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Research paper

# Prevalence and determinants of type 2 diabetes mellitus in a Greek adult population

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## ABSTRACT

**The prevalence of diabetes mellitus (DM) is increasing worldwide reaching epidemic proportions. The aim of the present study was to estimate the prevalence of DM in Thessaly, a large region of Central Greece, and to extrapolate our results to the population of the entire country. A random sample of 805 adults (421 females and 384 men) living in Thessaly, aged 18-80 years, was surveyed. After completing a questionnaire about health status and a thorough physical examination, a blood sample was obtained from each participant for biochemical analysis. Participants with fasting glucose levels between 100-125 mg/dl underwent an oral glucose tolerance test (OGTT). A second survey was also conducted, via telephone call-interviews, in a randomly selected sample age- and sex-stratified to the country's adult population in order to extrapolate the DM data from Thessaly to the whole country. The frequency of DM based on patient history and fasting blood glucose levels was 6.96%, comparable to that observed in the telephone-based nationwide survey (7.38%, p=0.669). However, after the OGTT an additional 3.72% of the population had undiagnosed DM, increasing DM prevalence to 10.68% (age adjusted 11.77%). The prevalence of pre-diabetes was 8.70%, with impaired fasting glucose at 5.84% and impaired glucose tolerance at 2.86%. The prevalence of DM was significantly higher in men (14.58%) than in women (7.13%, p<0.001), increased with age in both sexes and was more prevalent in hypertensive (p<0.001) and obese subjects (p=0.001) and in those living in rural areas (p=0.003). In the multiple logistic regression analysis, significant predictors of pre-diabetes and DM together were age, homeostasis model of assessment of insulin resistance (HOMA-IR), alcohol consumption and educational status, whereas those of DM alone were age, HOMA-IR and triglycerides. Extrapolating our data to the whole country, the age-adjusted prevalence of DM was estimated at 11.97% (men 13.98%, women 9.25%), clearly indicating a major public health problem.**

**Key words:** Diabetes mellitus, Frequency, Greece, OGTT, Prevalence, Thessaly

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## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by a constellation of abnormalities of glucose homeostasis, which are associated with significant acute and chronic complications. It constitutes a global health problem, as the number of people with DM is increasing worldwide, this due to population growth, aging, urbanization, lifestyle modifications and the increasing prevalence of obesity and physical inactivity.[1] Currently, DM has reached epidemic proportions; the prevalence of DM worldwide was 2.8% in the year 2000, 6.4% in 2010 and is predicted to reach 7.7% by 2030,[2-4] while the prevalence of impaired glucose tolerance (IGT) was 7.9% in 2010 and is predicted to be 8.4% by 2030.[2-4] IGT is a serious condition, considering that pre-diabetic individuals may develop type 2 DM in the subsequent 10 years and are also at higher risk for cardiovascular diseases than normoglycemic individuals.[5,6]

Data from different studies indicate that the prevalence of DM varies widely worldwide among populations due to differences in genetic susceptibility and environmental factors.[7] In Greece, only a limited number of population-based studies have been conducted on the prevalence of DM. Most of these studies concern small areas, either rural or urban, are based on self-reported data and are retrospective or pertain to non-randomly selected populations.

The aim of this study was to estimate the prevalence of DM and IGT in the population of Thessaly, a large region of Central Greece. Secondary aims of the study were: a) to determine factors related to DM and b) to extrapolate the results to the entire Greek population using the self-reported data from a nationwide survey.

## SUBJECTS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was signed by all the participants and the study protocol was reviewed and approved by the scientific and ethics committee of the University Hospital of Larissa.

### *Sample selection*

The sample of the study consisted of 805 individuals, 421 females and 384 males, who were drawn from the Adult Regional Greek Obesity Survey (ARGOS),[8] a community-based health and nutrition study. This survey was carried out in the region of Thessaly, Central Greece, with a population of approximately 625,000 adult inhabitants, aged 18-80 years, living in urban (60%) or rural (40%) areas for at least one year. The details of the random sample selection were described in our previous study.[8] Briefly, the sample was randomly selected from the capital city of each of the four provinces of Thessaly, as well as from other towns and villages, in proportion to their population. The baseline evaluation included: demographic characteristics, age, gender, profession, personal and family history of DM, hypertension, hypercholesterolemia, smoking, dietary and alcohol consumption habits. According to the population census, areas with less than 2,000 inhabitants were defined as rural.[9] The data were collected from 2003 to 2005.

In order to extrapolate these data to the prevalence of DM throughout the country, we conducted a second survey in a randomly selected sample, age- and sex-stratified to the country's adult population according to the census of 2001 of the National Service for Statistics.[9] The communication was performed via telephone call-interviews and was selected by a List-Assisted Random Digit Dialing (RDD) sampling method. Interviews were performed with 10,000 individuals (aged 18-80 years). The sample size for the whole country's population survey was estimated according to power analysis accepting a confidence level of 99%, a margin of error of 1.5% and a response distribution of 50%. From the 10,000 adults reached by telephone, 7,238 agreed to participate in the study (refusal rate 28%).

Each subject was asked whether he/she had any problem with their blood glucose level. In the subgroup of individuals who responded that they had DM, a second telephone-based interview was conducted which included questions about demographic and socioeconomic characteristics, duration of DM, physical activity, kind of treatment, etc. This study was conducted from 24/9/2008 to 2/10/2008.

### *Procedure*

The participants from the region of Thessaly were asked to come to the nearest public health center in the morning (8.30-9.30 am) after having fasted for at least 12 hours. Subjects were asked to bring all of their medications.

Each subject underwent a thorough physical examination. Body weight and height, waist and hip circumference and blood pressure were measured as previously described.[8] A blood sample was obtained from all the participants for the measurement of glucose, insulin, total cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides.

The blood samples were centrifuged on site and the serum and plasma specimens were transferred immediately, in cold boxes filled with ice, to the university hospital laboratories and stored at -70°C until the measurement. In addition, each participant was asked by the doctor about his/her health status and health behaviors (smoking, alcohol intake, dietary habits, etc.).

Subjects with fasting plasma glucose (FPG) levels ≥126mg/dl in two consequent measurements were considered as diabetics and those with FPG levels <100mg/dl normoglycemic. Participants with FPG levels between 100 and 125 mg/dl were considered to have impaired fasting glucose (IFG) and 64 out of 100 subjects with IFG underwent an oral glucose tolerance test (OGTT) after 3 days of *ad libitum* carbohydrate diet. Subjects were classified as being diabetics, with IGT or IFG, when the 2-hour plasma glucose level was ≥200mg/dL, ≥140 but <200mg/dL or <140mg/dl, respectively, according to the WHO criteria.[10] Pre-diabetes is a term used to describe a high-risk state for the development of diabetes.[11] It is assumed that pre-diabetes is the combination of IFG and IGT. For the quantification of insulin resistance, the homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated.[12] Fasting total cholesterol levels ≥200mg/dl, triglycerides levels ≥150mg/dl and HDL-C levels <40mg/dl for men and <50mg/dl for women were respectively defined as hypercholesterolemia, hypertriglyceridemia and low HDL cholesterol according to the National Cholesterol Educational Program Adult Treatment Panel III guidelines.[13] Participants using lipid lowering agents were considered as having hyperlipidemia.

Body mass index (BMI; kg/m$^2$) was calculated from the body weight and height according to Quetelet's formula: BMI= weight (kg)/height$^2$ (m$^2$).[14] Waist circumference (WC) and the calculated waist-to-hip ratio (WHR) were used as estimates of central obesity. Abdominal obesity was defined by a WC greater than 102cm for men and greater than 88cm for women.[15] Weight status was classified according to the WHO definitions:[16] underweight (UW): BMI <18.5, normal weight (NW): BMI 18.5 - 24.9, overweight (OW): BMI 25 - 29.9, obese: BMI ≥30 and extremely or morbidly obese (MO): BMI ≥40. Hypertension was defined as blood pressure ≥140 or ≥90mmHg for systolic or diastolic blood pressure, respectively, or the use of antihypertensive medication. Those who had smoked for over a year and those who had stopped smoking during the last year were defined as smokers. The rest were non-smokers.

### *Laboratory analysis*

Plasma insulin levels were measured using a commercially available immunoradiometric assay (IRMA) kit (Immunotech Beckman Counter Company, Marseille, France, PW). The assay's sensitivity for insulin measurements was 0.5l IU/mL and the interassay coefficient of variation (CV) 3.4% without any cross-reactivity with proinsulin. Total cholesterol, HDL-C, triglycerides and glucose were measured by standard methods on an automatic analyzer (Olympus 600; Medicon, Athens, Greece). Specifically regarding plasma glucose, this was measured by an automated enzymatic assay (hexokinase). LDL-C was calculated according to the Friedwald equation.

## STATISTICAL ANALYSIS

Results are presented as mean ± standard deviation (SD) for normally distributed continuous variables, as median (range) for non-normally distributed continuous variables and as frequencies for qualitative variables. The Kolmogorov-Smirnov test was used to check the normality of distributions of the continuous variables. The independent sample Student's t-test or the Mann-Whitney U-test was used to compare between group differences for continuous variables when there were two groups. The chi-square test or Fisher's exact test was used to compare between group differences for qualitative variables. The Cochran-Armitage test was also used to explore whether there was a clear trend of DM rate with age and BMI, treated as categorical variables. One-way ANOVA, with Bonferonni correction for multiple pairewise comparisons, was used to compare between group differences for continuous variables when there were more than two groups. The age-adjusted prevalence of DM, IFG, IGT and prediabetes was calculated by the direct method. The mid-year (2007 and 2008) population estimates by sex and age groups was used as a "standard" population.[17]

Multiple logistic regression analysis ("stepwise" method) was performed to identify variables independently associated with DM. All variables that provided p-value <0.01 in univariate analysis were entered in each model of multiple regression analysis. Variables that were not normally distributed were logarithmically transformed for the need of these analyses. A two-sided p-value <0.05 was considered statistically significant in all the above tests. Regression analyses were performed with SPSS 21.0 for Macintosh (IBM Corp., Armonk, NY, USA).

## RESULTS

A total of 805 individuals (384 (47.7%) men and 421 (52.3%) women), aged 47.0±13.3, were included in the study. According to BMI, 29.3% had normal weight, 40.5% were overweight and 30.2% were obese (men: 17.7%, 51.1%, and 31.2%; women: 39.9%, 30.9%, and 29.2%, respectively). Abdominal obesity was present in 42.5% (39.1% of men and 45.6% of women).

The prevalence of DM, based on patient history and fasting plasma glucose levels, was 6.96%, without any significant difference between males and females (Table 1). 12.42% of individuals had IFG, with significantly higher rates in men compared to women (Table 1). In individuals with IFG who underwent an OGTT, we found that 29.70% of them were diabetics, 23.40% had IGT and the remaining 46.90% had IFG (Table 2). Similar rates of undiagnosed DM were observed in men and women, despite a non-significant trend towards higher rates in men. After extrapolating the frequency of DM, IGT and IFG to the whole number of subjects with fasting plasma glucose 100-125mg/dl, it was found that an additional 3.72% of subjects had undiagnosed DM, increasing the overall prevalence of DM in our sample population to 10.68% with significantly higher frequency in men compared to women (14.58% vs. 7.13%, p<0.001) (Table 3). The overall prevalence of pre-diabetes was 8.70% (IFG 5.84% and IGT 2.86%), with significantly higher frequency of IFG and pre-diabetes in males compared to females (Table 3).

In the group of 7,238 subjects interviewed by telephone, known DM was declared by 531 (7.38%),

**Table 1.** Prevalence of normoglycemia (NG), impaired fasting glucose (IFG) and diabetes mellitus (DM) based on fasting plasma glucose levels

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| **Plasma glucose levels (mg/dl)** | **n** | **%** | **n** | **%** | **n** | **%** |
| <100 (NG) | 280/384 | 72.92 | 369/421 | 87.65* | 649/805 | 80.62 |
| 100-125 (IFG) | 72/384 | 18.75 | 28/421 | 6.65* | 100/805 | 12.42 |
| ≥126 (DM) | 32/384 | 8.33 | 24/421 | 5.70 | 56/805 | 6.96 |

*p<0.001 compared to males

**Table 2.** The frequency distribution of IFG, IGT and DM in the 64 subjects who underwent OGTT

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| **Plasma glucose levels (mg/dl)** | **n** | **%** | **n** | **%** | **n** | **%** |
| 2 hours after the 75 gr glucose load | 46 | | 18 | | 64 | |
| <140 (IFG) | 21 | 45.65 | 9 | 50.00 | 30 | 46.90 |
| 140-199 (IGT) | 10 | 21.74 | 5 | 27.78 | 15 | 23.40 |
| ≥200 (DM) | 15 | 32.61 | 4 | 22.22 | 19 | 29.70 |

**Table 3.** Prevalence of NG, IFG, IGT and DM in our group after adjusting for the frequency in the total number of subjects with impaired fasting glucose

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| NG | 280 | 72.92 | 369 | 87.65* | 649 | 80.62 |
| IFG | 33 | 8.59 | 14 | 3.32** | 47 | 5.84 |
| IGT | 15 | 3.91 | 8 | 1.90 | 23 | 2.86 |
| DM | 56 | 14.58 | 30 | 7.13* | 86 | 10.68 |

*p<0.001, **p=0.002 compared to males

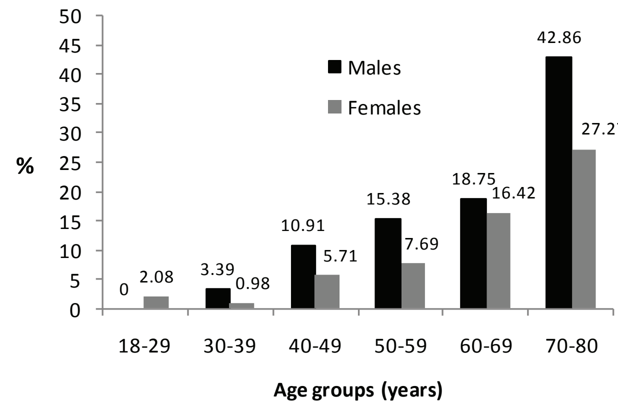


**Figure 1.** The rate of diabetes in males and females in the various age groups.

indicating a prevalence comparable to that found in Thessaly (p=0.669). After adjustment for age, the prevalence of DM in Thessaly was found to be 11.77%, whereas after extrapolating these data to the whole country, the age-standardized prevalence of DM was calculated at 11.97% (Table 4).

The subsequent analyses included 769 subjects after exclusion of those who declined to undergo the OGTT. The prevalence of DM was found to increase significantly with age (p=0.001) in both sexes, reaching its highest level in the group of 70-80 year-olds without any significant difference between men and women (Figure 1, Table 5). Rural residents had a significantly higher prevalence of DM than urban residents; when it was examined separately, women living in rural regions had significantly higher rates of DM, whereas statistical significance was marginally lost among men. However, this difference was no longer significant after controlling for age. The prevalence of DM was significantly higher in married than in single individuals, but it lost statistical significance when tested separately in men and women (Table 5). Education inversely influenced the frequency of DM: participants with a lower educational level (primary education) had a significantly higher prevalence of DM (Table 5) compared to those with a higher educational level (secondary and tertiary).

**Table 4.** The age-adjusted prevalence of diabetes mellitus (DM), impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and pre-diabetes in adults aged 20-79 in Thessaly and the whole country

| | DM (%) | IGT (%) | IFG (%) | Pre-diabetes (%) |
|---|---|---|---|---|
| **Thessaly** | | | | |
| Male | 13.70 | 4.17 | 9.62 | 13.79 |
| Female | 9.20 | 2.13 | 2.64 | 4.77 |
| Total | 11.77 | 3.01 | 5.90 | 8.91 |
| **Greece** | | | | |
| Male | 13.98 | 4.01 | 9.57 | 13.58 |
| Female | 9.25 | 1.90 | 2.76 | 4.66 |
| Total | 11.97 | 2.81 | 6.03 | 8.84 |

Comparative data regarding cardiovascular risk factors are presented in Table 6. As expected, men and women with higher BMI or abdominal obesity had a significantly higher prevalence of DM. On the other hand, subjects with DM or IGT had significantly higher BMI and WC compared to individuals with normoglycemia (31.51±6.64 vs. 27.72±5.24 kg/m$^2$, p=0.001; 106.57±13.15 vs 93.37±14.79 cm, p=0.001 and 30.91±5.75 vs 27.72±5.24 kg/m$^2$, p=0.006; 101.03±12.57 vs 93.37±14.79 cm, p=0.003, respectively). An association was also found between DM and hypertension. Men and women with hypertension had a significantly higher prevalence of DM compared to individuals without hypertension (Table 6). Smoking was also negatively associated with DM rates. Smokers had lower rates of DM compared to non-smokers. Hypercholesterolemia was not associated with DM prevalence, nor were hypertriglyceridemia and low HDL (data not shown).

In multiple logistic regression analysis, age, HOMA-IR, alcohol consumption and educational status were independently associated with the presence of T2DM/pre-diabetes (IFG and IGT) when compared

**Table 5.** The prevalence of diabetes mellitus among men and women based on sociodemographic characteristics

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Age** (years) (n=769) | | | | | | |
| 18-29 | 0/26 | 0.00 | 1/48 | 2.08 | 1/74 | 1.35 |
| 30-39 | 2/59 | 3.39 | 1/102 | 0.98 | 3/161 | 1.86 |
| 40-49 | 12/110 | 10.91 | 6/105 | 5.71 | 18/215 | 8.37 |
| 50-59 | 12/78 | 15.38 | 6/78 | 7.69 | 18/156 | 11.54 |
| 60-69 | 12/64 | 18.75 | 11/67 | 16.42 | 23/131 | 17.56 |
| 70-80 | 9/21 | 42.86 | 3/11 | 27.27 | 12/32 | 37.50 |
| p value | | 0.001 | | 0.001 | | 0.001 |
| p value (Cochran-Armitage test) | | <0.001 | | <0.001 | | <0.001 |
| **Marital status** (n=741) | | | | | | |
| Single | 3/50 | 6.00 | 1/49 | 2.04 | 4/99 | 4.04 |
| Married | 41/299 | 13.71 | 26/343 | 7.58 | 67/642 | 10.44 |
| p value | | 0.167 | | 0.227 | | 0.043 |
| **Education** (n=769) | | | | | | |
| Primary | 30/154 | 19.48 | 20/141 | 14.18 | 50/295 | 16.95 |
| Secondary | 15/136 | 11.03 | 7/202 | 3.47 | 22/338 | 6.51 |
| Higher | 2/68 | 2.94 | 1/68 | 1.47 | 3/136 | 2.20 |
| p value | | 0.001 | | 0.001 | | 0.001 |

**Table 6.** Prevalence of diabetes mellitus among men and women based on cardiovascular risk factors

| | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **BMI** ($kg/m^2$) (n=769) | | | | | | |
| BMI <25 | 3/62 | 4.84 | 6/162 | 3.7 | 9/224 | 4 |
| BMI 25-29,9 | 21/184 | 11.41 | 5/129 | 3.88 | 26/313 | 8.3 |
| BMI ≥30 | 23/112 | 20.53 | 17/120 | 14.17 | 41/232 | 17.67 |
| p value | | 0.001 | | 0.001 | | 0.001 |
| p value (Cochran-Armitage test) | | <0.001 | | <0.001 | | <0.001 |
| **Abdominal obesity** (n=769) | | | | | | |
| Yes | 29/154 | 18.83 | 23/199 | 11.56 | 52/353 | 14.73 |
| No | 18/204 | 8.82 | 5/212 | 2.36 | 23/416 | 5.53 |
| p value | | 0.007 | | <0.001 | | <0.001 |
| **Hypertension** (mmHg) (n=769) | | | | | | |
| Yes | 28/121 | 23.14 | 12/84 | 14.28 | 39/205 | 19.02 |
| No | 19/237 | 8 | 16/327 | 4.89 | 35/564 | 6.2 |
| p value | | 0.001 | | 0.006 | | <0.001 |
| **Smoking** (n=769) | | | | | | |
| Yes | 17/180 | 9.44 | 2/102 | 1.96 | 19/282 | 6.74 |
| No | 30/178 | 16.85 | 26/309 | 8.41 | 56/487 | 11.5 |
| p value | | 0.042 | | 0.023 | | 0.032 |
| **Hypercholesterolemia** (n=769) | | | | | | |
| Yes | 35/254 | 13.78 | 18/263 | 6.84 | 53/517 | 10.25 |
| No | 12/104 | 11.54 | 10/148 | 6.76 | 22/252 | 8.73 |
| p value | | 0.610 | | >0.999 | | 0.605 |

with non-diabetic individuals (Table 7); individuals of higher age, HOMA-IR and alcohol consumption, but lower educational status were at higher risk for T2DM. These results remained essentially unchanged when wine consumption replaced alcohol consumption in this regression model.

Age, HOMA-IR and serum triglycerides were independently associated with the presence of T2DM when pre-diabetes (IFG and IGT) was excluded from the analysis (Table 8); individuals of higher age, HOMA-IR and triglycerides were at higher risk for T2DM.

## DISCUSSION

The present study assessed the prevalence of DM in a random sample of adults living in a large region of Central Greece with both urban and rural areas. We found that a large proportion of adults (10.68%; men 14.58% and women 7.13%) had DM, while a smaller proportion (2.86%) had IGT and 8.70% had pre-diabetes. It should be emphasized that DM was undiagnosed in 34.88% of cases.

Epidemiological data regarding the prevalence of DM are rare in Greece. The first epidemiological studies concerning its prevalence, using glycosuria as a screening method, were conducted in the early 70's showing low rates of DM.[18,19] Twenty years later, similar estimates (1.52%) were found by Lionis et al in a retrospective study based on reviewing all medical records of a small rural district health care center and performing OGTT in subjects with non-diagnostic values of fasting glucose, based on the WHO criteria.[20] Our estimated prevalence of DM is in accordance with that of a study synchronous to our own conducted in the urban area of Attica[21] (DM prevalence 6.74%), in subjects free of apparent cardiovascular diseases, indicating a potential selection bias. Compared to another synchronous study conducted in a rural area, including individuals aged 1-99 years,[22] our DM prevalence is higher (10.68% vs. 7.40%). However, when we restricted their age-range to 20-80 years, the results concerning DM prevalence were comparable to our data in the rural area (9.35% vs. 11.52%). Close to our results is also the prevalence of DM in Cyprus (10.3%; 6.5% with known DM and 3.8% with undiagnosed DM) with population characteristics comparable to those of Greece.[23]

The prevalence of DM seems to be on the increase worldwide, although different racial, cultural, financial and habitual factors may influence its frequency across

**Table 7.** Multiple logistic regression analysis (stepwise method) for independent associates of diabetes and pre-diabetes vs. healthy controls

| **Covariate** | **B coefficient** | **Adjusted Odds Ratio** | **p-value** | **95% CI for adjusted odds ratio** |
|---|---|---|---|---|
| Age (years) | 0.054 | 1.056 | 0.001 | 1.022 – 1.090 |
| HOMA-IR | 0.293 | 1.340 | <0.001 | 1.216 – 1.477 |
| Alcohol consumption (Y/N) | 0.980 | 2.664 | 0.002 | 1.415 – 5.017 |
| Educational status (Lower vs Higher) | -0.591 | 0.554 | 0.029 | 0.326 – 0.942 |

Individuals without T2DM or IFG or IGT were rated as 0 and those with T2DM or IFG or IGT as 1 within the dependent variable.

Variables initially selected but finally excluded from the equation were: gender, fat mass, BMI, waist circumference, systolic arterial pressure, diastolic arterial pressure, total cholesterol, triglycerides and smoking.

**Table 8.** Multiple logistic regression analysis (stepwise method) for independent associates of diabetes vs. healthy controls

| **Covariate** | **B coefficient** | **Adjusted odds ratio** | **p-value** | **95% CI for adjusted odds ratio** |
|---|---|---|---|---|
| Age (years) | 0.082 | 1.086 | <0.001 | 1.044 – 1.129 |
| HOMA-IR | 0.258 | 1.294 | <0.001 | 1.161 – 1.442 |
| Triglycerides (mg/dL) | 0.004 | 1.004 | 0.020 | 1.001 – 1.007 |

Individuals without T2DM or IFG or IGT were rated as 0 and those with T2DM as 1 within the dependent variable.

Variables initially selected but finally excluded from the equation were: gender, permanent residence, educational status, smoking status, fat mass, BMI, waist circumference, mean arterial pressure, total cholesterol, HDL-cholesterol.

the world. In Europe, the known comparative age-standardized prevalence of DM in 2010 ranged from 2.1% to 12%, according to the International Diabetes Federation.[2] Using only FPG for the diagnosis, the overall prevalence of DM in Greece (6.96%) appears to be lower than that documented recently in the USA in adults over 20 years old (9.3%).[24] Undiagnosed DM has been reported to carry a similar risk of mortality to that of diagnosed DM.[25-27] However, the estimated prevalence depends on the method used. The WHO 1999 protocol is considered the gold standard for estimating undiagnosed DM, using measurements of FPG and 2-hour glucose.[28] According to the 2013 IDF Diabetes Atlas, globally, undiagnosed DM is estimated to account for 45.8% of all cases, with considerable variability across different world regions ranging from 24.5% to 75.1%.[27] This variability is attributed to a number of determinants, among which income is an important one affecting health care and the educational level of citizens. Health systems are generally more developed in high-income countries and thus DM is likely to be detected earlier. However, even within each country, access to health care may be lower in rural compared to urban areas. The proportion of undiagnosed DM ranges in Europe from 30%, based on FPG,[29] to 44-61%, based on OGTT, in two regional[30,31] and four nationwide studies.[26,32-34] Compared to data found in the well-controlled European studies concerning the prevalence of undiagnosed DM based on OGTT, our results are lower (approximately 35% of DM), possibly indicating more timely diagnosis of DM in Thessaly. Of course, regional differences in the proportion of undiagnosed DM are likely to affect the total prevalence of DM and may partly explain its variability among different countries with a comparable socioeconomic environment.[35]

The OGTT-based studies provide estimates of pre-diabetes (combined IFG and IGT), which is an important risk factor for DM. Regarding the prevalence of pre-diabetes in Greece, to the best of our knowledge, there is only one previously mentioned survey in a rural region, conducted in 2002.[22] In the age-comparable group of the above study, the prevalence of pre-diabetes was 4.22%, this being similar to our results when we compared the group of participants living in rural areas (5.56%). Our results regarding the prevalence of pre-diabetes (8.7%) are comparable to those found in Cyprus (9.5%), but lower than those in the abovementioned European countries where prevalence ranges from 14% to 30%,[35] and the results of the NHANES (2005-2008) survey which showed that the pre-diabetes rate among non-Hispanic whites in the USA was 29.5%.[36]

The prevalence of DM in our cohort was found to be significantly higher in men compared to women, the latter being analogous to published data from Spain.[37] It was observed that the prevalence of diabetes was higher in rural areas, but after controlling for age, the statistical significance of this difference was lost, confirming previously reported results from Greece.[38]

Age, education, HOMA-R and alcohol consumption were independently associated with DM/pre-diabetes. When pre-diabetes was excluded from the regression analysis, only age, HOMA-R and triglycerides remained independently associated with DM. Given that this was an observational study, a causal relationship cannot be established; however, we could speculate that alcohol consumption may influence factors that contribute to progression of metabolic disturbances (e.g., inflammation, oxidative stress and/or beta-cell dysfunction). Our results are in accordance with those found in a recent meta-analysis[39] showing that alcohol consumption of more than 50 gr/day increases the risk for DM. Other risk factors such as obesity and sedentary life associated with alcohol consumption may also explain our results.

Age is an independent risk factor for DM as observed in our series, this concurring with published data from developed countries.[40] Therefore, the expected increase in life expectancy represents a factor contributing to the worldwide increase of DM.

Lower educational status was also found to be associated with DM in our study. This inverse association is in agreement with published data from developed countries.[41,42] It should also be stressed that a lower educational level is usually associated with low income.

As expected, HOMA-IR, an index of insulin resistance, was independently associated with DM. Obesity is a major negative determinant of insulin sensitivity, as has been shown in human and animal studies, since weight gain correlates positively with insulin resistance.[43] Insulin resistance is a key component of DM, driving beta-cells to a compensatory enhancement of insulin secretion until the time they can no longer produce sufficient insulin, resulting initially in IGT and eventually in type 2 DM.[44]

In agreement with published data, we found that cardiovascular risk factors, such as obesity, abdominal obesity and hypertension, are more common in diabetic than non-diabetic individuals.[45,46] Obesity is an established risk factor for DM.[47] This study showed that the frequency of DM in obese subjects was four times higher compared to individuals with normal weight. This association was also evident among individuals from rural areas, where obesity is significantly higher compared to urban areas.[8]

DM prevalence was lower in smokers than non-smokers. Other studies have also shown that BMI in smokers is lower than in non-smokers,[48] indicating that smokers tend to be thinner, this possibly explaining the inverse association of smoking with DM. Furthermore, since this was an observational study, lower rates of DM in smokers may simply indicate that some ex-smokers had stopped smoking after the diagnosis of DM. On the other hand, smoking may play a role in the development of DM, as this is indicated in a recent study showing that smoking cessation in type 2 diabetics was associated with amelioration of their metabolic parameters.[49] Moreover, smoking is often associated with other unhealthy behaviors such as lack of physical activity, unhealthy diet and high alcohol consumption, factors that favor weight gain[50] and consequently increase the risk of DM.

Our findings are particularly alarming taking into account that DM is associated with increased incidence of long-term microvascular and macrovascular complications that will inevitably result in higher mortality, as this is indicated in the INTERHEART case-control study in Europians.[51]

The present study has certain limitations. First, this was an observational study, therefore no cause-effect relationship could be established. Second, the region of Thessaly may not accurately represent the whole country, although the prevalence of diagnosed DM in our telephone-conducted survey was not different; thus the extrapolation of our data to the whole country should be accepted with some reservation. Moreover, the extrapolation of data of 64 subjects subjected to OGTT to the 100 subjects with IFG may have slightly influenced our results. Finally, we did not measure HbA1c due to limited resources; this might have underestimated the prevalence of DM.

In conclusion, the prevalence of DM and pre-diabetes in Thessaly seems to be comparable to that observed in other European countries. This should be seriously considered by the Greek Health Agency, since DM-associated complications lead to increased cost, morbidity and mortality. Screening programs may be of importance so as to earlier diagnose individuals who are unaware of being diabetics and thereby more efficiently follow up those with pre-diabetes.

**CONFLICT OF INTEREST STATEMENT**

The authors declare that there is no conflict of interest and that they received no specific funding for this article.

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