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Reference values for fasting serum resistin in healthy children and adolescents

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ABSTRACT

Background: Resistin is a hormone, mainly produced in macrophages and monocytes, believed to play an important role in the inflammatory response. It has been linked to several chronic diseases such as heart failure, inflammatory bowel disease, and insulin resistance. Pediatric reference levels are needed for the risk stratification and interpretation of individual serum resistin concentrations.
Methods: A total of 1191 healthy, non-obese Danish schoolchildren (727 girls) aged 6–18 years (median 11.9) were included. Fasting serum resistin concentrations were quantitated by Human Resistin ELISA Development kit, Duo Set (R & D Systems) following optimization.
Results: The overall median resistin concentration was 8.93 ng/mL (interquartile range (IQR): 6.19–13.33, range 1.57–35.84) in boys and 10.42 ng/mL (IQR: 7.25–15.68, range 1.60–44.00) in girls. The resistin concentration correlated to relative BMI in both boys ($p = 0.02$) and girls ($p < 0.0001$). Percentiles for each age group were calculated alongside smoothed percentile curves and an age correlated increase was demonstrated, albeit only in girls ($p = 0.02$) and not in boys ($p = 0.35$).
Conclusion: Fasting serum resistin concentrations differ between sexes in healthy children and adolescents and are correlated both with the sex- and age adjusted BMI, and in girls to age.

1. Introduction

1.1. Origin and function of resistin

Resistin is a member of the resistin-like molecule (RELM) hormone family and was discovered in 2001 [1]. In humans, the main sources of resistin secretion are macrophages and monocytes [2–5]. Furthermore, resistin has been detected in a variety of other tissues including skeletal muscle, kidneys, adrenal glands, and brown adipose tissue [6]. The physiological role of resistin in many of these organs remains to be fully elucidated [7].

Resistin is believed to play an important role in the inflammatory responses [8,9] and has been linked to several chronic diseases such as coronary heart disease [10], heart failure [11], and inflammatory bowel disease [12]. The hormone has been linked to obesity [13,14] as well as insulin resistance [15] and it appears that macrophages infiltrating the visceral white adipose tissue are the predominant contributor to the circulating resistin concentration in individuals with obesity [16]. Yet, the exact role of resistin in the obese body is still a matter of debate [14].

1.2. Reference values in pediatrics

Many laboratory variables in pediatrics vary not only with age but also with sex, growth, and development and consequently, the reference values for a given variable should ideally be established in the

Abbreviations: BMI, body mass index; GAMLSS, General Additive Model for Location Scale and Shape; SDS, standard deviation score

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pediatric age ranges for both sexes. Various methods for establishing reference intervals have been proposed [17] and large study groups of presumably healthy subjects are necessary to enable an age and sex stratification. Yet, for practical reasons, large groups of normal children are rarely studied, and furthermore, ethical considerations may preclude the blood sampling in healthy children.

1.3. Resistin in pediatrics

Similarly, the interpretation of serum concentrations of resistin in children, and thus an assessment of the clinical utility of resistin is hampered by the relative lack of reference values from children and adolescents. Only a few studies on resistin concentrations in children and adolescents have been published, and the available data are largely obtained from small and heterogeneous study materials containing a limited number of healthy, non-obese children [14,18].

1.4. Study aims

The objective of this study is to explore the naturally occurring serum concentrations of resistin in a large ethnically homogenous cohort of healthy, non-obese Danish schoolchildren aged 6 to 18 years and subsequently to establish reference ranges for children and adolescents across sex and age groups.

2. Material and methods

2.1. Subjects

Danish schoolchildren from several municipalities in the region of Zealand, Denmark were included between January 2010 and November 2013. The exclusion criteria were regular use of statins (n = 0) or anti-inflammatory drugs (n = 0) as they have been known to influence resistin concentrations [19]. Due to the possible link to obesity, all children with obesity, defined as a body mass index (BMI) above the 95th percentile for sex and age [20], at the time of inclusion were excluded (n = 274). To adjust for genetic variation, ethnicity other that Danish/North European white were excluded (n = 160). Finally, twins were excluded (n = 6). All participants and/or parents gave informed consent and signed a consent document. The study was approved by the Danish Data Protection Agency and the Regional Scientific Ethics Committee (protocol no. SJ-104). The study is part of The Danish Childhood Obesity Biobank, and is registered at ClinicalTrials.gov ID-no.: NCT00928473.

2.2. Anthropometric measurements

The participants were examined by skilled research assistants immediately prior to blood sampling. Height and weight were measured while wearing light indoor clothes and no shoes, using a stadiometer to the nearest millimetre and a BC-418 Segmental Body Composition Analyzer (Tanita, Tokyo, Japan) to the nearest 100 g, respectively. A BMI standard deviation score (SDS) was calculated by the LMS method by converting BMI into a normal distribution by sex and age using the median, the coefficient of variation, and a measure of the skewness [21] based on the Box-Cox power plot from Danish BMI charts [22]. The baseline BMI is expressed in SDS in order to reflect the relative weight adjusted for age, sex and growth during childhood and adolescence.

2.3. Additional data collection

Additional data on socioeconomic status and health status were obtained through a structured family-based questionnaire. Similarly, the pubertal developmental stage was self-assessed using a questionnaire with standardized pictures of the five pubertal developmental stages *ad modum* Tanner [23,24] accompanied by a text describing each category and thereby allowing the participants and their parents to estimate the appropriate pubertal developmental stage. Self-evaluated pubertal staging has been shown to adequately describe pre-pubertal versus pubertal status. Therefore, pubertal stages were defined as pre-pubertal (Tanner 1) or pubertal (Tanner 2–5) [25].

2.4. Biochemical analyses

After an overnight fast, venous blood samples were collected from each child between 7:00 and 9:00 am. The samples were processed immediately and the serum was stored at − 80 °C until further analysis.

The serum resistin concentration was quantitated *in singlo* using the Human Resistin ELISA Development kit, Duo Set (DY1359, R & D Systems, Minneapolis, MN, USA) as suggested by the manufacturer following appropriate sample dilution. The functional lower detection limit of the resistin assay was 31.25 ng/mL. The intra- and inter-assay coefficients of variation (CVs) were < 5% and < 10%, respectively. A highly purified *E. coli*-expressed recombinant human resistin produced by the kit manufacturer was used as a calibrator.

An analysis of pre-analytical variation demonstrated that storage for 56 h at room temperature, storage at − 20 °C for three months as well as 10 freeze-thaw cycles did not influence resistin concentration measurements.

2.5. Statistical analyses

Statistical modeling was performed using the statistical software R (version 3.2.4) [26]. Skewness was estimated by D'Agostino test and log transformation of data was performed when appropriate. Differences between sexes were evaluated non-parametrically for the entire group and for each age interval using the Wilcoxon–Mann–Whitney test. Previous studies [27] and initial analyses of our data demonstrated, that the resistin concentrations differ between the sexes, and therefore, the data were analysed separately for each sex and subsequently adjusted for age and BMI SDS.

Smoothed percentile curves for resistin as a function of age were calculated as a continuous variable using the General Additive Model for Location Scale and Shape (GAMLSS) [28] with the penalized cubic spline function and the Box-Cox *t*-distribution family (best fit determined by the Akaike Information Criterion). Percentiles for age groups applied exactly for the midpoint of each age group were calculated with the GAMLSS package. Furthermore, the correlations between resistin and both age and BMI SDS were evaluated using a generalized linear model [29].

3. Results

3.1. Demography

A total of 1191 healthy children (727 girls), 6–18 years of age (median 11.9) were included in the study. The resistin concentrations were non-normally distributed in the entire population (Shapiro–Wilk test, $p < 0.0001$) as well as in boys and girls when analysed separately ($p < 0.0001$ and $p < 0.0001$, respectively). The two sexes did not differ in terms of age ($p = 0.09$), BMI SDS ($p = 0.95$), or socio-economic status ($p = 0.15$).

3.2. Relation to sex

The overall resistin concentrations were significantly lower in boys compared to girls ($p < 0.001$). For boys, the overall median resistin concentration was 8.93 ng/mL (IQR: 6.19–13.33, range 1.57–35.84) in boys and 10.42 ng/mL (IQR: 7.25–15.68, range 1.60–44.00) in girls. The percentiles for each age group were calculated in a GAMLSS model as presented in Table 1 and Figs. 1 and 2. In a generalized linear model,

Table 1
Percentiles of resistin (ng/mL) calculated with GAMLSS.

Age (years)	Percentiles for boys							Percentiles for girls						
	2.5	5	25	50	75	95	97.5	2.5	5	25	50	75	95	97.5
6	3.26	3.96	6.62	8.70	11.48	19.61	24.19	3.74	4.54	7.50	9.74	12.70	21.46	26.43
7	3.15	3.84	6.52	8.76	11.77	20.06	24.47	3.63	4.42	7.44	9.86	13.08	22.08	26.93
8	3.05	3.72	6.42	8.82	12.08	20.49	24.74	3.51	4.29	7.38	9.99	13.47	22.68	27.42
9	2.94	3.59	6.31	8.88	12.40	20.91	24.99	3.38	4.16	7.31	10.11	13.88	23.29	27.90
10	2.82	3.46	6.20	8.94	12.72	21.32	25.24	3.24	4.02	7.23	10.24	14.30	23.89	28.38
11	2.70	3.33	6.09	9.00	13.05	21.72	25.47	3.10	3.87	7.14	10.36	14.74	24.49	28.85
12	2.58	3.19	5.97	9.06	13.38	22.12	25.71	2.94	3.70	7.05	10.49	15.19	25.90	29.31
13	2.44	3.04	5.84	9.12	13.72	22.50	25.95	2.77	3.53	6.95	10.62	15.65	25.69	29.78
14	2.30	2.88	5.71	9.18	14.07	22.89	26.18	2.59	3.34	6.83	10.75	16.12	26.28	30.25
15	3.26	3.96	6.62	8.70	11.48	19.61	24.19	2.39	3.13	6.71	10.89	16.61	26.88	30.72
16	3.15	3.84	6.52	8.76	11.77	20.06	24.47	2.18	2.91	6.57	11.02	17.11	27.48	31.20
17	3.05	3.72	6.42	8.82	12.08	20.49	24.74	1.95	2.68	6.43	11.16	17.62	28.09	31.68
18	2.94	3.59	6.31	8.88	12.40	20.91	24.99	1.71	2.42	6.27	11.30	18.14	28.69	32.17

the resistin concentration was not correlated to age in boys ($p = 0.45$) and adjustment for BMI SDS and socioeconomic status did not alter the result ($p = 0.35$). In girls, the resistin concentration correlated with age ($p = 0.02$) and the correlation persisted when the model was adjusted for BMI SDS and socioeconomic status ($p = 0.02$).

In a generalized linear model, the resistin concentrations were positively correlated with BMI SDS in boys ($p = 0.02$) and girls ($p < 0.0001$). Adjustment for age did not alter the correlations ($p = 0.02$ and $p < 0.001$, respectively).

3.3. Relation to pubertal stage

In a subset of 745 included cases (493 girls), the pubertal stages *ad modum* Tanner [24] were registered. Using a Wilcoxon-Mann-Whitney test, the pre-pubertal and pubertal groups were compared, but no significant differences in resistin concentrations were detected in neither boys nor girls ($p > 0.05$ for both sexes). Similarly, using Tanner stage I (i.e. pre pubertal) as a reference, the Tanner stage groups II through IV were compared individually, but no significant differences in resistin concentrations were detected in neither boys nor girls ($p > 0.05$ for both sexes).

4. Discussion

4.1. Differences between sexes

In the present study, we provide serum resistin concentrations in a cohort of 1191 healthy, non-obese Danish schoolchildren. We observed significantly higher concentrations of resistin in girls as compared to boys; an observation that is in accordance with previous data by other groups [18,27]. We found this sex-based difference to increase with age, which is also in accordance with previous data [18,30]. Interestingly, the age-dependent increase in resistin concentrations was only observed in girls. Accordingly, our data emphasize the need for sex- and age dependent reference values in children.

4.2. Population/geographic differences

Previous studies have reported a difference in resistin concentrations between different ethnical groups [18]. As expected, we observed

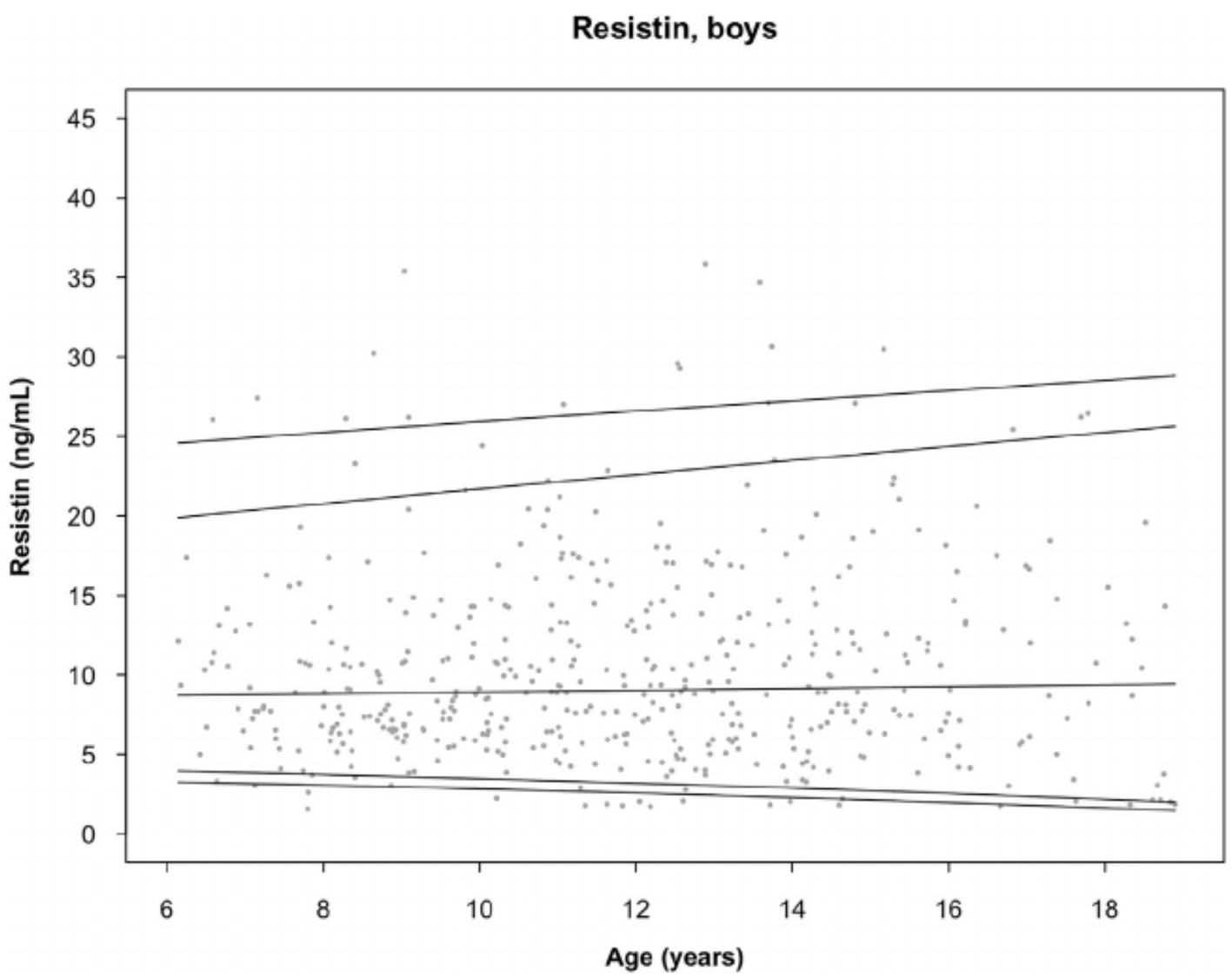

Fig. 1. Resistin as a function of age in boys.

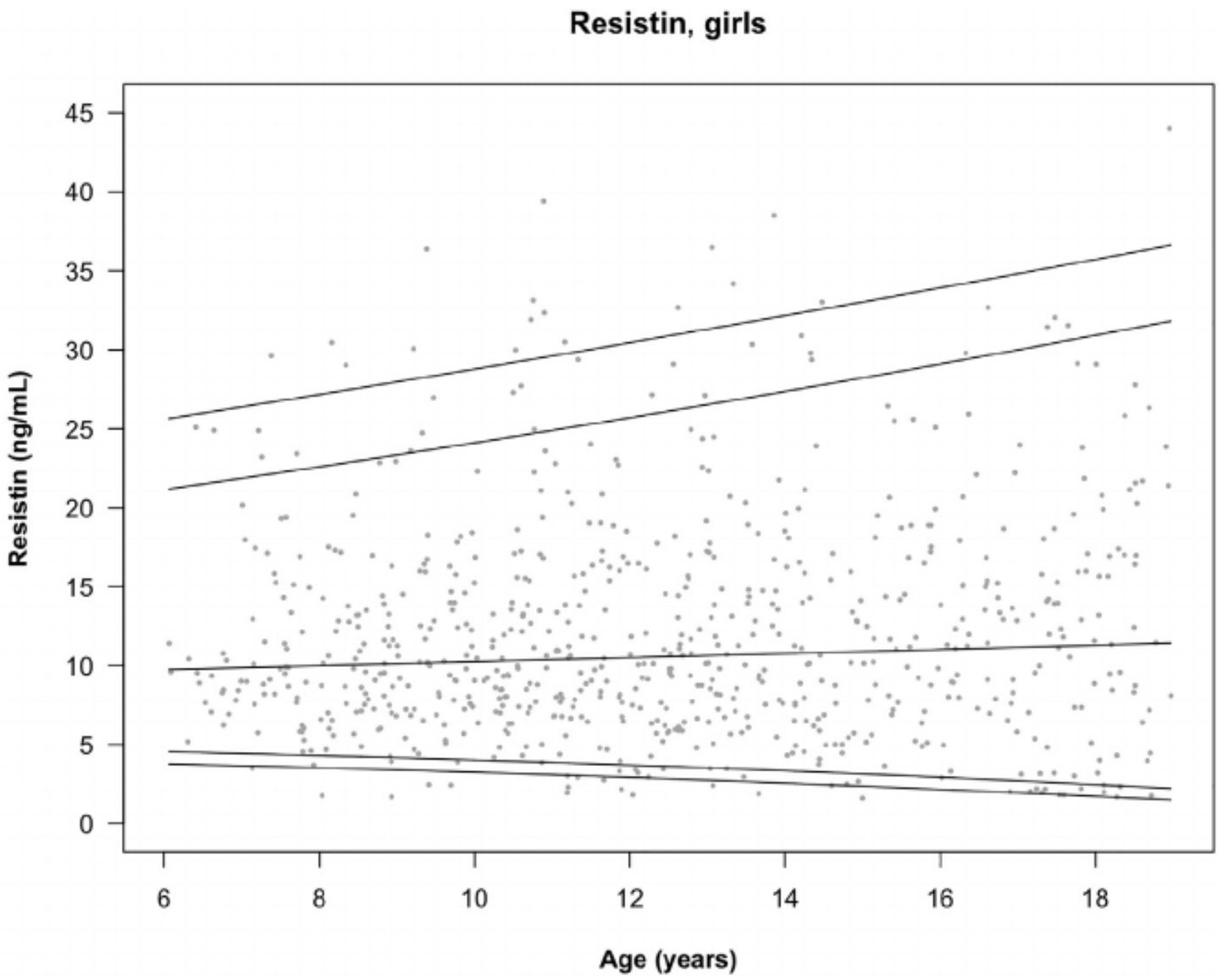

Fig. 2. Resistin as a function of age in girls.

resistin concentrations that were similar to those reported for Italian and American populations as opposed to those reported for Asian populations, which exhibited higher concentrations [18]. Our data therefore support that resistin concentrations varies between different ethnic and/or geographic groups. As a consequence hereof, a degree of caution must be noted in the comparison of data from various populations. Furthermore, only few comparable international studies have been published, which further hampers direct comparison. Our data come from a relatively homogeneous population of Danish schoolchildren of northern European white ancestry and thus the influence of a potential ethnical/genetic bias is less likely.

4.3. Genetic differences

The reported differences between ethnic groups also suggest that underlying genetic variations between ethnic groups influence resistin concentrations. We demonstrated a large variability of more than a factor 10 in resistin concentration. It is likely, that this variability may be explained by genetic factors rather than simply reflect differences in relative body weight. Indeed, resistin concentration is believed to be highly heritable, as a study of nondiabetic, Caucasian Italian adults with obesity and their first-degree relatives showed that heritable factors accounted for approximately 70% of the observed variation in resistin concentrations [31]. Similarly, genome-wide association studies have confirmed the existence of several single nucleotide polymorphisms (SNPs) associated with circulating resistin concentrations, notable near the RENT, TYW3/CRYZ, and NDST4 genes [32].

It is plausible that several genetic subtypes exist within our study population; each with their own reference values. Hence, a weakness of the present study is the lack of genetic evaluation regarding resistin associated SNPs, since these may have had a noticeable impact on the results.

4.4. Relation to overweight

The current body of data is contradictory in regards to the correlation between resistin and obesity in children and adolescents. Some data report elevated resistin concentrations in obesity [33], albeit not all data can demonstrate significantly elevated resistin concentrations in obese children [34]. Other studies have found no signs of such a correlation [35–37].

In the present study, we observed an independent correlation between BMI SDS and resistin concentrations. Since, the study was designed to examine only healthy, non-obese children, the observed correlation is not necessarily valid in obese children and accordingly, our data do not irrefutably support the correlation between resistin and obesity.

4.5. Relation to Tanner

In contrast to previous findings [27], we did not find any difference in resistin concentrations between Tanner stages in either boys or girls. For boys, as no age dependent correlation was demonstrated in our cohort, it seems logical that no correlation with Tanner stages were found. However, for girls, the difference between our results and previous published data may reflect a true biological difference between the observed populations. Yet, as pubertal development was not registered in all study participants, the results are lacking relative power, why conclusions based upon these should be drawn with caution.

4.6. Strengths and weaknesses

Some variables are known to potentially influence resistin measurements and accordingly, precautions were taken to minimize the pre-analytical effect of food intake on resistin concentrations [38,39] as all participants underwent an overnight fast and the blood samples were drawn in a relatively narrow time span from 7 to 9 am. Since all laboratory analyses were done in-house and in-batch, the presented data can be considered valid regarding potential biases, i.e. variation in the analytical method both with respect to location and time. Test of the pre-analytic variability demonstrated stability of resistin in the blood sample. As the samples were stored at −80 °C and only subjected to one freeze-thaw cycle, no pre-analytic condition is likely to have influenced the results.

4.7. Conclusion

Resistin has recently gained increasing interest as a potential biomarker for several chronic diseases; especially in diseases where inflammation is believed to play a role [8,9]. The present study provides important reference values for resistin concentrations in a large, relatively homogeneous, healthy, non-obese cohort of Danish/North-European white schoolchildren. The data demonstrate age and sex dependent variation in resistin concentrations in children and this data may therefore potentially help in future risk stratification of children; a task that is likely to gain importance in the future.

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