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No association between early maternal HbA1c and offspring birthweight among women without pre-existing diabetes in Greenland

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ABSTRACT

Studies of the association between maternal blood glucose measured by glycated haemoglobin (HbA1c) during pregnancy and the offspring's birthweight have been heterogeneous. The aim of this study was to examine the association between maternal HbA1c level before gestational week 20 and the offspring's birthweight among predominantly indigenous women in Greenland. A retrospective cohort study including all women ($n = 503$) and their offspring delivered from September 2015 to September 2016 at Queen Ingrid's Hospital in Nuuk was conducted. Data were obtained from the electronic medical record. Linear regression models were used to analyse the effect of maternal HbA1c on the offspring's birthweight with adjustment and stratification for relevant confounders and effect modifiers. Birthweight increased with 3.3 g per mmol/mol increase in HbA1c. Yet, no significant association between maternal HbA1c and the offspring's birthweight was found after adjustment for maternal age, ethnicity, residence, smoking, and parity ($\beta = 0.058$, $p = 0.711$). Among obese women, a borderline significant positive association ($\beta = 0.657$, $p = 0.059$) was found. For term newborns, this corresponded to an increase in birthweight of 31 g per mmol/mol increase in HbA1c. Based on the current study, the use of HbA1c during pregnancy to detect the risk of delivering a newborn with macrosomia is not recommended in Greenland.

Abbreviation: HbA1c: glycosylated haemoglobin; GA: gestational age; SD: standard deviation; CI: confidence interval.

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Glycosylated haemoglobin; birthweight; pregnancy; Greenland

Introduction

Birthweight has been identified as an important predictor of type 2 diabetes, cardiovascular disease and inflammatory disease later in life [1–3]. Recently, this association has also been documented among Inuit in Greenland. High birthweight was associated with adiposity in adulthood while low birth weight increased the risk of adult glucose intolerance [4,5]. Birthweight is determined by a number of factors, including the delivery of glucose to the foetus [6]. The Pedersen hypothesis [7] suggests that maternal hyperglycaemia leads to foetal hyperglycaemia, foetal hyperinsulinemia and excess growth. Hyperglycaemia among adults has increased in Greenland during the last two to three decades [8]. In the same period, average birthweight and proportion of infants with high birthweight have increased in Greenland [9]. The increase in birthweight, and also increased growth among younger children,

has been suggested to be a consequence of genetic admixture, maternal overweight, changes in nutrition and improved health [10].

Glycated haemoglobin (HbA1c) reflects the average blood glucose level over the 8–12 weeks preceding the test [11]. Maternal HbA1c during pregnancy has been shown to be associated with adverse pregnancy outcomes, including birthweight, among pregnant women with diabetes [12,13] as well as among normoglycemic women [6,14–16], but the findings are heterogeneous and inconclusive. An early HbA1c at or above 41 mmol/mol (5.9%) identified women at increased risk of poorer pregnancy outcome including a threefold increase in children born with macrosomia, independently of gestational diabetes diagnosis later in pregnancy in a multiethnic population in Spain [16]. The same threshold, 41 mmol/mol (5.9%), has been reported optimal for detecting gestational diabetes, in another multiethnic

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Key message: No association between early maternal HbA1c and the offspring's birthweight was found in a predominantly indigenous Greenlandic population with no pre-existing diabetes.

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population study from New Zealand [15]. Furthermore, HbA1c measurements were readily performed in contrast to low attendance to oral glucose tolerance test [15]. In line with this study, the use of oral glucose tolerance test to detect gestational diabetes in Greenland has been reported suboptimal with around a third of all pregnant women tested [17]. A possible association between maternal HbA1c and birthweight has yet to be studied among Inuit. Potentially, universal HbA1c screening early in pregnancy could be used to predict the risk of delivering an infant with high birthweight. The aim of this study was to examine the possible association between maternal HbA1c level before gestational week 20 and the offspring's birthweight among women with no pre-existing diabetes giving birth in Nuuk, Greenland.

Methods

This study was performed as a retrospective cohort study conducting secondary analysis of data collected for clinical purposes in the electronic medical record in Greenland.

Greenland is the world's biggest island covering approximately 2 million km² [18]. The 56,000 inhabitants live in 16 towns and approximately 60 settlements along the coastline. Healthcare is delivered by one united tax-funded public healthcare system. Around half of all deliveries in Greenland take place in the capital Nuuk, where the country's only obstetric department is located. Pregnant women experiencing complications are therefore referred to Nuuk for delivery. The remaining births take place locally at small hospitals in towns and settlements. All prenatal care and medical information are documented in a systemised medical record.

All women with a permanent address in Greenland who gave birth to a singleton born at gestational week 28 or later at Queen Ingrid's Hospital in Nuuk from September 2015 to September 2016 were included consecutively in the study. Women with multiple pregnancies, known pre-existing diabetes, polycystic ovary syndrome or treated with oral steroids were excluded ($n = 10$). Furthermore, it was not possible to calculate a birthweight z-score for 14 newborns as their birthweight either was missing ($n = 1$) or they were delivered in a gestational week where no other was delivered ($n = 13$ born ≤ 35 gestational weeks or ≥ 42 gestational weeks). The birthweight z-score was used as a continuous variable in the analyses. The final study population, therefore, consisted of 503 women and their newborns, which is equivalent to approximately 62% of all births in Greenland during a year.

HbA1c was defined as the first measurement of maternal HbA1c during pregnancy taken before gestational week 20. HbA1c was measured by a high-performance

liquid chromatography method that gives an elution profile in which the glycosylated and non-glycosylated haemoglobin components are resolved in a time-dependent manner by using a Tosoh G8 HPLC analyser in the laboratory at Queen Ingrid's Hospital in Nuuk [19]. HbA1c is measured as part of the routine blood samples among pregnant women. Outside Nuuk, blood tests are routinely collected on specific days with respect to flight schedules to minimise transportation time. Except for traffic delays, blood samples are generally analysed within 5 days.

Birthweight was obtained shortly after delivery without a diaper using a calibrated electronic scale by the midwife. Gestational age (GA) at delivery was based on the subject's self-reported last menstrual period and the date of the delivery. In cases where the last menstrual period was unknown and in cases where an ultrasound-based GA calculation deviated 2 weeks or more from the last menstrual-period-based GA, the ultrasound-based GA was used. Birthweight z-scores were calculated separately for males and females for each gestational week with the formula.

Birthweight z – score

$$= \frac{\text{birthweight} - \text{mean birthweight for sex and gestational week}}{\text{Standard deviation for sex and gestational week}}$$

Maternal age was calculated by subtracting the mother's birth year from the year of birth.

Women born in Greenland were considered Greenlanders, whereas women born outside Greenland were considered non-Greenlanders.

Place of residence was classified as Nuuk or the rest of Greenland. Women living in Nuuk were part of a general population while women living outside Nuuk were part of a high-risk pregnant population as they were referred to Nuuk to deliver due to experiencing complications during pregnancy.

Maternal BMI (kg/m²) before pregnancy was based on the subject's self-reported weight and height before pregnancy. Pre-pregnancy overweight was defined as a BMI at or above 25 kg/m² and pre-pregnancy obesity was defined as a BMI or above 30 kg/m². Women were considered normal weight if BMI was below 25 kg/m². This categorisation is in accordance with the WHO classification [20]. Women were categorised as smokers if they reported any tobacco smoking at the first prenatal visit. Women were defined as nulliparous if they had no former delivery of a child after GA 28 weeks.

Statistical analyses

Data were analysed using IBM SPSS Statistics version 24.0 (IBM, Corp., Armonk, NY, USA, released 2016). Descriptive statistics included means and standard deviations (SD) for continuous variables and number

and percentages for categorical variables. The crude and adjusted associations between HbA1c and birthweight z-score were analysed using multiple linear regression analysis. The adjusted associations were adjusted for maternal age, maternal ethnicity, maternal residence, smoking during pregnancy, and parity.

The assumptions for the linear regression models of linearity in the association between the independent and dependent variables, homoscedasticity and normally distributed residuals were tested and fulfilled for all analyses. The assumptions were tested with scatter plots and Q-Q plots. For the continuous variables, it was examined whether the association between the variables and birthweight z-score was best explained by the continuous variables or the variable raised in the second or third power. The association between all continuous variables and birthweight z-score was best explained by a linear model. Pearson's correlation coefficients were calculated to test for multicollinearity between the independent variables (data not shown). The highest observed correlation coefficient was 0.397, indicating no multicollinearity between the independent variables.

The analyses were additionally stratified for pre-pregnancy BMI, as it was assessed by an interaction analysis to be an effect modifier for the potential association. Missing data were not included in the analysis. Ninety-five per cent confidence intervals (CI) were used in the study. A two-sided p-value below 0.05 was used as the level of significance.

Ethical approval

The study was approved by The Ethics Committee for Medical Research in Greenland (2014–24) and The Agency of Health and Prevention in Greenland.

Results

The baseline characteristics of the study population are presented in Table 1. The mean birthweight was 3581 g, ranging from 1066 g to 5272 g and the newborns were delivered at median 276 days of gestation. Delivery before 37 weeks of gestation was observed in 7.8% (n = 39). The included women delivered slightly more boys than girls (53.3% vs. 46.7%). HbA1c ranged from 25 mol/l (4.4%) to 46 mol/mol (6.4%) with a mean of 38 mmol/mol (5.6%). The GA at the time of HbA1c measurement varied from 25 days to 139 days of gestation (median = 63 days, IQR = 47–84 days). There was a negative correlation ($r = -0.215$, $p < 0.001$) between HbA1c and GA at the time of HbA1c measurement. Maternal age at delivery ranged from 15 to 44 years with a mean of 28.2 years. A little more than half of the women had residence outside Nuuk. Any smoking during

Table 1. Characteristics of the study population (N = 504).

	<i>n</i>	Mean ± SD
Birthweight (g)	502	3,580.8 ± 602.6
Birthweight z-score	489	0.0 ± 1.0
HbA1c (mmol/mol)	378	38 ± 3.7
Maternal age (years)	504	28.2 ± 5.6
GA at birth (days)	504	274.7 ± 13.2
	<i>n</i>	%
Maternal residence		
Nuuk	238	47.3
Outside Nuuk	265	52.7
Maternal ethnicity		
Greenlander	449	89.3
Non-Greenlander	54	10.7
Pre-pregnancy BMI		
Normal weight	230	51.5
Overweight	118	26.4
Obesity	99	22.1
Smoking during pregnancy		
No smoking reported	301	59.8
Any smoking reported	202	40.2
Parity		
Nulliparous	200	39.8
Previous delivery	303	60.2
Offspring sex		
Female	235	46.7
Male	268	53.3

Missing: birthweight: 1, birthweight z-score: 14, HbA1c: 125, pre-pregnancy BMI: 56.

pregnancy was observed among 40.2% of the women included in the study. The vast majority were born in Greenland and thus defined as Greenlanders. The majority (51.5%) was normal weight with BMI below 25 kg/m².

Also, 24.8% of the women included in the study did not have a measurement of HbA1c before gestational week 20, and consequently they were not included in the linear regression analyses. Table 2 presents the differences between the women who had a measurement of HbA1c and the women who did not. Women without a measurement of HbA1c delivered newborns with significantly lower birthweight and at a significantly lower GA. However, there was no statistical significant difference in birthweight z-score. HbA1c was measured significantly more among women who did not live in Nuuk, but otherwise, there were no statistically significant differences between women with and without a measurement of HbA1c.

The univariate associations between age, ethnicity, BMI, smoking, place of residence, parity and birthweight are illustrated in Table 3. Women below 25 years old delivered infants with a mean birthweight z-score of -0.234 which was significant lower ($p = 0.001$) than women aged 25–35 years who delivered newborns with a mean birthweight z-score of 0.138.

Table 4 presents the results from the analyses of the effect of pre-pregnancy BMI on the association between HbA1c and birthweight z-score. The inclusion of an interaction term showed almost statistical significance in both model 1 ($p = 0.059$) and model 2 ($p = 0.052$).

Table 2. Differences between women with and without a HbA1c measurement.

	HbA1c measured (n = 378)		HbA1c not measured (n = 125)		p-value
	n		n		
Birthweight (g), mean ± SD	377	3617.5 ± 557.3	125	3470.2 ± 713.5 ^a	0.037
Birthweight z-score, mean ± SD	371	0.006 ± 1.005	118	-0.015 ± 0.996 ^a	0.838
Maternal age (years), mean ± SD	378	28.0 ± 5.4	125	28.8 ± 6.1 ^a	0.188
Pre-pregnancy BMI (kg/m ²), median (IQR)	335	24.8 (21.6–29.3)	112	24.0 (21.8–26.9) ^b	0.104
GA at birth (days), median (IQR)	378	278.0 (271.0–284.0)	125	275.0 (268.0–281.5) ^b	0.038
		%		%	
Maternal age					
<25 years	106	28.0	35	28.0 ^c	0.207
25–35 years	223	59.0	66	52.8	
≥35 years	49	13.0	24	19.2	
Maternal residence					
Nuuk	167	44.2	71	56.8 ^c	0.014
Outside Nuuk	211	55.8	54	43.2	
Smoking during pregnancy					
No smoking reported	230	60.8	71	56.8 ^c	0.424
Any smoking reported	148	39.2	54	43.2	
Maternal ethnicity					
Greenlander	343	90.7	106	84.8 ^c	0.063
Non-Greenlander	35	9.3	19	15.2	
Parity					
Nulliparous	154	40.7	46	36.8 ^c	0.435
Previous delivery	224	59.3	79	63.2	
Pre-pregnancy BMI					
Normal weight	164	49.0	66	58.9 ^c	0.086
Overweight	89	26.6	29	25.9	
Obesity	82	24.5	17	15.2	
GA at birth					
Born at time (GA ≥37 weeks)	352	93.1	112	89.6 ^c	0.202
Preterm delivery (GA <37 weeks)	26	6.9	13	10.4	
Offspring sex					
Female	173	45.8	62	49.6 ^c	0.457
Male	205	54.2	63	50.4	

^a: unpaired *t*-test was performed for comparison. ^b: Mann–Whitney U test was performed for comparison. ^c: χ^2 -test was performed for comparison.

This suggested that pre-pregnancy BMI might be an effect modifier for the association. This was supported by the stratified analysis which indicated that the association between HbA1c and birthweight z-score differed depending on the mother's BMI before pregnancy. For normal weight women, there was a tendency for increasing HbA1c to be associated with decreasing birthweight z-score when adjusted for the confounders. However, for both overweight and obese women increasing HbA1c tended to be associated with increasing birthweight z-score. Consequently, the adjusted analyses of the association between HbA1c and birthweight were stratified for BMI.

The results of the linear regression analyses of the effect of maternal HbA1c on the offspring's birthweight are presented in Table 5. There was no crude significant association between maternal HbA1c and birthweight ($\beta = 0.123$, $p = 0.428$). Yet, a positive association was observed since birthweight increased with 3.3 g per mmol/mol increase in HbA1c.

The adjustment for maternal age, maternal residence, smoking during pregnancy, maternal ethnicity and parity did not change the findings ($\beta = 0.058$, $p = 0.711$). The adjusted analyses were stratified for pre-pregnancy BMI as

it was assessed to be an effect modifier for the potential association. The results remained insignificant. However, among women with BMI ≥ 30 kg/m² a borderline significant positive association ($\beta = 0.657$, $p = 0.059$) was found. For term newborns, this corresponded to an increase in birthweight of 31 g per mmol/mol increase in HbA1c.

Discussion

No overall statistically significant association between maternal HbA1c and the offspring's birthweight was found in this study population of women with no pre-existing diabetes indicating that early HbA1c cannot be used to identify an increased risk of high birthweight. The findings from other studies of associations between maternal HbA1c in the first trimesters of pregnancy among women with no pre-existing diabetes and the offspring's birthweight are heterogeneous and inconclusive. Some studies have found similar results of no association between HbA1c and birthweight [21–24], while others have found an association [6,15,16]. Hughes et al. [15] and Mañé et al. [16] found HbA1c at or above 41 mmol/mol (5.9%) at the first prenatal visit to be associated with

Table 3. Mean birthweight z-score and HbA1c within variables and pairwise comparison.

	Birthweight z-score				
	n	Mean (g) ± SD	P-value for pairwise comparison		
			1 vs. 2	1 vs. 3	2 vs. 3
Maternal age					
<25 years	136	-0.234 ± 0.910	<i>0.001^b</i>	0.597	0.185
25–35 years	282	0.138 ± 1.021			
≥35 years	71	-0.093 ± 1.012			
Maternal residence					
Nuuk	231	-0.086 ± 0.989	0.068 ^a	–	–
Outside Nuuk	258	0.079 ± 1.008			
Smoking during pregnancy					
No smoking reported	294	0.066 ± 1.010	0.078 ^a	–	–
Any smoking reported	195	-0.097 ± 0.984			
Maternal ethnicity					
Greenlander	436	0.044 ± 1.000	<i>0.007^a</i>	–	–
Non-Greenlander	53	-0.351 ± 0.949			
Parity					
Nulliparous	193	-0.129 ± 0.984	<i>0.021^a</i>	–	–
Previous delivery	296	0.086 ± 1.006			
Pre-pregnancy BMI					
Normal weight	225	-0.198 ± 0.902	<i>0.001^b</i>	<i><0.001</i>	0.812
Overweight	115	0.202 ± 1.067			
Obesity	97	0.285 ± 1.043			

^a: unpaired two-tailed t-test was performed for comparison. ^b: ANOVA and Tukey-Kramer test were performed for comparison. – : analysis not performed.

P-values below 0.05 in italic.

Table 4. The effect of pre-pregnancy BMI on the association between maternal HbA1c and birthweight z-score.

	Increase in birthweight z-score per unit increase in variable	
	β-coefficient [95%-CI], p-value	
	Model 1	Model 2
Normal weight HbA1c (%)	-0.156 [-0.562–0.249], <i>p = 0.447</i>	-0.154 [-0.568–0.259], <i>p = 0.462</i>
Overweight HbA1c (%)	0.307 [-0.505–1.118], <i>p = 0.454</i>	0.312 [-0.520–1.145], <i>p = 0.458</i>
Obesity HbA1c (%)	0.552 [-0.052–1.155], <i>p = 0.073</i>	0.628 [-0.014–1.271], <i>p = 0.055</i>
p-Value for interaction	0.059	0.052

Model 1: unadjusted model. Model 2: adjusted for maternal age, maternal residence and smoking during pregnancy.

P-values below 0.05 in italic.

large-for-gestational-age and macrosomia, respectively. Furthermore, Karcaaltincaba et al. [6] found HbA1c measured at GA 24–28 weeks to be an independent predictor of birthweight. Yet, HbA1c was measured somewhat later at GA 24–28 weeks than in our study, where all measurements of HbA1c were done before GA 20 weeks. Studies conducted among women with type 1 diabetes with repeated measures of HbA1c showed a tendency for the association to differ depending on when HbA1c was

measured during the pregnancy [13,25]. HbA1c measured in second and third trimester tends to be more strongly associated with the offspring's birthweight than HbA1c measured in the first trimester [13,25].

The mean HbA1c among pregnant women in our study was 38 mmol/mol (5.6%), which is somewhat higher than in similar studies [6,15]. The same has been seen among non-pregnant Greenlandic Inuit compared to other populations [26]. The mean birthweight was 3,581 g and the national mean birthweight in 2014 was 3,540 g [9], both including preterm births. In the INTERGROWTH-21st Project, the mean birthweight ranged from 2,900 g in India to 3,500 g in the UK [27]. Thus, the mean birthweight in Greenland is somewhat higher compared to other populations. Furthermore, the average birthweight in the present study is much higher than earlier reported in Greenland, 3251 g in 1954 and 3376 g in 1990 [9]. The high proportion of women with pre-pregnant overweight and obesity in the present study may be contributing to the high average birthweight observed, since maternal overweight is associated with high birthweight [28]. It cannot be excluded that the high proportion of women with elevated pre-pregnancy BMI may have blurred the contrast between low or normal BMI compared to high BMI. Similarly, the high proportion of women smoking during pregnancy in this study may also have blurred a possible association, since smoking may increase HbA1c at the same time as it reduces birthweight [29,30].

This study is the first to investigate the association between maternal HbA1c among women with no pre-existing diabetes and the offspring's birthweight in Greenland and in a predominantly indigenous population. The prospectively collected data were collected within the past 2 years and thus largely reflect the current situation in Greenland. The number of participants in this study is equivalent to approximately 62% of all births in Greenland during the study period. Yet, only women who gave birth in Nuuk were included in the study. We only had access to birth certificates among the women who delivered in Nuuk; thus, all births in the whole of Greenland during the study period could not be included. Women residing outside of Nuuk are referred to Queen Ingrid's Hospital in Nuuk in case of complications; wherefore, women with complicated pregnancies are likely overrepresented in our study.

The use of data from the EMR holds some drawbacks including missing data, potentially observation variation from one health-care professional to another, between instruments and information or recall bias among women. On the other hand, the variation was not considered systematically. However, missing data were

Table 5. The association between maternal HbA1c and birthweight z-score.

	Increase in birthweight z-score per unit increase in variable β -coefficient [95%-CI], <i>p</i> -value	
	Unadjusted	Adjusted*
HbA1c	0.123 [−0.181–0.426], <i>p</i> = 0.428	0.058 [−0.250–0.366], <i>p</i> = 0.711
Normal weight HbA1c (%)	−0.156 [−0.562–0.249], <i>p</i> = 0.447	−0.273 [−0.679–0.133], <i>p</i> = 0.186
Overweight HbA1c (%)	0.307 [−0.505–1.118], <i>p</i> = 0.454	0.213 [−0.637–1.064], <i>p</i> = 0.619
Obese HbA1c (%)	0.552 [−0.052–1.155], <i>p</i> = 0.073	0.657 [−0.026–1.339], <i>p</i> = 0.059

*Adjusted for maternal age, maternal residence, smoking during pregnancy, maternal ethnicity and parity.

frequent and limit the statistical power of the analysis. Thus, around 25% of the women included in the study did not have a measurement of HbA1c before GA 20 weeks.

Only two women in the study population were diagnosed with gestational diabetes mellitus as they had a 2-h capillary whole-blood glucose value of 8.5 mmol/l or above following a 75 g 2-h glucose tolerance test. Therefore, it was decided to include the two women and their newborns in the analyses since exclusion of them could have biased the results. Also, the use of birthweight z-scores in a genetically mixed population may be problematic since birthweight varies among different ethnic groups. However, the only information about ethnicity available was the place of birth, which is not optimal to determine ethnicity. Some genetically Inuit are born in Denmark and some genetically Danes are born in Greenland. Also, among present Greenlanders, in average 25% of their genes are of European origin [31]. Thus, in this study, we found it relevant to include the minority of women born outside Greenland and thereby examine women representative for the actual population in Greenland in line with a study of other multiethnic populations mentioned in the introduction.

In conclusion, no overall significant association between maternal HbA1c and the offspring's birthweight was found among women with no pre-existing diabetes. Based on the current study, the use of HbA1c during pregnancy to detect the risk of delivering a newborn with macrosomia in non-diabetes is not recommended in Greenland.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Author contribution

All authors contributed to the study design. MLP was in charge of the data collection. KVR analyzed the data and wrote the first draft of the manuscript with inputs from KKN and MLP. All authors revised the manuscript and approved the final version.

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