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HbA$_1c$ levels in non-diabetic Dutch children aged 8–9 years: the PIAMA birth cohort study

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Abstract

Aim Glycated haemoglobin (HbA$_1c$) is considered the best index of glycaemic control in established diabetes. It may also be useful in the diagnosis of diabetes and as a screening tool. Little is known about the distribution of HbA$_1c$ in healthy children and its predictors. The aim of this study is to describe the distribution of HbA$_1c$ in non-diabetic Dutch children aged 8–9 years and to investigate potential associations of HbA$_1c$ in this group.

Methods HbA$_1c$ was measured in 788 non-diabetic children aged 8–9 years participating in the PIAMA birth cohort study. Data on parents and children were collected prospectively by questionnaires. Weight, height and waist and hip circumference of the children were measured when blood samples were taken.

Results Mean (SD) HbA$_1c$ was 4.9 ± 0.33%, range 3.5–6.0%. HbA$_1c$ was significantly higher in boys (4.9 ± 0.31 vs. 4.9 ± 0.33%) and in children of mothers with gestational diabetes (5.0 ± 0.37 vs. 4.9 ± 0.32%). We found a significant inverse association between HbA$_1c$ and haemoglobin (regression coefficient: −0.169 (95% CI −0.221 to −0.118), P < 0.001). HbA$_1c$ was not significantly associated with age, body mass index, waist circumference, parental diabetes or maternal body mass index.

Conclusions We found no significant relation between known risk factors for Type 2 diabetes and HbA$_1c$ at age 8–9 years. Moreover, there was a significant inverse association between haemoglobin and HbA$_1c$. These results suggest that HbA$_1c$ may not only reflect the preceding blood glucose levels, but seems to be determined by other factors as well.

Keywords children, glycated haemoglobin, non-diabetic

Abbreviations BMI, body mass index; HbA$_1c$, glycated haemoglobin; PIAMA, Prevention and Incidence of Asthma and Mite Allergy

Introduction

Glycated haemoglobin (HbA$_1c$) is currently considered the best index of glycaemic control for diabetic patients [1]. The level of HbA$_1c$ is associated with the development and progression of microvascular complications [2] and with mortality in adults [3,4]. In addition, HbA$_1c$ may be useful in the diagnosis of diabetes [5] and as a screening tool for detecting Type 2 diabetes in adults [6,7] and in children [8]. Compared with the oral glucose tolerance test, HbA$_1c$ measurement is quicker and can be performed at any time of the day. Moreover, the consensus statement on the worldwide standardization of HbA$_1c$ measurement of the Consensus Committee of the American Diabetes Association will contribute to worldwide comparability of HbA$_1c$ results [9]. With the rapid increase in incidence and prevalence of diabetes, there will be an accompanying increased use of HbA$_1c$ measurements in adults and in children. Therefore, it is important to develop reference levels and standards for HbA$_1c$ for adults and children.

The normal distribution for HbA$_1c$ for adults has been described and standardized by Simon et al. [10]. They found, in a population of 3240 healthy adults aged 40.2 ± 11.8 years,
an approximately normal distribution of HbA1c, with a slight difference between mean and median values at all ages in both sexes. There was no difference in mean HbA1c according to gender: 5.0 ± 0.53% in men vs. 5.1 ± 0.55% in women. HbA1c increased with deterioration of glucose tolerance and with all the known risk factors for diabetes (e.g., age, obesity and family history of diabetes). This study indicates that HbA1c in adults is influenced only by factors closely linked to diabetes.

Although the normal distribution for HbA1c has been described for adults, less is known about the distribution of HbA1c in healthy children, particularly in those younger than 10 years. With the expected future increase in use of HbA1c, it is important to develop reference levels and standards for HbA1c. Moreover, HbA1c could be an alternative measure to investigate early life and childhood determinants of impaired glucose tolerance and Type 2 diabetes in children. Therefore, the aim of this study is to describe the distribution of HbA1c in a large population of Dutch children aged 8–9 years without diabetes mellitus and to investigate associations of HbA1c in this group.

**Methods**

The study population consisted of 788 Dutch children born in the years 1996–1997 who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. Details of the study design have been published previously [11]. Recruitment took place in the years 1996–1997. A screening questionnaire on maternal allergy [12] was distributed to 10 232 pregnant women visiting one of 52 antenatal clinics in three different regions in the Netherlands (North, Central, West). Based on this screening, 7862 women were invited to participate in the study; 4146 agreed and gave written informed consent. Of those, 183 participants were lost to follow-up before any data on the child had been obtained, so that the study began with 3963 newborn children. Questionnaires were sent to the participating parents during pregnancy, at 3 months and yearly from 1 to 8 years of age. At 8 years of age, a subgroup of the study population (n = 1554), consisting of all children of allergic mothers (n = 988) and a random sample of the children of non-allergic mothers (n = 566), was invited for a hospital-based medical examination where a blood sample was taken and bronchial hyper-responsiveness was determined. From 1060 children, an EDTA blood sample was taken. Parents of 845 children gave informed consent to store plasma, erythrocytes and butyrate for later analysis of parameters other than the asthma-related parameters. Parents of 826 children eventually gave written informed consent for the measurement of HbA1c, in the stored blood samples. Of these 826 samples, in 790 an HbA1c value could be assessed. Two children with Type 1 diabetes were excluded from the current analyses.

For HbA1c analysis, erythrocytes were stored at -20°C between 33 and 322 days prior to assay. A 5-μl cell mass was lysated and HbA1c was measured by ion-exchange chromatography using the HA-8140 Hi-Auto HbA1c analyser (Menarini Diagnostics Benelux, Valkenswaard, The Netherlands). This analyser was standardized on Diabetes Control and Complications Trial (DCCT) standards. Between-batch imprecision (coefficient of variation) was 1.5% for a mean HbA1c of 6.0% and 2.0% for a mean HbA1c of 10.7%.

During the medical examination of the 8-year-olds, children were weighed and measured in their underwear. Weight was measured to 0.1 kg and height to 0.1 cm by trained research staff using calibrated measuring equipment. Body mass index (BMI) was calculated as weight/height squared (kg/m²). ‘Overweight’ and ‘obesity’ were defined according to age- and gender-specific international standards [13]. We use the term ‘overweight’ for the group of children who are overweight but not obese. Waist circumference, to the nearest 0.1 cm, was measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration with a measuring tape. Hip circumference, to the nearest 0.1 cm, was measured at the greater trochanter. Waist and hip circumference were measured twice and the mean of the two measurements was used in the analysis. Birthweight data were obtained from the questionnaire sent to the participating parents 3 months after birth. Infant feeding data were collected by questionnaires at age 3 months and 1 year. These data were used to derive a variable categorized as never breastfed, less than 16 weeks breastfed and more than 16 weeks breastfed. Data on ethnicity of each parent (born in the Netherlands and of Dutch ethnicity, born in another Western country and of Dutch or another Western ethnicity, not born in a Western country or of non-Western ethnicity), educational level of each parent (three categories: low, intermediate and high), maternal BMI and parental diabetes were obtained by questionnaire. Parental educational level was defined as the highest educational level of father or mother. Data on lifestyle of the children, such as eating behaviour and hours spent watching television, were obtained from questionnaires sent to and filled out by the parents around the child’s 8th birthday.

From the answers to the questions about eating behaviour, the variable ‘snack score’ was calculated. Parents answered questions about the frequency certain food and drink products were used, such as sweets and confectionery, fried snacks and soft drinks (there were five categories: never, less than once a week, on 1–2 days per week, on 3–5 days per week or on 6–7 days per week). All products were scored by a dietician on the basis of their average nutritional value (kcal) per portion, based on the average consumption of different types of the product, for example, diet and non-diet, in this age group. Thus, for each child, a snack score (kcal per week) was calculated.

**Statistical methods**

We used Student’s t-test and one-way ANOVA to test for differences in mean HbA1c between groups. Differences in HbA1c between groups, adjusted for duration of sample storage, age and gender, were tested with ANCOVA. The relation between HbA1c and continuous variables was tested with linear regression, with and without adjusting for duration of sample storage, age and gender. For all analyses, a level of significance of P < 0.05 was applied. All analyses were performed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

At 8 years of age, a subgroup of the study population, consisting of all children of allergic mothers and a random sample of the children of non-allergic mothers, was invited for a hospital-based medical examination. Therefore, offspring of allergic mothers were over-represented in our population. We repeated all analyses.
in the two different groups: the offspring of allergic mothers and the offspring of non-allergic mothers.

**Results**

Characteristics of the study population are described in Table 1. Figure 1 displays the distribution of HbA1c in the whole study population. Mean (±SD) HbA1c was 4.9 ± 0.33% (range 3.5–6.0%). None of the children had an HbA1c > 6.0%. HbA1c was higher in boys compared with girls (Table 2). In addition, HbA1c was higher in children classified as obese compared with children classified as normal weight and overweight, although this was not statistically significant. HbA1c was significantly higher in children from the Northern region compared with children from the West and Central regions. Moreover, HbA1c was significantly higher in the offspring of mothers with gestational diabetes compared with the offspring of mothers without gestational diabetes. HbA1c was higher in the offspring of obese mothers and in children watching television for more than 2 h per day, although these differences were not significant. HbA1c was not different between the children of parents with different educational levels. We found no differences in HbA1c between these groups (data not shown).

We found a significant relation between HbA1c and the duration of sample storage. HbA1c decreased by 0.001% (~0.001 to 0.000%) per day storage ($P < 0.001$). Mean HbA1c values, after adjusting for duration of sample storage, age and
gender, are given in Table 2. Most differences listed above remained. In addition, we found a lower mean (sd) HbA1c in children who are not a member of a sports club (4.8 ± 0.31%) compared with children who are a member of a sports club (4.9 ± 0.32%). However, this finding could arise by chance.

We found a significant association between HbA1c and haemoglobin, with a 0.169% (95% CI −0.221 to −0.118) decrease in HbA1c (% per mmol/l haemoglobin) (adjusted for duration of sample storage, age and gender) (P < 0.001).

We found no significant association between HbA1c and age in this population of children aged 8–9 years. There was also no significant association between the continuous variables of birthweight, anthropometric measures at 8 years (BMI, waist and hip circumference and waist-to-hip ratio), maternal BMI or snack score and HbA1c (P > 0.10).

Because offspring of allergic mothers were over-represented in our population, we repeated all analyses in the offspring of allergic and non-allergic mothers separately. The results were similar in both groups.

### Discussion

In this population of 788 non-diabetic Dutch children aged 8–9 years, HbA1c is normally distributed, with a mean (sd) HbA1c of 4.9 ± 0.33% (range 3.5–6.0%). HbA1c is higher in boys compared with girls and in the offspring of mothers with gestational diabetes compared with the offspring of mothers without gestational diabetes. We also found a higher HbA1c in children from the Northern region and an inverse association between haemoglobin levels and HbA1c. We found no significant relation between HbA1c and other known risk factors for Type 2 diabetes.

Saaddine et al. described the distribution of HbA1c in children and young adults in the USA by use of data from the Third National Health And Examination Survey [14]. A total of 7974 non-diabetic children, adolescents and young adults aged 5–24 years were included. The overall mean (sd) HbA1c was 5.0 ± 0.50%, varying from 4.9% (95% CI ± 0.04) in non-Hispanic whites, 5.1 ± 0.02% in Mexican-Americans and 5.2 ± 0.02% in non-Hispanic blacks. We included only children aged 8–9 years and in our study population, whereas 94.6% of the children were of Dutch ethnicity. The younger study population and differences in ethnicity could explain the difference in reported mean HbA1c. As in our current study, Saaddine et al. also found a higher HbA1c in men and in overweight participants. Pettitt et al. established the distribution of HbA1c in 400 children aged 11–13 years [8]. They found a mean (sd) HbA1c of 4.8 ± 0.39% (range 3.4–5.7%). In contrast to our data, they found no difference in HbA1c between boys and girls.

Eldeirawi and Lipton investigated predictors of HbA1c in almost 5000 non-diabetic children and adolescents aged 4–17.0 years. In their study population, HbA1c also differed significantly between boys and girls, with boys having a higher HbA1c than girls [15]. Also Shultis et al. found a higher HbA1c in boys compared with girls [16].

In contrast to the studies of Eldeirawi and Lipton and Shultis et al., we found no relation between HbA1c and age. This could be explained by the very small age range in our study population.

We found a significantly higher HbA1c in the children from the Northern region compared with the HbA1c in children from West and Central regions. Controlling for potential confounding factors (duration of sample storage, age, gender, gestational diabetes of the mother and haemoglobin level) did not change this relation. There are no differences between the three regions in the way the blood samples were taken, processed and stored. Thus, the higher HbA1c in children from the Northern region remains largely unexplained.

<table>
<thead>
<tr>
<th>Table 2 Clinical characteristics and HbA1c</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Crude mean</td>
<td>Adjusted mean</td>
<td>SD</td>
</tr>
<tr>
<td>Girls</td>
<td>4.8</td>
<td>3.49</td>
<td>0.13</td>
</tr>
<tr>
<td>Boys</td>
<td>4.9</td>
<td>3.49</td>
<td>0.13</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>0 weeks</td>
<td>4.8</td>
<td>0.33</td>
</tr>
<tr>
<td>&lt; 16 weeks</td>
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<td>0.32</td>
<td>0.11</td>
</tr>
<tr>
<td>≥ 16 weeks</td>
<td>4.9</td>
<td>0.31</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI</td>
<td>Normal</td>
<td>4.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Overweight</td>
<td>4.9</td>
<td>0.34</td>
<td>0.15</td>
</tr>
<tr>
<td>Obese</td>
<td>5.0</td>
<td>0.39</td>
<td>0.32</td>
</tr>
<tr>
<td>Region</td>
<td>North</td>
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</tr>
<tr>
<td>West</td>
<td>4.8</td>
<td>0.28</td>
<td>0.28</td>
</tr>
<tr>
<td>Central</td>
<td>4.8</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>Parental educational level</td>
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<td>0.37</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4.9</td>
<td>0.32</td>
<td>0.12</td>
</tr>
<tr>
<td>High</td>
<td>4.9</td>
<td>0.32</td>
<td>0.10</td>
</tr>
<tr>
<td>Maternal BMI</td>
<td>Normal</td>
<td>4.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Overweight</td>
<td>4.9</td>
<td>0.36</td>
<td>0.16</td>
</tr>
<tr>
<td>Obese</td>
<td>4.9</td>
<td>0.25</td>
<td>0.26</td>
</tr>
<tr>
<td>Parental diabetes</td>
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<td>4.9</td>
<td>0.26</td>
</tr>
<tr>
<td>No</td>
<td>4.9</td>
<td>0.33</td>
<td>0.10</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Yes</td>
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<tr>
<td>No</td>
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<td>0.32</td>
</tr>
<tr>
<td>Member of a sport club</td>
<td>Yes</td>
<td>4.9</td>
<td>0.33</td>
</tr>
<tr>
<td>No</td>
<td>4.8</td>
<td>0.32</td>
<td>0.11</td>
</tr>
<tr>
<td>Time watching TV</td>
<td>≤ 2 h</td>
<td>4.9</td>
<td>0.33</td>
</tr>
<tr>
<td>&gt; 2 h</td>
<td>5.0</td>
<td>0.27</td>
<td>0.28</td>
</tr>
<tr>
<td>Time playing outside</td>
<td>≤ 3 times/week</td>
<td>4.9</td>
<td>0.32</td>
</tr>
<tr>
<td>&gt; 3 times/week</td>
<td>4.9</td>
<td>0.33</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*P < 0.05; †adjusted for duration sample storage, age and gender. BMI, body mass index; HbA1c, glycated haemoglobin; SD, standard deviation.
At least two studies have prospectively examined the role of exposure to diabetes in utero on childhood growth, later obesity and risk for Type 2 diabetes in the offspring [17,18]. In both studies, higher glucose concentrations and a higher prevalence of diabetes was found in the offspring of mothers with diabetes during pregnancy. This supports our finding of a higher HbA1c in the offspring of mothers with gestational diabetes.

The negative association between haemoglobin and HbA1c is in line with a decrease of HbA1c after iron supplementation in iron-deficient patients [19,20]. Thus, HbA1c levels are not only the result of preceding blood glucose levels and this should be taken into account when considering HbA1c as a screening tool.

Birthweight is associated with greater insulin resistance in children [21,22]. However, in our study population, in the study population of Shultis et al. [16], as well as in Jamaican schoolchildren [23], no association was found between HbA1c and birthweight. Breastfeeding recently has been suggested as being protective against the development of Type 2 diabetes in youth, mediated in part by current weight status in childhood [24]. In our study population, we found no association between HbA1c and breastfeeding. Also in the study of Shultis et al., breastfeeding initiation and exclusivity were not associated with HbA1c in 1645 non-diabetic children aged 9–11 years [16]. Family history of diabetes is strongly associated with Type 2 diabetes in children [25,26]. However, as with Shultis et al. [16], we found no relation between parental history of diabetes and HbA1c in children.

Taken together, we did not find an association between known risk factors for Type 2 diabetes and HbA1c in children aged 8–9 years. At this young age, the increased insulin resistance as a result of these risk factors presumably is not yet present or is fully compensated for by increased insulin production, resulting in normal glucose and HbA1c levels. Unfortunately, we did not assess insulin levels in our study.

Our study population is not representative of all Dutch children of similar age. It contains less overweight and obese children and ethnic minorities are under-represented. Several studies found higher HbA1c levels in children from minority populations in the USA [9,14,16] and Shultis et al. found a slightly higher HbA1c in children from non-white ethnic background in their study population of 1645 UK children (95.3% white, 4.7% non-white). In our study population, only 3.2% of the children were from non-Western origin, which is not representative of all Dutch children of similar age. Potential differences in HbA1c between children from different ethnic groups in the Dutch population of children aged 8–9 years could be missed. In the PIAMA birth cohort study, pregnant women were recruited from the general population by means of a validated screening questionnaire on maternal allergy.

In this cohort of 788 non-diabetic Dutch children, HbA1c was normally distributed. We found a higher HbA1c in boys and in the offspring of mothers with gestational diabetes, compared with their counterparts. We found no significant relationship between HbA1c and other known risk factors for Type 2 diabetes. Moreover, we found a significant inverse association between haemoglobin levels and HbA1c and an unexplained higher HbA1c in children from the north of the Netherlands. Thus, it could be argued that HbA1c values should be interpreted with caution. They may not only reflect the preceding blood glucose levels, but seem to be determined by other factors as well.

Competing interests
Nothing to declare.

References


