# $HbA_{1c}$ in Nondiabetic Dutch Infants Aged 8–12 Months

## The GECKO-Drenthe birth cohort study

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**OBJECTIVE**—An international committee of experts recommended using $HbA_{1c}$ for diagnostic testing for diabetes. Little is known about normal values of $HbA_{1c}$ in infants. The aim of this study is to describe the distribution of $HbA_{1c}$ in 8- to 12-month-old nondiabetic infants.

**RESEARCH DESIGN AND METHODS**—$HbA_{1c}$ was measured in 86 infants participating in the Groningen Expert Center for Kids with Obesity (GECKO)-Drenthe birth cohort study. Anthropometric measurements were performed at Well Baby Clinics. Data on parents and children were collected prospectively using questionnaires.

**RESULTS**—$HbA_{1c}$ was normally distributed with a mean (SD) $HbA_{1c}$ level of 5.38% (0.24), range 4.8–6.0% or 35.29 mmol/mol (2.65), range 29.1–42.1 mmol/mol. Age, sex, birth weight, duration of breastfeeding, anthropometric measurements, and maternal BMI were not associated with $HbA_{1c}$.

**CONCLUSIONS**—We found a normal distribution of $HbA_{1c}$ with a relatively high mean $HbA_{1c}$ of 5.38%. No significant association between risk factors for type 2 diabetes and $HbA_{1c}$ levels was found.

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An international committee of experts recommended using $HbA_{1c}$ as an indicator for diagnosing diabetes, and, with the prevalence of type 2 diabetes rising, an increase in use of $HbA_{1c}$ can be expected (1). Accordingly, reference levels for $HbA_{1c}$ will need to be developed for all age groups. This study's aim is to describe the distribution of $HbA_{1c}$ in nondiabetic infants aged 8–12 months, and to investigate predictors of $HbA_{1c}$.

## RESEARCH DESIGN AND METHODS

The study population consisted of 86 Dutch infants participating in the Groningen Expert Center for Kids with Obesity (GECKO)-Drenthe study. This population-based birth cohort study within the GECKO was designed to examine risk factors for developing childhood obesity (2). A random subgroup ($N$ = 100) of this study population, aged about 8 months, was invited to participate in the current study. Eighty-seven parents agreed to participate, and in eighty-six infants, an $HbA_{1c}$ value could be assessed. This study was approved by the Medical Ethics Committee of the University Medical Center Groningen.

$HbA_{1c}$ was measured in a capillary blood sample using a turbidimetric inhibition immunoassay on a Cobas Integra 800 CTS analyzer (Roche Diagnostics, Nederland BV, Almere, the Netherlands). This method has been standardized against the reference method of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Results (mmol $HbA_{1c}$/mol Hb) were converted to units (% $HbA_{1c}$) traceable to the Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP) using the Roche master-equation. Between-batch imprecision (coefficient of variation) was 2.1% for a mean $HbA_{1c}$ of 5.5% and 1.9% for a mean $HbA_{1c}$ of 10.6%.

Anthropometric measurements were performed by trained staff at Well Baby Clinics (2). Forty-eight percent of the infants did not visit the Well Baby Clinic within 2 weeks around blood sampling. For these infants, weight, length, and waist circumference were determined by linear interpolation. Weight, waist circumference, and weight-for-length $z$-scores were calculated using Growth Analyzer 3.5 (Growth Analyzer B.V., Rotterdam, the Netherlands), based on Dutch reference values (3,4). Growth velocity was defined as increase in weight between birth and time of blood sampling, in grams per week.

Data on gestational age, birth weight, infant feeding, gestational diabetes, maternal BMI, and parental educational level were obtained through questionnaires, and missing data was obtained from Well Baby Clinic files. Small for gestational age (SGA) and large for gestational age (LGA) were defined as birth weight below the 10th percentile and above the 90th percentile, respectively, for gestational age compared with Dutch reference values by parity and sex (5).

We used ANOVA to test for differences in mean $HbA_{1c}$ between groups and linear regression to test the relationship between continuous variables and $HbA_{1c}$. For all analyses, a level of significance of $P < 0.05$ was applied. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Chicago, IL).

## RESULTS

Of the 86 infants included, 43 were girls and 43 were boys, with a mean (SD) age of 9.42 months (1.14). Mean (SD) $HbA_{1c}$ was 5.38% (0.24), range was 4.8–6.0%, with a skewness (SE) of 0.215 (0.260) and a kurtosis (SE) of −0.004 (0.514). According to IFCC values, mean (SD) $HbA_{1c}$ was 35.29 mmol/mol (2.65), range 29.1–42.1 mmol/mol (Fig. 1).

$HbA_{1c}$ was unrelated to age or sex. Birth weight, growth velocity, anthropometric

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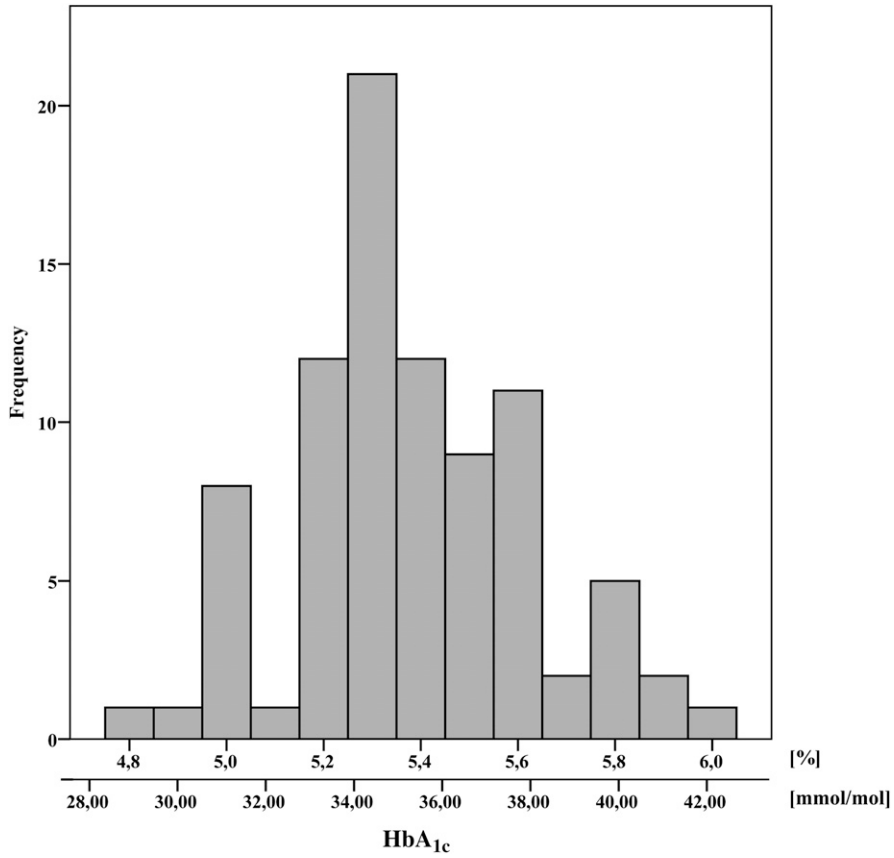


**Figure 1—***Distribution of $HbA_{1c}$ in infants aged 8–12 months. Mean (SD): 5.38% (0.24) or 35.29 mmol/mol (2.65).*

measurements, duration of breastfeeding, gestational diabetes, maternal BMI, and parental educational level were all unassociated with $HbA_{1c}$. $HbA_{1c}$ did not differ between infants born SGA and infants not born SGA, or between infants born LGA and those not born LGA.

**CONCLUSIONS**—In this nondiabetic infant population, aged 8–12 months, $HbA_{1c}$ was normally distributed, with a mean (SD) $HbA_{1c}$ of 5.38% (0.24), range 4.8–6.0%.

The mean $HbA_{1c}$ of 5.38% observed in the current study is higher than that found by studies in adults and older children (6–9). Because $HbA_{1c}$ below 6% is considered normal, the clinical relevance of the difference between an $HbA_{1c}$ level of 4.9% seen in adults and children, compared with 5.4% in our study population, is arguable. However, because the rate of formation of $HbA_{1c}$ is directly proportional to ambient glucose concentration, our results could indicate higher glucose levels in 8- to 12-month-old infants. The predominant fuel for human cells is glucose, and survival of the brain depends on a continuous supply, yet the brain cannot synthesize glucose nor store more than a few minutes supply as glycogen. The infant brain is large relative to body mass and, especially in this period, rapid brain growth and differentiation takes place. To meet the high demand for glucose, the rate of glucose production in infants and young children is two to three times that of older children and mature adults (10). This high demand for glucose by the brain and the subsequent higher rate of glucose production might explain the higher $HbA_{1c}$ levels observed in this study. Another explanation for the relatively high $HbA_{1c}$ levels might be the higher percentage of infant fat mass compared with older children; fat mass is known to be positively related to insulin resistance (11,12). Unfortunately, glucose and insulin levels were not assessed, so we could not test these hypotheses.

At birth, between 55 and 65% of total hemoglobin synthesis consists of HbF. After birth, the production of the γ-chain declines to values of <5% by the age of 6 months; normal adult HbF values of <1% are usually reached by age 1 year (13). Because our study population's age ranged from 8.1–12.3 months, somewhat higher levels of HbF might be expected. Glycated HbF is not detected by the turbidimetric inhibition immunoassay we used; HbF, however, is included in total hemoglobin determination. Because $HbA_{1c}$ is expressed as a proportion, infants with high amounts of HbF (>10%) may have lower than expected $HbA_{1c}$ values (14). However, this does not explain the relatively high $HbA_{1c}$ levels found in our study.

The life span of a fetal erythrocyte is approximately 60–80 days, and the life span of erythrocytes in infants is still less than the 120-day life span of erythrocytes in adults (15). A shorter life span for erythrocytes should show lower $HbA_{1c}$ levels instead of the higher levels we found.

To our knowledge, this is the first study describing the distribution of $HbA_{1c}$ in nondiabetic infants. Compared with known $HbA_{1c}$ levels in older children, we found a relatively high mean $HbA_{1c}$ of 5.38%. No significant association between known risk factors for type 2 diabetes and $HbA_{1c}$ was found.

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