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Mariana da Rocha Almeida Brandão

Family History of Diabetes: the role of grandparents data to identify adolescents at diabetes risk

Abril, 2010

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
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Projecto de Opção do 6º ano - DECLARAÇÃO DE REPRODUÇÃO

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Family History of Diabetes: the role of grandparents data to identify adolescents at diabetes risk

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Assinatura: _____

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Projecto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Mariana da Rocha Almeida Brandãio, abaixo assinado, nº mecanográfico 040801184, aluna do 6º ano do Mestrado Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração deste projecto de opção.

Neste sentido, confirmo que NÃO incorri em plágio (acto pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 16/04/2010

Assinatura: _____

Abstract

Objective: to determine the prevalence of adolescents with impaired fasting glucose (IFG)/DM, to evaluate characteristics associated with IFG and to evaluate the role of grandparents' history of DM to identify adolescents at high risk of diabetes.

Study design and setting: we evaluated 1276 population based adolescents, aged 13-year-old, from Portugal. Data was collected by self-reported questionnaires and a clinical evaluation was performed, including a fasting blood sample.

Results: the prevalence of IFG/DM was 3.7% using American Diabetes Association (ADA) criteria and 0.55% using WHO criteria. Combining parental with grandparental history it lead to a 5.5 fold increase in the identification of adolescents with a positive family history. The Odds for IFG considering only parental history was 0.91 (95%CI: 0.57-1.47) and combining data from parents and grandparents the Odds was 1.17 (95%CI: 0.83-1.65).

Conclusion: The prevalence of IFG/DM is 3.7% by ADA criteria and 0.55% by WHO criteria. Combining both parental and grandparental history, 468 adolescents were additionally identified as having positive family history, performing a total of 571 adolescents (45%). However there's no significant association between IFG and a positive family history, both considering only data from parents and when data from grandparents was also taking in account.

'What is new?'

Key finding: combining parental with grandparental family history leads to a 5.5 fold increase in the identification of adolescents with a positive family history, however there is no association between a combined parental plus grandparental family history of diabetes and IFG in 13-year-old adolescents;

What this adds to what was known: data from a population based sample of adolescents with a homogeneous age;

What is the implication: follow-up studies should be made to define if identifying adolescents based on their grandparental FDMH, would target who is more at-risk of developing IFG or DM.

Key words: Diabetes Mellitus; Adolescent; Grandparents; Family History; Impaired Fasting Glucose

Running title: **“Family History of Diabetes to identify adolescents at diabetes risk.”**

Word count: 3705 words

Introduction

The prevalence of Diabetes Mellitus (DM) is increasing worldwide and there are estimates that, between 2010 and 2030, there will be a 69% increase in numbers of adults with DM in developing countries and a 20% increase in developed countries (1). At the same time, both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) prevalence are rising all over the world among children and adolescents (2-4).

As the age of onset of T2DM is becoming younger (5) and the patient's life span is longer, there's a bigger propensity to the development of the multiple chronic complications of DM. We know from adults that approximately 30% of patients with prediabetes (Impaired Fasting Glucose, IFG or Impaired Glucose Tolerance, IGT) will convert to T2DM within 5 years (6). Besides, children with prediabetes have an increased risk for developing cardiovascular diseases before progressing to DM (7-8). Thus, an early identification would help these children to have earlier and proper care and to minimize the consequences of prediabetes and DM.

In agreement with this potential of prevention, the Consensus Panel of the American Diabetes Association (ADA) recommends that the screening of children and adolescents should be initiated at the age of 10 or at onset of puberty, if puberty occurs at a younger age. To identify adolescents to be screened, besides the criteria of being overweight or obese, one of the criteria is to have a family history of T2DM in first- or second-degree relative (9).

Using family history (FH) information as a screening tool is appealing because it is easy and inexpensive to collect in both the clinical and community setting. However, as the age recommended to start screening is 10-year-old or at the onset of puberty, most of the parents will not have a diagnose of T2DM, as they are still in their 40s and 50s. Nonetheless, previous data suggest that a family Diabetes Mellitus history in grandparents was associated with increased risk of disease in grandchildren (3), making this information potentially interesting to identify adolescents at risk. Although, another study (10), based on a sample of overweight children and adolescents shows no relationship between grandparental DM history and an increased risk of prediabetes.

So, however in literature, there isn't yet a consensus about the role of grandparental DM history in the increasing of risk of prediabetes, the goals of our study was: a) to determine the prevalence of adolescents with IFG or DM in our population; b) to evaluate which of their characteristics is associated with IFG or DM; c) to evaluate the role of grandparents history of DM to identify adolescents with FDMH.

Methods and Participants

Participants

Participants in this study were selected during 2003 as part of the assembling procedure of the Epidemiological Health Investigation of Teenagers in Porto (EPITeen) cohort, which aims to follow children born in 1990 and registered at every public and private school in Porto, Portugal. To achieve this goal, every executive board of schools attended by 13-year-old adolescents was contacted and asked to provide students' contacts. Of the 27 public and 24 private schools contacted, all public schools and 19 private schools (79%) agreed to participate and allowed us to contact eligible students and families.

Approximately 200 eligible students were present in nonparticipating schools. However, no effort was made to contact them using alternative approaches and they remained unaware of the project. In compliant schools, we identified 2787 eligible adolescents (2126 in public and 661 in private schools): 44 (1.6%) could not be reached (missing classes during the study period) and 583 (20.9%) did not return signed consent forms and were considered refusals. This resulted in a 77.5% overall proportion of participation, similar in public (77.9%) and private schools (77.0%; p=0.71), with 2160 students providing information for at least part of the proposed assessment.

Ethics

The Ethical Committee of the University Hospital São João, Porto approved the study. Parents and adolescents received written and spoken information about the purpose and design of the study and at least one meeting at a time which best suited parents was arranged in every school, to describe the study procedures and to overcome any possible concern of the families regarding the adolescents' participation in the cohort. Written informed consent was obtained both from parents and adolescent. A separate specific consent was provided for blood sample collection.

Data collection

The baseline evaluation included two self-administered questionnaires (one completed at home, another at school) and a physical examination. The home questionnaire, answered by adolescents and

parents, inquired into demographic, social, behavioral and clinical history including Diabetes Mellitus of the adolescent and family (parents and grandparents). Parents also reported their usual weight and height (this information being used to calculate body mass index) and their smoking status. Based on parents' education, adolescents were classified taking into account the parent with a higher level of education, and this information was used as a proxy for socioeconomic status.

As part of the home questionnaire information about a medical diagnosis of DM were asked separately for mother, father and each of the grandparents. We have classified Parental Family History as: a) positive, when at least one of the adolescent's parents had a diagnosis of DM; b) negative, when both parents reported has not having DM; c) missing, when for , at least, one of the parents, reported to "be unaware" or didn't answer. Total Family History was computed taking into account the information on parental and grandparental diagnosis of DM. We have classified Total FH as: a) positive, when at least one of the adolescent's relatives (parents or grandparents) had a diagnosis of DM; b) negative, when all of the adolescent's relatives were classified has not having DM; c) missing, when the available information about family history showed no diagnosis of DM, but there was missing or "unaware" information about, at least, one relative.

After receiving completed home questionnaires, our research team visited the schools and the adolescents answered an additional questionnaire (school questionnaire) to collect information on physical activity and behaviors, particularly smoking and alcohol consumption.

During this visit, a physical examination was performed, between 8 a.m. and 10 a.m., by a team of experienced nurses, nutritionists and physicians. Anthropometrics were obtained with the subject in light indoor clothes and no shoes. Weight was measured using a digital scale - Tanita® (in kilograms, to the nearest 0.1 kg), and height was measured (in centimeters, to the nearest tenth) using a portable stadiometer. Body Mass Index (BMI) was calculated as weight (kg) divided by squared height (m^2) and was classified according to the age-specific percentiles developed by the United States Centers for Disease Control and Prevention (11) as overweight (BMI between the 85^{th} and the 95^{th} percentile) and obese (BMI above the 95^{th} percentile).

A 12-h overnight fasting blood sample was drawn from consenting participants. The fasting status was evaluated by the question “when was the last time you ate something?”. Blood analyses were made no more than three hours after blood collection. Blood glucose was measured using automatic standard routine enzymatic methods in use at the central pathology laboratory of the University Hospital of Sao Joao, Porto. Insulin was measured by radioimmunoassay (Coat-A-CountR, Diagnostic Products Corporation, Los Angeles, California, USA). Insulin resistance was assessed by the homeostasis model method (HOMA-IR), based on fasting glucose and insulin concentrations: HOMA-IR= Fasting Insulin (μU/ml)*Fasting Glucose (mg/dl)/405 (12). Insulin sensitivity was determined by the Quantitative Insulin Sensitivity Check Index method (QUICKI): QUICKI = 1/[Log (Fasting Insulin, μU/ml) + Log (Fasting Glucose, mg/dl)] (13).

According to the American Diabetes Association recommendations (9), we divided our subjects in: a) normal fasting glucose (NFG) status: fasting plasma glucose (FPG) < 100 mg/dl (5.6 mmol/l) and b) impaired fasting glucose (IFG)/DM status: FPG ≥ 100 mg/dl (5.6–6.9 mmol/l). The World Health Organization (WHO) and many other diabetes organizations have other criteria (14-15): the cut-point between NFG and IFG is FPG = 110 mg/dl.
We also have defined two groups according to the 75^{th} percentile of FPG in our sample, which was 91 mg/dl.

From the 2160 participants, we had 2054 participants who had a physical examination, but 388 did not agree to a venopuncture, 274 were not fasting at the time of examination and 6 samples were lost during the handling procedures. Of the 1387 participants with blood sample, 105 did not hand back their parents questionnaire and 5 had a previous diagnosis of DM. So, to this study, we analyzed data from 1276 participants (59% of the first pool of eligible participants).

Comparing with participants who were not considered in the analyses, those with complete information presented a higher proportion of girls and adolescents whose parents had a higher economic status (showed by their higher education and their enrollment to a private school). No

significant differences were found between those groups in terms of FDMH in parents or grandparents, categories of BMI or age at menarche (**table 1**).

Statistics

Missing data, due to absent or incomplete questionnaires is presented in the tables but was not considered for **statistical analysis**. Proportions were compared using the Chi-square test or Fisher's exact test. Means were presented as mean (± standard deviation) and compared using the T-Student test or One-Way ANOVA. Odds ratio (OR) and 95% confidence interval (95% CI) were estimated by unconditional Logistic Regression and used to estimate the magnitude of the associations. Statistical significance was accepted at a p value of 0.05. All analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois).

Results

We found a prevalence of IFG/DM of 3.7% (n=47) using ADA guidelines (9), and 0.55% using WHO criteria(14). The only factor associated with ADA's IFG/DM was sex, with boys having more IFG/DM than girls (4.9% vs. 2.6%, p=0.046).

Considering FPG values, the 75th percentile in our sample was 91 mg/dl. As expected, regarding FPG, FPI and insulin resistance and sensitivity indexes (HOMA-IR and QUICKI), those with FPG≥75th percentile were significantly more insulin resistant, had lower insulin sensitivity and higher insulin values (**table 2**).

When we used data only from parental family history, we had identified 103 adolescents with a positive family history (8% of participants). However, when combining both parental and grandparental history, 468 adolescents were additionally identified as having positive history, performing a total of 571 adolescents (45%) with positive family history. This represents a 5.5 fold increase in the number of adolescents with positive family history (**figure 1**).

After adjustment, the Odds of having FPG≥75th was significantly lower in girls and in the adolescents who had routine medical visits. However it was higher in adolescents who had parents with lower years of education (7 – 9 years) and in girls with menarche at 12-year-old comparing with those that reported an early menarche. No significant association was found between FPG and adolescent BMI and FDMH, considering only parents information or the combination of parents and grandparents (**table 3**). Also no significant association was found with family history of DM and the IFG/DM status, using ADA criteria or WHO criteria, either with Parental Family History or Total Family History (data not shown).

For a large proportion of adolescents we didn't have information that allowed the classification of adolescents as positive or negative on Parental FH. We found that a higher economic status (measured by: to be enrolled on a private school, to have a higher parental education and a private doctor as the usual health care provider) is related to a higher availability of Parental FH. Available

parental and available grandparental family histories are positively related. We also found that, parents with lower BMI and higher number of mother's medical visits tend to have a non-available Parental FH (**table 4**).

On **table 5**, we presented data on the comparison of FPG as a continuous variable, FPI, HOMA-IR and QUICKI, according to the family history status. We found significant differences only for FPG means according to the Total FH status (higher on the group with Negative Total FH: 86.4 mg/dl, then on the group with Positive Total FH and lower on the Missing Total FH group – 83.3 mg/dl).

Discussion

In our sample of 13-year-old adolescents, the prevalence of IFG/DM by the ADA criteria was 3.7% and by WHO criteria was 0.55%. As expected, in the present study, the prevalence of IFG/DM was higher using the ADA criteria (9) than when using the WHO criteria (14). This large difference (6.7 fold increase) was related with the very small number of adolescents classified as positive. Our prevalence was lower than that based on the WHO criteria (14) found in England and Wales (1.5%) (16) and in Turkey (1.96%) (17).

Also when the ADA criteria (9) was used, our estimates were lower than in other studies: IFG's prevalence was 7.0% in a very large American study (18) and 22.2% in a Mexican population (19). The difference for our data can be explained by the fact that these studies' populations comprise a wider range of adolescents' age, which can lead to higher FPG values.

There is an important debate around which should be the cut-point for the definition of IFG. The ADA defends that it should be 100 mg/dl (9), while the WHO and other organizations use 110 mg/dl (14). Nonetheless, it is assumed by the WHO that the existing approaches to define the best cut-point for defining IFG do not provide a consistent and unequivocal solution (8). Besides, there is a continuous cardiovascular and diabetic risk even with a plasma glucose range considered as normal (8), so, we have decided to use the percentile 75 of our sample to identify those at higher risk to develop DM. Therefore, the cut point chosen for FPG was 91 mg/dl, a value similar to the one included in the ADA definition. Our decision was also supported by the results showing that those with FPG≥75th percentile had a significant worse insulin profile regarding data from two important insulin resistance and sensitivity indexes, HOMA-IR and QUICKI.

To measure insulin resistance and sensitivity we used HOMA-IR and QUICKI indexes because: a) HOMA-IR has a reasonable linear correlation with the reference standard glucose clamp method and minimal model estimates of insulin sensitivity/resistance in several studies of distinct populations and b) QUICKI is a simple, robust, accurate, reproducible method that has been extensively validated against the glucose clamp method (20). Both indxes are good predictors of diabetes and some of its related diseases, such as obesity, metabolic syndrome, and many cardiovascular diseases (20)

In our sample, boys have more IFG than girls, which is consistent with data from adult studies (21-22). In girls, we have found differences of IFG according to age at menarche, but only in those reporting an age at menarche of 12 years. As our sample is homogeneous for age, this is in accordance with the knowledge that glucose metabolism varies throughout childhood and adolescents go through a period of insulin resistance going through puberty that is transient (23). However, because there were no physical conditions at school to assure the privacy needed to evaluate adolescents' pubertal development according to Tanner criteria (24), age at menarche was the only pubertal development indicator recorded.

In the present study, a higher proportion of adolescents with FPG≥75th P was found among adolescents with parents with lower education. This is in agreement with several studies (25-26) that show that a lower socio-economic status is related to a higher prevalence of T2DM and microvascular complications in adults. We have also found that adolescents who had more than one routine medical visits per year were less prone to have FPG. Although this association was adjusted to parents' education, this result can be because, more frequently, adolescents from lower social class did not have any routine medical visit.

Surprisingly, there was no relationship between adolescents' categories of BMI and FPG. However, we found significant differences for FPI, HOMA-IR and QUICKI means according to BMI categories: overweight and obese adolescents had higher FPI levels and were more insulin resistant (data not shown). This is consistent with the fact that obesity is considered the major cause of peripheral insulin resistance in childhood and it is strongly related to the development of altered glucose metabolism (27). Probably, we did not find an association because we did not have enough power due to the lower number of adolescents with FPG and obesity.

There is a relatively high amount of missing data regarding Parental and Total Family History. This is a frequent problem, not only in research, but also in the clinical context. Our results show that a higher economic status was associated to a higher proportion of available information on FH, both

parental and grandparental, which could be explained by the higher capacity of those participants to answer a self-reported questionnaire. This relation with social class could also enlighten the higher proportion of those with data on family history that use the private doctor as usual health care provider. Among those with non-available information on parents' history of DM, the proportion of parents with lower BMI was higher. The most possible explanation to understand this fact could be related with the lower probability of those parents to have diabetes, which increased the probability to leave the question without answer.

In our sample, there was no association between a positive Parental FH or a Total FH and IFG/DM, using any of the three criteria (ADA, WHO or the 75th percentile). The same results were obtained when we used the different indexes. We only found significant differences for FPG, but the statistical difference was for those with missing information, which is in favor that this group is more similar to those without familial history. About results on Parental FH these could be partly explained by the fact that these adolescents' parents are still young (father's mean age: 44.8; mother's mean age: 42.0), so most of those that in twenty years will have a diagnosis of DM, doesn't have it yet. For this reason, the association's strength may be diluted. This may be supported by the fact that, in our sample, the prevalence of DM on parents was 4.2%, lower than the estimated for the European population between 40-49 years, which was 5.4% on men and 4.2% on women(22); and than the 12.6% estimated to Portuguese individuals aged 40-59 years (28).

We found that combining parental with grandparental FDMH lead to a 5.5 fold increase in the identification of adolescents with a positive FDMH. Even so we did not find an association between family history and IFG. A follow-up study would help to define if identifying these extra-adolescents, based on their grandparental family history, would better target who is more at-risk of developing IFG or DM. However, in our study, the use of grandparental FH information increased the amount of adolescents classified as missing data. This could be a source of misclassification that may attenuate the differences according to family history of diabetes.

Other possible explanations could be identified to explain these no differences between adolescents with and without familial history of disease. One could be related with validity of that information. We have identified two studies that evaluated it: in the Family Heart Study (29) investigators determined the validity of reported family history of diabetes by comparing the proband's report with that of their relatives (reference standard). The sensitivity of the proband's report of diabetes was 0.87, 0.72, and 0.83 for parents, siblings, and spouses, respectively, and specificity was 0.98 for each relative type. In the San Luis Valley Diabetes Study (30) there was complete agreement between proband and family reports, suggesting that family history information collected from the proband is reliable and accurate. Another explanation to the lack of differences according to family history is that these adolescents are still too young (13 years) and don't have a sufficient range of values of the parameters evaluated that would allow the identification of differences.

Weaknesses

Glucose assays were only run once, not in duplicate: two studies which assessed the reproducibility of IFG with retesting within 6 weeks showed that the proportion of people classified as IFG on the first test and on retesting was 64% and 51%, respectively, with the majority being reclassified as normal and less than 10% as having diabetes on repeat testing (31). An oral glucose tolerance test (OGTT) could add some information because FPG and OGTT identify different types of individuals. However, it is impossible to perform OGTT to a large sample and reduce the sample may affect the external validity. On the other hand, we used FPG, which, according to the ADA, is the best screening test for diabetes and it is also a component of diagnostic testing (32).

The lack of pubertal indicators is a limitation of this study, and we had to rely only on menarche. However, no appropriate conditions for privacy were available at school, so we were unable to classify the adolescents according to secondary sexual characteristics.

Strenghts

A major strength of our study is its relatively large sample size: we have 1276 adolescents, who were taken from a nonclinical population. In Portugal, education is mandatory till 9th grade (adolescents who are 15th year-old), so recruiting 13-year-old adolescents from school gave us a good population

sample basis. Besides, there were almost no differences between those participants not considered in the analyses and those with complete information, which minimizes a possible selection bias. Therefore, we have a high confidence that our results give a good perspective of our teenage population.

This cohort is now being re-evaluated: so, we will be able to check in which direction these adolescents with IFG evolved. Another goal to this re-evaluation is to test how the evaluated familial history predicts the occurrence of diseases.

Conclusion

In our sample of 13-year-old adolescents, the prevalence of IFG/DM by the ADA criteria was 3.7% and by WHO criteria was 0.55%,. There was no significant association between IFG (by any of the three criteria used) and a positive family history of DM, both considering only data from parents and when data from grandparents was also taken into account.

A future evaluation of these adolescents may enlighten if those identified as positive for family history of DM based on grandparents' data have an increased risk to develop IFG/DM.

Acknowledgments

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Table 1 – comparison between Participants with complete information and Participants not considered in the analyses (n (%))

	Participants		
	No complete information n=884	With complete information n=1276	p - value*
Type of school			
Private	184 (20.8)	325 (25.5)	**.014**
Sex			
Female	432 (48.9)	684 (53.6)	**.034**
Parents education (years)			**.022**
≤ 6	247 (30.6)	320 (25.4)	
7 – 9	143 (17.7)	278 (22.1)	
10 – 12	204 (25.3)	333 (26.4)	
> 12	212 (26.3)	328 (26.1)	
Missing	78	18	
Smoking parents			.930
None	129 (21.5)	267 (21.3)	
One	256 (42.7)	527 (42.1)	
Both	214 (35.7)	459 (36.6)	
Missing	285	23	
BMI – Parents			.105
< 24,9	248 (36.6)	388 (31.9)	
25 – 29,9	308 (45.5)	588 (48.3)	
≥ 30	121 (17.9)	241 (19.8)	
Missing	207	59	
Diabetes in parents			.717
None	453 (87.6)	964 (87.6)	
At least one	45 (8.7)	103 (9.4)	
Unaware	19 (3.7)	33 (3.0)	
Missing	367	176	
Diabetes in grandparents			.560
None	148 (31.1)	306 (30.4)	
At least one	255 (53.6)	524 (52.0)	
Unaware	73 (15.3)	177 (17.6)	
Missing	408	269	
Usual health care provider			**.041**
Primary care center	291 (48.7)	662 (54.8)	
Private doctor	206 (34.5)	349 (28.9)	
Hospital	60 (10.1)	104 (8.6)	
Other	40 (6.7)	92 (7.6)	
Missing	287	69	
Routine medical visits (adolescent)			.356
0	68 (11.6)	154 (12.9)	
1	185 (31.5)	330 (27.6)	
2	149 (25.4)	306 (25.6)	
≥ 3	185 (31.5)	404 (33.8)	
Missing	297	82	
Regular practice of sports			.933
No	295 (49.7)	626 (50.1)	
Yes	298 (50.3)	624 (49.9)	
Missing	291	26	
Age at menarche			.894
8 – 11	107 (37.7)	210 (37.0)	
12	119 (41.9)	234 (41.2)	
13 – 14	58 (20.4)	124 (21.8)	
Categories of body mass index			
Below the 85th percentile	572 (74.8)	923 (72.4)	.517
Between 85th–95th percent	119 (15.6)	217 (17.0)	
Above the 95th percentile	74 (9.7)	134 (10.5)	
Missing	119	2	

* p-value: missing categories not included for evaluating the statistical significance of the comparisons

Table 2 – comparison between adolescents with fasting plasma glucose (FPG)<75th percentile and those with FPG≥75th percentile, regarding FPG, FPI, HOMA-IR and QUICKI:

	Total Mean (±sd)	**< 75th percentile** Mean (±sd)	**≥ 75th percentile** Mean (±sd)	**p-value***
FPG (mg/dl)	85.02 (±9.52)	81.35 (±7.86)	95.48 (±4.94)	**<.001**
FPI (µU/ml)	8.22 (±5.53)	7.73 (±5.16)	9.60 (±6.27)	**<.001**
HOMA-IR	1.75 (±1.23)	1.56 (±1.05)	2.28 (±1.53)	**<.001**
QUICKI	0.38 (±0.09)	0.39 (±0.09)	0.36 (±0.08)	**<.001**

FPG 75th percentile = 91 mg/dL. FPI: Fasting Plasma Insulin; HOMA-IR: homeostatic model assessment; QUICKI: quantitative insulin sensitivity check index.

*p-value refers to the comparison between the group with FPG<75th percentile and those with FPG≥75th percentile.

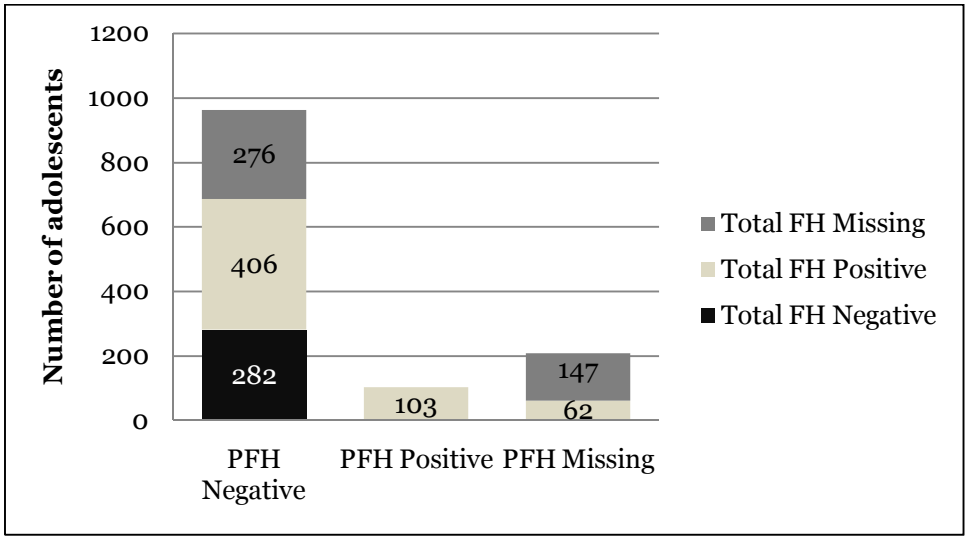

Figure 1 – Description of the distribution of adolescents according Total Family History (comprising both parents and grandparents DM family history) by Parental Family History (PFH).

Table 3 – Association of fasting plasma glucose (FPG) with individual and familial adolescents' characteristics.

	<75th perc n (%)	≥75th perc n (%)	OR (95% CI)	OR adjusted* (95% CI)	p – value
Type of school					
Private	245 (26.0)	80 (24.1)	0.91 (0.68 – 1.21)	1.01 (0.74 – 1.38)	.558
Sex					
Female	527 (55.8)	157 (47.3)	**0.70** (0.54-0.90)	**0.71** (0.55 – 0.91)	**.007**
Parents education					
≤ 6	242 (25.9)	78 (24.0)	1	1	
7 – 9	188 (20.2)	90 (27.7)	1.11 (0.77 – 1.59)	**1.46** (1.02 – 2.08)	**.036**
10 – 12	249 (26.7)	83 (25.5)	**1.64** (1.15 – 2.38)	0.99 (0.69 – 1.41)	
≥ 12	254 (27.2)	74 (22.8)	1.14 (0.80 – 1.64)	0.87 (0.60 – 1.25)	
Missing	11	7			
Smoking parents					
None	204 (22.0)	63 (19.4)	1	1	
One	383 (41.3)	144 (44.3)	0.89 (0.63 – 1.27)	1.25 (0.89 – 1.77)	.521
Both	341 (36.7)	118 (36.3)	1.09 (0.82 – 1.44)	1.15 (0.81 – 1.65)	
Missing	16	7			
BMI – Parents					
< 24,9	290 (32.2)	98 (31.1)	1	1	
25 – 29,9	437 (48.4)	151 (47.9)	1.02 (0.76 – 1.37)	0.90 (0.62 – 1.30)	.829
≥ 30	175 (19.4)	66 (21.0)	1.12 (0.78 – 1.61)	0.89 (0.63 – 1.25)	
Missing	42	17			
Parental Family History					
Negative	707 (74.9)	257 (77.4)	1	1	.620
Positive	77 (8.2)	26 (7.8)	0.93 (0.58 – 1.48)	0.91 (0.57 – 1.47)	
Missing & Unaware	160 (16.9)	49 (14.8)	0.84 (0.59 – 1.20)	0.76 (0.53 – 1.11)	
Total Family History					
Negative	214 (22.7)	68 (20.5)	1	1	.399
Positive	412 (43.6)	159 (47.9)	0.96 (0.68 – 1.37)	1.17 (0.83 – 1.65)	
Missing & Unaware	318 (33.7)	105 (31.6)	1.17 (0.88 – 1.56)	0.95 (0.65 – 1.37)	
Usual health care provider					
Primary care center	475 (53.6)	187 (58.4)	1	1	.310
Private doctor	267 (30.1)	82 (25.6)	1.33 (0.80 – 2.23)	0.84 (0.54 – 1.19)	
Hospital	74 (8.3)	30 (9.4)	1.04 (0.60 – 1.79)	1.07 (0.67 – 1.70)	
Other	71 (8.0)	21 (6.6)	1.37 (0.72 – 2.61)	0.78 (0.45 – 1.36)	
Missing	57	12			
Routine medical visits (adolescents)					
0	103 (11.6)	51 (16.7)	1	1	.151
1	250 (28.2)	80 (26.1)	**1.55** (1.03 – 2.32)	**0.63** (0.41 – 0.96)	
2	229 (25.8)	77 (25.2)	1.00 (0.71 – 1.40)	**0.65** (0.42 – 0.99)	
≥ 3	306 (34.5)	98 (32.0)	1.05 (0.74 – 1.48)	**0.64** (0.42 – 0.96)	
Missing	56	26			
Regular practice of sports					
No	468 (50.7)	158 (48.3)	1	1	.498
Yes	455 (49.3)	169 (51.7)	0.91 (0.71 – 1.17)	1.13 (0.86 – 1.48)	
Missing	21	5			
Age at menarche					
8 – 11	176 (39.4)	34 (28.1)	1	1	.052
12	174 (38.9)	60 (49.6)	**1.79** (1.12 – 2.86)	**1.75** (1.09 – 2.82)	
13 – 14	97 (21.7)	27 (22.3)	1.44 (0.82 – 2.53)	1.48 (0.84 – 2.60)	
Missing	80	36			
Categories of BMI					
< 85th percentile	691 (73.4)	232 (69.9)	1	1	.371
85th – 95th perc.	158 (16.8)	59 (17.8)	1.11 (0.80 – 1.55)	1.11 (0.79 – 1.56)	
> 95th percentile	93 (9.9)	41 (12.3)	1.31 (0.88 – 1.95)	1.30 (0.87 – 1.94)	
Missing	2	0			

* OR adjusted for sex and parents education.

Table 4 – comparison of individual and familial characteristics between adolescents with available Parental Diabetes Family History and those without information (n(%)).

	Parental Family History		
	Not available 209	Available 1067	p – value
Type of school			
Private	27 (12.9)	298 (27.9)	**<.001**
Sex			
Female	110 (52.6)	574 (53.8)	.816
Parents education			
≤ 6	74 (38.1)	246 (23.1)	
7 – 9	52 (26.8)	226 (21.2)	**<.001**
10 – 12	41 (21.1)	291 (27.3)	
≥ 12	27 (13.9)	301 (28.3)	
Missing	15	3	
BMI – Parents			
< 24,9	79 (47.6)	309 (29.4)	
25 – 29,9	58 (34.79	530 (50.4)	**<.001**
≥ 30	29 (17.5)	212 (20.2)	
Missing	43	16	
Mother's number of medical visits			
None	9 (7.3)	88 (9.3)	
One or two	38 (30.6)	395 (41.7)	**.023**
Three or more	77 (62.1)	464 (49.0)	
Missing	85	120	
Father's number of medical visits			
None	15 (24.6)	194 (20.9)	
One or two	27 (44.3)	448 (48.3)	.755
Three or more	19 (31.1)	285 (30.7)	
Missing	148	140	
Grandparental Diabetes History			
Not available	130 (62.2)	316 (29.6)	**<.001**
Available	79 (37.8)	751 (70.4)	
Usual health care provider			
Primary care center	137 (70.6)	525 (51.8)	
Private doctor	27 (13.9)	322 (31.8)	**<.001**
Hospital	19 (9.8)	85 (8.4)	
Other	11 (5.7)	81 (8.0)	
Missing	15	54	

Table 5 – comparison of fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostatic model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI) according familial history of diabetes.

		Negative FH	Positive FH	Missing FH	P – value
Parental Family History	FPG (mg/dl)	85.2	84.7	84.2	.415
	FPI (μU/ml)	8.13	8.42	8.54	.611
	HOMA-IR	1.73	1.78	1.81	.698
	QUICKI	0.38	0.37	0.38	.853
Total Family History	FPG (mg/dl)	86.4	85.5	83.3	**<.001**
	FPI (μU/ml)	7.86	8.13	8.58	.236
	HOMA-IR	1.69	1.74	1.80	.523
	QUICKI	0.38	0.38	0.38	.581

Total family history: Parents and Grandparents combined DM family history.