, 12.83)
C-peptide-insulin ratio (% change)	1255	-4.43 (-7.98, -0.73)	-4.15 (-7.73, -0.43)	-1.71 (-5.23, 1.95)	966	0.07 (-3.64, 3.92)

Model 1: adjusted for age and sex. Model 2: model 1 additionally adjusted for birthplace, family history of diabetes, admixture and *TBC1D4* variant. Model 3: model 2 additionally adjusted for BMI. Model 4: model 3 additionally adjusted for VAT. Only fasting individuals without self-reported T2DM are included in analyses.

studies investigating T2DM [11,13] with most focus towards low birth weight (<2500 g). A meta-analysis by Whincup et al. of 28 studies found an OR of T2DM of 0.76 per 1 kg increase in birth weight and 0.70 after adjustment for BMI, which correspond to what we find in the linear regression models with the same adjustments [25]. Another meta-analysis by Harder et al. of 14 studies reported a u-shaped association between birth weight and T2DM [26]. Most former studies have analysed birth weight as a categorical variable based on arbitrary categories. A major strength of our study is that we analysed birth weight as a continuous variable and used splines to assess a potential non-linear association over the entire birth weight scale. The spline figures showed a slight indication of a u-shaped association for HOMA-IR and $ISI_{0,120}$, but there was a high uncertainty in the ends and the numerical tests confirmed linearity. In analyses with birth weight categorised there was a tendency towards a j-shaped association with T2DM and a positive with hyperglycaemia but all insignificant. When categorising birth weight, extreme observations may be driving the associations and given the relatively few cases this should be interpreted with caution. The shape of the association between birth weight and T2DM in two native North American populations was estimated to be u-shaped [25], which may be more comparable populations to Inuit than European ancestry populations. Furthermore, the meta-analysis by Whincup et al. [25] suggested that associations in younger populations from later birth cohorts are less inverse and perhaps positive. Thus, a j- or u-shaped association with T2DM in our population cannot be excluded.

The pathophysiological mechanisms linking birth weight with later glucose markers and insulin resistance are not fully understood. Our results indicate that low birth weight is linked to hepatic and peripheral insulin resistance in Greenlandic Inuit. This is consistent with other studies showing that the link goes through insulin resistance [10] rather than beta-cell dysfunction [27]. It has also been suggested that birth weight and T2DM may be manifestations of the same genotype, which could be due to impairment of beta-cell development that is genetically programmed [28]. Arctic Inuit have a high frequency of the gene variant, *TBC1D4* p.Arg684-Ter, which is strongly associated with muscle insulin resistance and T2DM [3]. Adjustment for the *TBC1D4* variant did not change the estimates markedly but modified the association between birth weight and 2-h plasma glucose with a positive association for homozygous carriers. This opposite effect of birth weight for homozygous carriers indicates that a higher birth weight may be more problematic and suggests that the mechanisms involved in the development of T2DM are specific for this group. The *TBC1D4* finding needs to be investigated further and replicated in future studies. However, there may be known and unknown common genetic mechanisms contributing and/or modifying the observed association between birth weight and glucose metabolism in our study.

The associations reported were only significant after adjustment for current body size, indicating birth weight effects independently of adiposity in adulthood. We have previously shown for this study population that higher birth weight was associated with adiposity measured by BMI, waist
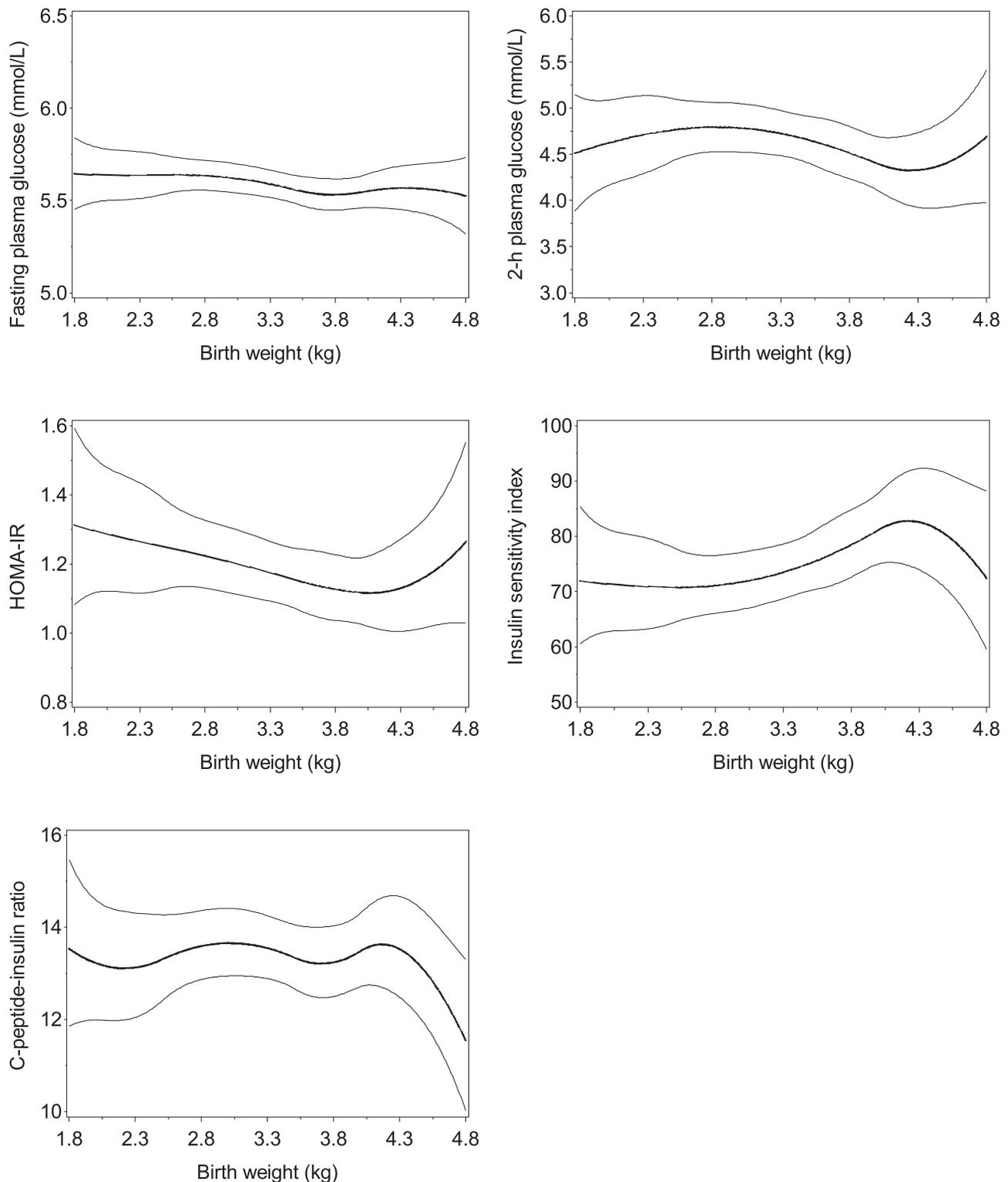
Fig. 1 – Quadratic splines of the association between birth weight and fasting plasma glucose, 2-h plasma glucose, HOMA-IR, insulin sensitivity index and c-peptide-insulin ratio. The thick lines represent the relation with 95%CI predicted for a man, aged 33 years, full Inuit, born in a town, with no family history of diabetes, TBC1D4 non-carrier and a BMI of 25 kg/m².

circumference, fat mass index, fat-free mass index and subcutaneous adipose tissue [14]. Thus, when current body size is adjusted for, any positive associations between birth weight

and glycaemia and insulin resistance that are mediated through adiposity or body size are removed. It is therefore not surprising that direct associations with birth weight are

Table 3 – Odds ratios (95%CI) for hyperglycaemia and type 2 diabetes per kg increase in birth weight.

	n	Model 1	Model 2	Model 3	n	Model 4
Fasting hyperglycaemia[*]	1257	0.76 (0.54, 1.07)	0.79 (0.56, 1.11)	0.68 (0.47, 0.97)	966	0.67 (0.43, 1.04)
Postprandial hyperglycaemia[*]	1113	0.95 (0.62, 1.47)	1.02 (0.63, 1.62)	0.95 (0.59, 1.54)	956	0.91 (0.54, 1.54)
Type 2 diabetes[**]	1163	0.76 (0.44, 1.30)	0.80 (0.46, 1.41)	0.70 (0.39, 1.25)	989	0.52 (0.27, 0.99)

Model 1: adjusted for age and sex. Model 2: model 1 additionally adjusted for birthplace, family history of diabetes, admixture and *TBC1D4* variant.
Model 3: model 2 additionally adjusted for BMI. Model 4: model 3 additionally adjusted for VAT.
[*] Compared to individuals with normal glucose tolerance. Only fasting individuals without self-reported T2DM are included in analyses.
[**] T2DM (including self-reported diabetes) versus rest.

expressed only following adjustment for current body size. Other studies have similarly found associations with T2DM independently of current BMI in African Americans [29] and Japanese women [30]. It has been pointed out that controlling for variables on the casual pathway can introduce a statistical artefact – the reversal paradox [31]. Adjustment for BMI generally strengthened the inverse relationships, and only the association with HOMA-IR was reversed after adjustment. Lucas et al. [32] argued that when birth weight is only related to later health outcomes after adjustment for current size this may be a measure of change in size between birth and adulthood. In line with this, more recent studies on early in life nutrition associations with adult disease, indicate that compensatory growth in infancy or early childhood, rather than in the womb, may be the primary contributor to cardiometabolic changes in adult life [33,34]. As such it is possible that the associations observed in the current study reflect effects of catch-up growth following a lower birth weight rather than birth weight per se. We did not have repeated measures of growth through childhood, so we cannot determine if it is birth weight per se or catch-up growth that is related to insulin resistance.

A main limitation of the study is that information on gestational age was not available, so we were not able to differentiate infants born preterm from growth restricted infants. However, studies from other populations have shown that the associations exist independently of gestational age [10,25]. Furthermore, birth weight is only a proxy of fetal growth reflecting maternal, genetic and environmental factors that may both directly and indirectly program to disease in the offspring. Especially, maternal smoking and gestational diabetes has been linked to birth size and T2DM in the offspring [35,36] and could have introduced unmeasured confounding in our study.

Metabolic disorders in adulthood may be a result of different lifestyle and social factors through the life course e.g. socioeconomic status. Although we adjusted for birth place as a proxy of socioeconomic status at birth that should reflect parental living conditions in urban and rural areas, it could not capture social position across the life course. Information on smoking, alcohol and physical activity in adulthood was not included in the analyses since these are not considered confounders in the association. Family history of diabetes and self-reported diabetes was based on questions of diabetes overall and although the prevalence of type 1 diabetes is very small in the Greenlandic population [37], we cannot rule out that type 1 diabetes is included in these cases.

Lastly, participants from the two included studies differed on some of the covariates (e.g. age, birth weight, birth place, waist circumference, 2-h plasma glucose, 2-h insulin and c-peptide); however, tests for modification by study did not indicate any study differences in the associations.

In conclusion we found that a higher birth weight was associated with lower fasting glucose, and lower hepatic and peripheral insulin resistance independently of current adiposity. There were some indications of u-shaped associations, but these were not significant and consistent across the models. Overall, the findings indicate that factors leading to small size at birth independently or in combination with catch-up growth in childhood may affect adult glucose markers in a Greenlandic Inuit population. This may be a contributing factor to the high levels of T2DM seen in Greenland which has undergone a nutrition transition where a large part of the population is exposed to an increasingly obesogenic environment and a more sedentary lifestyle. The results emphasize the importance of prevention among pregnant women in Greenland targeting nutrition and other early life risk factors to ensure a healthy life start for the offspring.

Author contributions

MEJ, PB, GSA and PFR contributed to the conceptual design of the study. MEJ, PB, IKD, CVLL and NG contributed to data collection. PFR, LS and GSA analysed the data. PFR and GSA wrote the paper. All authors contributed to interpretation of results and approved the final manuscript.

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Conflicts of interest

MEJ, GSA and PFR was until December 31, 2016, employed by Steno Diabetes Center A/S, a research hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. MEJ and GSA own shares in Novo Nordisk. PFR, LS, PB, IKD, CVLL and NG have nothing to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.005.

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