Birth weight and risk of adiposity among adult Inuit in Greenland

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Running head (max 50 characters):

Abbreviations:

ABSTRACT (max 300 words)

Background: The Inuit population in Greenland has undergone rapid socioeconomic and nutritional changes simultaneously with an increasing prevalence of obesity. Fetal programming has been suggested as part of the aetiology. To our knowledge, the impact of birth weight on development of adiposity has never been addressed in Arctic populations.

Objective: To examine the association between birth weight and measures of body composition and fat distribution in adulthood among the Inuit in Greenland.

Design: The study was based on cross-sectional data from a total of 1,473 adults aged 18-61 years within two population-based surveys conducted in Greenland between 1999-2001 and 2005-2010. Information on weight at birth was collected from birth records. Besides anthropometric measures of adiposity, fat mass index (FMI) and fat-free mass index (FFMI) were assessed by bio impedance. Visceral (VAT) and subcutaneous adipose tissue (SAT) was estimated by ultrasound. The associations were examined by linear regression analyses and quadratic spline graphs. Analyses was stratified by sex, and adjusted for age, birthplace, ancestry and family history of obesity.

Results: Spline analyses showed linear relations between birth weight and adult adiposity. In multiple regression analyses birth weight was found to be positively associated with BMI, waist circumference, FMI, FFMI and SAT with weaker associations among women than men. An inverse association between birth weight and VAT appeared for men after adjustment for overall abdominal adiposity with an increase in VAT of -4,1 % (95% CI: -7,3;-0,9) per 1-kg increment in birth weight.

Conclusions: Findings suggest that higher birth weight is associated with adiposity in adulthood. However, among men, low birth weight seems to increase the risk for accumulation of VAT

when overall abdominal adiposity is taken into account, indicating a more adverse metabolic risk profile.

INTRODUCTION

The Inuit population in Greenland has undergone rapid social, nutritional and health transitions during the last decades, and especially high levels of obesity has been observed among the Inuit, as well as type 2 diabetes and ischemic heart disease (1,2).

Globally, changes in lifestyle behaviours, as a result of transition and urbanisation patterns may play an important role in explaining the observed increase in obesity prevalence and related co-morbidities (3), but also factors in intrauterine life ~~are~~ have been proposed to contribute significantly. The fetal origins hypothesis has been used to explain the role of fetal growth in the development of later chronic disease (4,5) by postulating a mismatch between intrauterine and adult life environments (6). Birth weight has been widely studied as a proxy of fetal growth and especially low birth weight has been linked to intrauterine growth restriction (IUGR) and adverse health outcomes including obesity (7,8). Despite an extensive research suggesting a link between birth weight and subsequent obesity, the relevant mechanisms in humans are still unclear and studies are not consistent in their findings with both linear, J- and U-shaped relations (4).

Positive associations has been established between birth weight and adult body mass index (BMI) (9). However, it is well-recognized that the use of BMI in studies is connected with several limitations. For instance BMI fails to differentiate between fat and lean mass, and does not reflect body fat distribution (10). Since the body composition and distribution of fat are important for the development of cardiometabolic disease (REF), research focusing on the relation between birth size and measures of body composition and fat distribution may be important. Several studies have consistently demonstrated positive associations between birth weight and fat-free mass in adults (11–16), indicating that the relation between birth weight and adult obesity rather is explained by an increase in fat-free mass than fat mass. Studies investigating measures of fat mass and fat-free mass are, however, contradictory in their results (17).

~~Furthermore,~~ less is known about the relation between birth weight and accumulation of visceral (VAT) and subcutaneous abdominal tissues (SAT) in adult life. A better understanding of the development of these tissues is important because excessive VAT has shown to be strongly associated with metabolic disturbances and related to insulin resistance (18), whereas SAT may have independent anti-atherogenic effects and other protective properties (19).

Comment [PR1]: skal evt. udspecificeres

The association between birth weight and adult fat distribution has only been investigated to a limited extent and mostly assessed by measuring waist circumference and skinfolds (12,13,20). More accurate measures of abdominal fat tissues such as magnetic resonance imaging (MRI), computed tomography (CT), or ultrasonography can help clarify the relation between birth weight and subsequent obesity, however, only few previous studies have used those techniques (21–23). Ultrasonography has been validated against the reference methods MRI and CT in large-scale studies, where these techniques are not feasible (24).

The role of birth weight in the development of obesity has to our knowledge never been studied in Greenland or in other Arctic populations. The aim of our study was therefore to investigate the relations between birth weight and adult body composition and fat distribution measured by ultrasonography among the adult Inuit population in Greenland.

SUBJECTS AND METHODS

Study population

The study was based on cross-sectional data from two population-based surveys conducted in Greenland between 1999-2001 and 2005-2010. Participants were selected through a random sample of adult Inuit in Greenland (aged 18+ years). For both studies, participants were recruited to fill out self-administered questionnaires and/or personal face-to-face interviews, and ~~in continuation hereof requested to~~ participate in a clinical examination. Informed consent was obtained from participants during investigation, and the studies were approved by the ethical review committee of Greenland. The study methods are described in detail elsewhere (25,26). From a total of 4,221 participants who went through clinical examinations, we excluded 37 individuals in the two studies with another ethnicity than Greenlandic. Moreover, we excluded individuals born before 1950, as birth weight before this year was not systematically registered (n=6 individuals). Participants with no information on birth weight (n=1,669) were excluded and 50 individuals were excluded due to missing values on one or more of selected covariates. Subsequently, the remaining 1,473 individuals constituted the study population of the present study, which corresponds 47.7 % of participants born after 1950.

Measurements

Information on birth weight (kg) was gathered from medical records at hospitals for all the participants where journals were accessible. This included birth records, midwife records and outpatient records of participants, and for the latest years information from the birth register of the general practitioner/chief medical officer.

The questionnaires used as survey instruments for personal interviews and self-administered questionnaires were available in Greenlandic and Danish. A trained research team performed all clinical measurements.

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

Ultrasonography. Measures of intra-abdominal tissue divided into SAT and VAT, were assessed by ultrasonography performed by a portable ultrasound scanner (Pie Medical) using a 3.5 MHz transducer with the participant in supine position and at the end of a normal expiration. The distances between the posterior edge of the abdominal muscles and the lumbar spine was measured using electronic calipers. Both measurements were obtained from where the xiphoid line and the waist circumference met. Distances were measured 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 and SAT (cm) was defined as the depth from the skin to the linea alba (25).

Bio impedance. Bio impedance and calculation of fat mass were performed on a leg-to-leg Tanita TBF-300MA (Tanita Corporation, Tokyo, Japan). Fat mass was calculated as the total weight of fat from the internal algorithm of the device based on height, weight, sex, impedance and age (25). Fat-free mass (kg) was calculated as the total body mass minus fat mass. FMI (kg/m^2) was calculated as fat mass divided by height squared and FFMI (kg/m^2) was calculated as fat-free mass divided by height squared.

Additional covariates. Information on sex and age was retrieved from the central personal register (CPR), while birth place, ancestry, and family history of obesity were collected from survey questionnaires. Birth place was categorized as follows: *1)* town and *2)* village. Ancestry was based on questions on ethnicity of the four grandparents, and if this information was missing, of the parents. The variable was subsequently recoded as *1)* full Inuit (all grandparents were Greenlanders) and *2)* mixed Inuit (at least one grandparent or parent was Greenlander). Family history of obesity was determined based on whether the participant' parents and/or siblings were reported obese or severely overweight. The variable was dichotomised as *1)* yes (parents, siblings or both was regarded obese/overweight) and *2)* no.

Statistical analyses

Spline analyses were used to visually investigate the continuous relations between birth weight and measures of adult adiposity (BMI, WC, FMI, FFMI, VAT and SAT). Fractional polynomial regressions were applied because of the advantage of not making any a priori assumption of the shape of the relations. We used quadratic splines based on predicted values for an average person with a given set of criteria of the covariates (33 years, full Inuit, born in a town and with a family history of obesity). The splines were interpolated with three knots for each outcome measure. Tests for linearity confirmed that linear regression models performed as good as the fractional polynomial models.

Further, linear regression models were used to assess the effect estimates of associations between birth weight and adiposity measures. Because of skewed distributions in outcome variables, the adiposity measures were all log-transformed, and the beta-coefficients were back transformed and expressed as percentage change per 1 kg change in birth weight. In all models we tested for sex interactions (birth weight · sex), which resulted in significant interactions in models with waist circumference and FFMI. We did, however, choose to stratify all analyses on sex, due to biological differences in body composition and fat distribution between genders. Regression analyses were performed in three steps; unadjusted analyses between the different birth size measures and each of the adiposity measures (**model 1**); multiple linear regression analyses with adjustment for the chosen potential confounders (age, birthplace, ancestry and family history of obesity) (**model 2**); and lastly analyses with further adjustment for waist circumference in models including VAT and SAT as outcome measures (**model 3**). The p-values reported are all two-tailed with statistical significance defined as $p<0.05$.

Statistical analyses were performed using the statistical software SAS, version 9.3 (SAS Institute Inc., Carey, NC, USA).

RESULTS

Characteristics of the study population

Population characteristics are summarized in **Table 1**. The mean age of participants was 33 years (range 18-61). Men had a greater mean birth weight than women (3415 ± 531 g vs. 3277 ± 569 g) while a total of 89 participants (6 %) had a low birth weight defined as a weight below 2,500 g. Obesity regarded as a BMI > 30 kg/m^2 was reported among 15 % of men and 19 % of women. Women showed to have a higher mean fat mass and mean SAT as compared to men, while men showed to have a higher mean fat-free mass and mean VAT as compared to women.

Shape of the associations

Figure 1 and **Figure 2** show the shape of the associations for the continuous relations between birth weight and the different adiposity outcomes estimated by second ordered piecewise polynomial models for men and women respectively. The spline analyses in general showed no indication of non-linear associations, except for a slightly inverse association between birth weight and VAT for men after further adjustment for waist circumference.

Birth weight and body composition

The results of multiple linear regression models are shown in **Table 2**. Birth weight was positively associated with BMI and FMI for both genders after adjustment for potential confounders (model 2). An increment in birth weight of 1 kg resulted in a 13.1 % (95% CI: 3.3; 23.8) increase in FMI for men, and an increase of 9.1 % (95% CI: 2.0; 16.8) for women. Moreover, there was a significant positive association between birth weight and FFMI among men only with an increase of 3.7 % (95% CI: 2.2; 5.3) in FFMI per 1-kg increment in birth weight.

Comment [PR2]: Muligvis udelades

Comment [PR3]: vi har igen diskuteret om splines analyses skal beskrives før eller efter vi præsenterer effekterne fra de multiple regressionsanalyser. Hvad tænker I?

Fat distribution

~~Results showed that~~ birth weight was positively related to waist circumference indicating an increased risk of overall abdominal obesity. There was, moreover, a positive association between birth weight and SAT among men only with an increase of 15.8 % (95% CI: 3.2; 30.1) in SAT per 1-kg increment in birth weight (model 2). Birth weight was found not to be significantly associated with VAT among either gender, until after further adjustment for waist circumference (model 3), which resulted in a significant inverse association between birth weight and VAT for men with a decrement of -4.1 % (95% CI: -7.3; -0.9) per kg increment in birth weight.

DISCUSSION

We aimed to investigate the relations between birth weight and adult body composition and fat distribution among the Inuit population in Greenland. Our findings showed that birth weight was positively associated with BMI, WC, FMI and FFMI with generally weaker associations among women than men. Birth weight was similar positively associated with SAT estimated by ultrasound, while in contrast there was an inverse association with VAT independently of abdominal adiposity for men only.

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Body composition

We found that birth weight was positively associated with BMI and FMI both among men and women, which emphasises that higher birth weight increases the risk of relative fat mass in adulthood. Furthermore, we observed that birth weight was more strongly associated with FMI than with FFMI. This finding contradicts results from other studies reporting positive associations between birth weight and fat-free mass rather than fat mass (27,28,15,29). For instance, Singhal *et al* suggested that an increase in birth weight of 1 SD was significantly associated with an increase of 0.9-1.4 kg (2–3%) in fat-free mass, and not in fat mass, among adolescents (15). Conversely, the studies further suggested that increased fat-free mass explained the observed associations between birth weight and BMI. Evidence on the relation between birth weight and fat mass is, however, not clear.

A challenge mentioned in the literature is that absolute measures of lean and fat mass represent, not only the proportion of compartment, but also body size itself (16). We addressed this problem by including indexes of fat and fat-free mass in analyses, which are considered as more appropriate measures because they are adjusted for variability in height (30).

To our knowledge, this is the first study conducted in Greenland or in any other Arctic population, examining birth weight and later development of adult adiposity. An alternative explanation of the observed associations between birth weight and measures of body composition is that the impact of fetal growth on the tendency to deposit fat relative to lean mass is specific for Inuit. ~~Values~~ of body mass varies within and between populations, and is for instance shown ~~significantly~~ higher in Artic and Pacific populations, as compared to African, Asian, Australian and South American populations (16). Moreover, ethnic differences in the accumulation of fat and lean mass in late gestation has been suggested (31). Furthermore, an association between the thermal environment at birth and body mass has been suggested in the literature, pointing at climatic adaptions which might already start during fetal life (32). Hence, mechanisms of thermogenesis in body weight regulation could partly explain the relation between birth weight and relative composition of adult fat mass and fat-free mass in Inuit found in the present study. Consequently, it might be problematic to generalise effects of birth weight on later body composition between populations due to ethnic differences in tissue development in fetal life.

Fat distribution

Independently of overall abdominal fat we found a statistical significant inverse association between birth weight and VAT among men. Rolfe *et al* found a similar relation for men and women together after adjustment for overall obesity (23). In contrast, studies by McNeely *et al* (22) and Choi *et al* (33) found no associations between birth weight and VAT, whereof McNeely *et al* similar adjusted for overall obesity. Small sample sizes in these studies could have underpowered their ability to find associations. A cohort study by Demerath *et al* measuring VAT and SAT by MRI in adults suggested that infant weight gain, and not birth weight, was positively associated with adult VAT (21). In comparison with these studies, our finding of an inverse association between birth weight and VAT among Inuit men was based on a large sample of adults, giving more statistical power to the analyses. As low birth weight is commonly followed by rapid catch-up growth (34,4,35,36), we cannot determine whether birth weight or postnatal growth is the factor ~~of most importance~~. With adiposity measured at a single point in adulthood, we were not able to rule out an effect of postnatal growth. A longitudinal study with repeated measures of adiposity from birth to adulthood would help clarify the role of postnatal growth. Nevertheless, some studies found associations between birth weight and adult adiposity independent of postnatal weight gain or rapid catch-up growth (9).

Our findings of positive associations between birth weight and SAT is in contrast to the findings by Rolfe *et al*, where birth size was suggested to have limited influence on SAT. A recent study suggest that the level of SAT among the Inuit population in general is higher compared to other populations, while VAT does not differ from other populations (37). It could be hypothesized that the observed tendency of increased accumulation of SAT is a result of evolutionary adaptions to climate regulating thermogenesis (38). Accordingly, suggested mechanisms possibly influence adaptions in Inuit, in terms of thicker subcutaneous layers, making them more likely to distribute fat subcutaneously because of cold temperatures. It is suggested that specific layers of abdominal SAT correlate favourable with health and disease risk in individuals (39).

Except for the association between birth weight and VAT among men, our results did not show an increase in adiposity among individuals with low birth weight. These findings are in agreement with results from a meta-analysis by Schellong *et al* suggesting no indication of U-shaped associations between birth weight and adult overweight (9).
Overall, our results indicate that birth weight influences later development of adult adiposity among Inuit in Greenland. Whether this, as suggested by the fetal origins hypothesis, is a result of a mismatch between nutritional insults in fetal life and a later excess of food, is difficult to determine. Greenland has like many other countries undergone a rapid transition towards a more westernized lifestyle (2), but this pattern might be specific for Greenland and incomparable with changes seen in other developing countries. For instance, the Inuit in Greenland still have a high intake of fish and sea mammals, even though imported foods constitute a large part of the diet today (40). Despite quite consistent evidence for fetal programming as a phenomenon playing a role for later health across populations (ref), the Inuit seem to be protected against some diseases compared to other populations e.g. lower blood pressure and lower cholesterol levels for a given value of overweight compared to Danes (41). These differences in risk profiles and disease

patterns could indicate ethnic-specific pathways by which development of disease is programmed.

A major strength of this study is that information on birth weight is collected from birth records in contrast to many previous studies using self-report, which could have introduced recall bias. There was no systematic difference in covariates between individuals with traced and non-traced birth records besides in regard to place of birth (town vs. village). However, a recent study shows no association between unhealthy dietary pattern and urbanisation in Greenland (42) or differences in obesity prevalence, between towns and villages (43). Furthermore, the large number of participants with fat distribution measured by ultrasound provides another strength of this study, especially in a logistic challenging context like Greenland. The relation between birth size and intra-abdominal fat distribution measured by ultrasound has to our knowledge only previously been studied by Rolfe *et al* examining 1,092 adults in the UK (23).

The use of splines to examine the shape of the associations in the current study made it possible for us to confirm non-linear relations between birth weight and adult adiposity. While studies consistently have found low birth weight to be associated with increased risk of a range of diseases like type 2 diabetes and cardiovascular disease (ref), evidence on the shape of the association between birth weight and adult adiposity is more unclear (9,17). Our findings suggested no relation between low birth and overall adiposity except with VAT after adjustment for waist circumference. Spline analyses are regarded a valuable tool for future studies to clarify potential linear and non-linear associations between birth size and later disease.

Limitations

We acknowledge that there are some limitations in our study. As a consequence of unavailable information on gestational age we were not able to differentiate between infants born preterm and IUGR infants. Gestational age could therefore confound our findings, however, a number of studies adjusting for gestational age, suggest that it only have limited impact on the association between birth size and later adiposity (28,16,9,44,45). Moreover, the use of birth weight as a proxy of fetal growth can be problematic, as fetal growth may not be reflected in birth weight, and maternal nutrition does not equal fetal nutrition (46). Studies with more accurate measures to detect fetal growth could help elucidate the causal relation with the IUGR.

Conclusion and further research

- The inverse association with VAT among men have implications for investigating the relation between birth weight and glucose outcomes in Greenland
- More large-scale studies using accurate measures to assess abdominal fat tissues.

This is definition, we dont need any more research!

ACKNOWLEDGEMENTs

Jeg savner lidt om effekten af log-transformation. Specielt sat i relation til hvad andre har gjort – det kan være en indikation af at I har valgt den rigtige og letforståelige måde at rapportere på.

REFERENCES

1. Jørgensen ME, Bjerregaard P, Kjærgaard JJ, Borch-Johnsen K. High prevalence of markers of coronary heart disease among Greenland Inuit. Atherosclerosis. Februar 2008;196(2):772–8.
2. Jørgensen ME, Borch-Johnsen K, Witte DR, Bjerregaard P. Diabetes in Greenland and its relationship with urbanization. Diabet Med. 2012;29(6):755–60.
3. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care. Juni 2011;34(6):1249–57.
4. Cottrell EC, Ozanne SE. Early life programming of obesity and metabolic disease. Physiol Behav. April 2008;94(1):17–28.
5. Gluckman PD, Hanson MA. Developmental Plasticity and the Developmental Origins of Health and Disease. I: Newnham JP, Ross MG, redaktører. Early Life Orig Hum Heal Dis. Basel: Karger; 2009.
6. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. Juli 1992;35(7):595–601.
7. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia. Januar 1993;36(1):62–7.
8. Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. November 1999;70(5):811–6.
9. Schellong K, Schulz S, Harder T, Plagemann A. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. PloS One. 2012;7(10):e47776.
10. Wells JCK. The Evolutionary Biology of Human Body Fatness: Thrift and Control. Cambridge University Press; 2010.
11. Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. Am J Clin Nutr. November 2005;82(5):980–7.
12. Loos RJ, Beunen G, Fagard R, Derom C, Vlietinck R. Birth weight and body composition in young adult men--a prospective twin study. Int J Obes Relat Metab Disord J Int Assoc Study Obes. Oktober 2001;25(10):1537–45.

P value for H_0: Linear association.

Table 2 Associations between birth weight and measures of adiposity stratified by sex

	% Increment per kg increment in birth weight (95% CI)		
	Model 1	Model 2	Model 3
Men			
BMI (kg/m^2)	5.0 (2.6 ; 7.5) *	5.1 (2.7 ; 7.6) *	
Waist circumference (cm)	3.8 (1.8 ; 5.8) *	4.0 (2.1 ; 5.9) *	
Fat mass index (kg/m^2)	13.6 (3.0 ; 25.2) *	13.1 (3.3 ; 23.8) *	
Fat free mass index (kg/m^2)	3.8 (2.2 ; 5.3) *	3.7 (2.2 ; 5.3) *	
Visceral Adipose tissue (cm)	3.8 (-1.5 ; 9.4)	3.2 (-1.8 ; 8.4)	-4.1 (-7.3 ; -0.9) *
Subcutaneous adipose tissue (cm)	17.4 (4.4 ; 32.1) *	15.8 (3.2 ; 30.0) *	-1.5 (-9.5 ; 7.3)
Women			
BMI (kg/m^2)	2.8 (0.5 ; 5.2) *	2.4 (0.2 ; 4.7) *	
Waist circumference (cm)	1.3 (-0.4 ; 3.1)	0.9 (-0.8 ; 2.6)	
Fat mass index (kg/m^2)	11.2 (3.7 ; 19.3) *	9.1 (2.0 ; 16.8) *	
Fat free mass index (kg/m^2)	0.2 (-1.1 ; 1.5)	0.2 (-1.1 ; 1.5)	
Visceral Adipose tissue (cm)	4.4 (0.1 ; 8.9) *	3.2 (-0.8 ; 7.3)	0.8 (-2.2 ; 3.8)
Subcutaneous adipose tissue (cm)	8.3 (0.8 ; 16.4) *	7.4 (-0.1 ; 15.4)	3.5 (-1.3 ; 8.5)

Model 1: Unadjusted model. Model 2: Adjusted for age, birthplace, ancestry and family history of obesity. Model 3: Additional adjusted for waist circumference. * $P < 0.05$

FIGURE LEGENDS

Figure 1 Relations between birth weight and adiposity outcomes for men. The curves show predicted values (thick lines) estimated for a person aged 33 years old, being full Inuit, born in a town, and reported family history of obesity. Full thin lines show the 95 % CI and dotted lines show the 95 % prediction interval.

Comment [PR5]: Figurerne skal rettes til i layout

Figure 2 Relations between birth weight and adult adiposity outcomes for women. The curves show predicted values (thick lines) estimated for a person aged 33 years old, being full Inuit, born in a town, and reported family history of obesity. Full thin lines show the 95 % CI and dotted lines show the 95 % prediction interval.