Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Lifestyle factors do not explain the difference on diabetes progression according to type of prediabetes: Results from a Spanish prospective cohort of prediabetic patients

Isabel Ezquerra-Lázaro [a], *Lucía Cea-Soriano* [a,b,*], *Carolina Giraldez-García* [b,c], *Antonio Ruiz* [b,d], *Josep Franch-Nadal* [b,e,f,g], *Javier Diez-Espino* [b,h], *Pedro Nogales* [b,i], *Francisco Carramiñana* [b,j], *F. Javier Sangros* [b,k], *Enrique Regidor* [a,b,l,m], *for the PREDAPS Study Group* [1]

[a] *Department of Public Health and Maternal Child Health, Faculty of Medicine, Universidad Complutense de Madrid, Spain*
[b] *redGDPSFoundation, Madrid, Spain*
[c] *Hospital Universitario Infanta Elena, Madrid, Spain*
[d] *Centro de Salud Pinto, Madrid, Spain*
[e] *USR Barcelona ciutat – IDIAP Jordi Gol, Barcelona, Spain*
[f] *CIBER Diabetes y EnfermedadesMetabólicasAsociadas (CIBERDEM), Madrid, Spain*
[g] *Departament de Medicina, Universitat de Barcelona, Barcelona, Spain*
[h] *Centro de Salud Tafalla, Navarra, Spain*
[i] *Centro de Salud Las Águilas, Madrid, Spain*
[j] *Centro de Salud San Roque, Badajoz, Spain*
[k] *Centro de Salud Torrero-La Paz, Zaragoza, Spain*
[l] *CIBER Epidemiología y SaludPública (CIBERESP), Madrid, Spain*
[m] *Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain*

ARTICLE INFO

Article history:
Received 18 January 2019
Received in revised form
29 April 2019
Accepted 23 May 2019
Available online 29 May 2019

ABSTRACT

Aims: We studied the role of lifestyle factors associated to type 2 diabetes (T2DM) onset according to type of prediabetes.

Methods: We used data from the observational prospective cohort study in Primary Health Care on the Evolution of Patients with Prediabetes in Spain (PREDAPS). Participants were classified by American Diabetes Association criteria using either fasting plasma glucose levels (100–125 mg/dL) (group 1), HbA1c (5.7%–6.4%) (group 2) or both impaired parameters (group 3). Relationship between lifestyles and diabetes onset according to prediabetes at third year of follow up were estimated by Hazard Ratios (HRs) using three sequential models.

Abbreviations: ADA, American Diabetes Association; BMI, Body mass index; CI, Confidence Interval; FPG, Fasting plasma glucose; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; HbA_{1c}, Glycated hemoglobin A_{1c}; HDL-C, High-density lipoprotein cholesterol; HR, Hazard ratio; HTG, Hypertriglyceridemia; HTN, Hypertension; OGTT, Oral glucose tolerance test; PREDAPS, Cohort study in Primary Health Care on the Evolution of Patients with Prediabetes in Spain; SD, Standard deviation; T2DM, Type 2 diabetes mellitus; WHO, World Health Organization

* Corresponding author at: Department of Public Health and Maternal Child Health, Faculty of Medicine, Complutense University of Madrid, Spain.
E-mail address: tlcea@ucm.es (L. Cea-Soriano).

https://doi.org/10.1016/j.diabres.2019.05.033

Results: Incidence rate of diabetes was 2.27 cases per 1000 person-years (95% CI: 1.4–3.6) for group 1, 1.18 (95% CI: 0.65–2.13) for group 2 and 6.68 (95% CI: 5.71–8.23) for group 3. The most important risk factors were: abdominal obesity (HR: 2.29 (95% CI: 1.49–3.52)) and hypertension (HR: 2.16 (95% CI: 1.41–3.30)). Using as reference group 2, group 3 had a HR of 5.82 (3.13–10.82) and 1.83 (95% CI: 0.85–3.93) for group 1, estimates remained constant when adjusting by lifestyle and metabolic factors.

Conclusions: Lifestyle and metabolic do not seem to explain the differences on T2DM onset by type of prediabetes.

1. Introduction

The global prevalence of type 2 diabetes mellitus (T2DM) has almost doubled in recent years, increasing from 4.7% in 1980 to 8.5% in 2014, representing a total of 422 million cases worldwide [1]. Of note, a great proportion of patients with T2DM are detected when either micro or macrovascular complications are already present, avoiding any implementation against its progression [2,3]. In order to decrease the prolonged asymptomatic phase of T2DM and to improve its early detection, the American Diabetes Association (ADA) [4] based on expert panels, recommends start diabetes testing by the health care providers for adults age over 45 years with at least one risk factor such as body mass index (BMI) > 25 kg/m^2,

[1] The other members of the PREDAPS Study Group are: Margarita Alonso (CS De la Eria, Asturias), Beatriz Álvarez (CS Andrés Mellado, Madrid), Fernando Álvarez (CS La Calzada 2, Asturias), J Carlos Álvarez (CS Eras de Renueva, León), Mª del Mar Álvarez (CS Hereza, Madrid), J Joaquín Antón (CS Murcia-Centro, Murcia), Oriol Armengol (EAP Poblenou, Barcelona), Sara Artola (CS Hereza, Madrid), Luis Ávila (Consultorio Almachar, Málaga), Carmen Babace (CS Rodríguez Paterna, La Rioja), Lourdes Barutell (CS Andrés Mellado, Madrid), Mª Jesús Bedoya (CS Hereza, Madrid), Belén Benito (EAP Raval Sud, Barcelona), Beatriz Bilbeny (EAP Raval Sud, Barcelona), Marti Birules (EAP Poblenou, Barcelona), Concepción Blanco (CS Sada, A Coruña), Mª Isabel Bobé (EAP La Mina, Barcelona), Carmen Boente (CS Porriño, Pontevedra), Antonia Borras (CS Canal Salat, Baleares), Remei Bosch (EAP Girona 2, Girona), Mª Jesús Brito (CS La Matanza, Santa Cruz de Tenerife), Pilar Buil (EAP Azpilagaña, Navarra), J José Cabré (EAP Reus-1, Tarragona), Ainhoa Cambra (CS Arrabal, Zaragoza), Francisco Carbonell (CS Mislata, Valencia), Lourdes Carrillo (CS La Victoria de Acentejo, Santa Cruz de Tenerife), Ana Casorrán (CS Fuente de San Luis, Valencia), Rafael Colas (CS Santoña, Cantabria), Blanca Cordero (CS Sta. María de Benquerencia, Toledo), Xavier Cos (EAP Sant Martí de Provençals, Barcelona), Gabriel Cuatrecasas (CAP de Sarrià, Barcelona), Cristina De Castro (CS Sta. María de Benquerencia, Toledo), Manuel De la Flor (CS Ntra. Sra. de Gracia, Sevilla), Carlos De la Sen (Consultorio San Gabriel, Alicante), Rosa Mar De Miguel (EAP Pubillas Casas, Barcelona), A María De Santiago (Unidad Docente de Atención Familiar y Comunitaria, Guadalajara), Mercedes Del Castillo (CS Andrés Mellado, Madrid), Mª Carmen Durán (CS Lavadores Vigo, Pontevedra), Patxi Ezkurra (CS Zumaia, Guipúzcoa), Paula Gabriel (EAP Badia del Vallès, Barcelona), Javier Gamarra (CS Medina del Campo Rural, Valladolid), Francisco García (CS Don Benito Este, Badajoz), F Javier García-Soidán (CS Porriño, Pontevedra), Luis García-Giralda (CS Murcia Centro, Murcia), Mª Teresa Gijón (CS Los Yébenes, Madrid), Albert Goday (Hospital del Mar, Barcelona), Ángel Gómez (CS Lasarte, Guipúzcoa), María del Carmen Gómez (CS Vélez-Málaga Norte, Málaga), J Carles González (EAP Girona 3, Girona), María González (CS Alcantarilla Sangonera, Murcia), Esteban Granero (CS Vista Alegre Murcia, Murcia), Ángela Trinidad Gutiérrez (CS El Calero, Las Palmas), Félix Gutiérrez (CS Bombarda-Monsalud, Zaragoza), Luisa Gutiérrez (CS Beraun, Guipúzcoa), M Ángel Gutiérrez (CS Ávila Sur Oeste, Ávila), Ana Mª Hernández (CS El Calero, Las Palmas), Mercedes Ibáñez (CS Vandel, Madrid), Rosario Iglesias (CS Lain Entralgo, Madrid), Dimas Igual (CAP Manuel Encinas, Cáceres), Jaime Innerárity (CS Hereza Leganes, Madrid), Yon Iriarte (CS Aizarnazabal-Getaria, Guipúzcua), Ángeles Jurado (CS Salvador Caballero, Granada), Rafael Llanes (Villanueva de la Cañada, Madrid), Flora López (EAP Martorell, Barcelona), Regina Lopez (EAP El Carmel, Barcelona), Riánsares López (CS Artilleros, Madrid), Ángela Lorenzo (CS Alcalá de Guadaira, Madrid), Carmen Losada (UGC Adoratrices, Huelva), Ramón Macía (CS Roces Montevil, Asturias), Fernando Malo (CS Ares, A Coruña), José Mancera (CS Ciudad Jardín, Málaga), Mª José Mansilla (CS Martín de Vargas , Madrid), Mª Teresa Marín (CS General Ricardos, Madrid), José Luis Martín (CS Salvador Caballero, Granada), Anna Massana (EAP Raval Salud, Barcelona), F Javier Martínez (CS Federica Monseny, Madrid), Juan Martínez (CS Yecla, Murcia), Rosario Martínez (CS Oñati, Guipúzcoa), Manel Mata (EAP La Mina, Barcelona), Mª Soledad Mayayo (CS Martín de Vargas , Madrid), J Javier Mediavilla (CS Burgos Rural, Burgos), Luis Mendo (CS Cadreita, Navarra), J Manuel Millaruelo (CS Torrero La Paz, Zaragoza), Alicia Monzón (CS Vecindario, Las Palmas), Ana Moreno (CAP San Roque, Badajoz), Pedro Muñoz (Unidad Docente de Medicina Familiar y Comunitaria, Cantabria), Xavier Mundet (EAP El Carmel, Barcelona), Teresa Mur (CAP Terrasa Sud, Barcelona), Emma Navarro (CS Añaza, Santa Cruz de Tenerife), Jorge Navarro (CS Salvador Pau, Valencia), J Carlos Obaya (CS Chopera, Madrid), Cristina Oria (CS Aizarnazabal-Getaria, Guipuzcua) Francisco Javier Ortega (CS Campos-Lampreana, Zamora), Francisca Paniagua (CS Ciudad Jardín, Málaga), José Luis Pardo (CS Orihuela I, Alicante), Francisco Carlos Pérez (CS Martín de Vargas, Madrid), Pedro P Pérez (CS Mallen, Sevilla), Neus Piulats (EAP Raval Sud, Barcelona), Raquel Plana (CS Ponteareas, Pontevedra), Nuria Porta (CAP Terrassa Sud, Barcelona), Santiago Poveda (CS Jumilla, Murcia), Luis Prieto (CS Cáceres-La Mejostilla, Cáceres), Ramón Pujol (EAP Tremp, Lleida), Sol Reixa (CS Arrabal, Zaragoza), Jazmín Ripoll (CS Fuente de San Luis, Valencia), Antonio Rodríguez (EAP Anglès, Girona), J José Rodríguez (CS Villaviciosa de Odón, Madrid), Mª Angeles Rollán (CS Los Yébenes, Madrid), Mª Teresa Rollan (CS Hereza, Madrid), Laura Romera (EAP Raval Nord, Barcelona), Jóse Félix Rubio (CS Lasarte, Guipúzcua), Irene Ruiz (EAP La Torrassa, Barcelona), Manuel Antonio Ruiz (CS Agost, Alicante), Isabel Sáenz (CS Espronceda, Madrid), Julio Sagredo (CS Los Rosales, Madrid), Alejandro Salanova (CS Fuente de San Luis, Valencia), L Gabriel Sánchez (CS Carballeda, Zamora), Manuel Sánchez (CS Vista Alegre Murcia, Murcia), Gloria Sanz (CS San José centro, Zaragoza), Mateu Seguí (UBS Es Castell, Baleares), Rosario Serrano (CS Martín de Vargas, Madrid), Josefina Servent (EAP El Carmel, Barcelona), Dulce Suárez (CS El Calero, Las Palmas), Eduard Tarragó (EAP Bellvitge, Barcelona), Jesús Torrecilla (CS Bombarda-Monsalud, Zaragoza), José Luis Torres (CS Rodríguez Paterna, La Rioja), Mercè Villaró (CAP, Terrasa Sud, Barcelona), Carmen Yuste (EAP Badia del Vallès, Barcelona).

history of hypertension (HTN), low levels of high-density lipoprotein cholesterol (HDL-C), history of gestational diabetes, among other conditions, targeting traditional risk factors for diabetes type 2 onset [5].

Another way to diminish the burden of diabetes type 2 is controlling and detecting early stages such as prediabetes status. Prediabetes is a clinical stage characterized by higher levels of fasting plasma glucose (FPG) without reaching the levels to consider diabetes. Between 5 and 10% of patients with prediabetes develop in to T2DM type 2 each year [6]. There is no worldwide consensus on the definition of impaired fasting glucose (IFG), coexisting different definitions. While the ADA [4] considers IFG as FPG levels between 100 and 125 mg/dL (5.6–6.9 mmol/L), the World Health Organization (WHO) [7] and Diabetes Canada 2018 Clinical Practice Guidelines [8] define IFG as FPG levels between 110 and 125 mg/dL (6.1–6.9 mmol/L). The WHO [7] and Diabetes Canada [8] consider prediabetes by any of the following criteria: IFG (FPG 110–125 mg/dL [6.1–6.9 mmol/L]), impaired glucose tolerance (IGT) (2-hour plasma glucose in a 75 g oral glucose tolerance test [OGTT]) 140–199 mg/dL (7.8–11.0 mmol/L), or glycated hemoglobin (HbA_{1c}) 6.0%–6.4%.

The ADA [4] considers prediabetes by any of the following criteria: IFG (FPG 100–125 mg/dL [5.6–6.9 mmol/L]), IGT (OGTT) 140–199 mg/dL (7.8–11.0 mmol/L), or HbA_{1c} 6.0%–6.4%.

Most of the controversy lies on the validity of these parameters, being FPG a more specific parameter but not sensitive and the lack of good sensitivity and specificity for HbA_{1c}, leading into overdiagnosis. More precisely, using ADA *versus* WHO criteria have shown to overestimate the cases of prediabetes ranged of 2–5-fold times higher [9,10].

Results from different studies and metanalysis, have reported a slowing down of the progression to T2DM among individuals who keep optimal lifestyle factors in prediabetic population. BMI reduction and physical activity at least 150 min per week have shown to reduce the incidence rate of T2DM by more than 50% [11,12]. Another key feature against diabetes onset includes a healthy diet which intends to reduce saturated fat and increase fiber intake [13].

Prior studies have evaluated the progression to T2DM according to prediabetes status suggesting lowest rates for isolated IFG, following by IGT, and highest for both impaired parameters. In contrast, HbA_{1c} 6.0–6.4% has shown a similar risk of T2DM than IFG [14]. Although, there is well knowledge of the established risk factors for both prediabetes and T2DM onset, there is a scarce knowledge about the importance of the type of impaired glycemic parameter on diabetes onset itself not explained via lifestyle factors and metabolic conditions. We conducted a prospective cohort study at the primary care setting with prediabetic patients in order to evaluate the impact of lifestyle factors on predicting T2DM onset in subjects with prediabetes.

2. Material and methods

2.1. Study design

The Cohort Study in Primary Health Care on the Evolution of Patients with Prediabetes (PREDAPS) is a prospective study conducted by 125 Primary Care physicians at their practices across different provinces in Spain. The details of the cohort have been previously cited [6]. Briefly, the study cohort included all subjects aged between 30 and 74 years with the absence of the following criteria: diagnosis of diabetes, terminal disease, pregnancy, surgery, hospital admissions in the previous 3 months at study entry or any hematologic disease which could alter HbA_{1c} values. Study subjects were subdivided into two mutually exclusive cohorts according to glycemic parameters following ADA criteria: prediabetic cohort included 1184 subjects with HbA_{1c} levels between 39 and 46 mmol/mol (5.7–6.4%) and/or FPG between 5.6 and 6.9 mmol/L (100–125 mg/dL); and the other cohort included 838 people without impaired glucose metabolism. Since this study focuses on prediabetes, analyses were restricted to the prediabetic cohort. Study period started on 2012 up to the third follow-up visit (2015).

2.2. Classification of prediabetes groups

Prediabetic cohort was subdivided in three groups mutually exclusive based on impaired glycemic parameters. The *group 1* included all subjects with only IFG (FPG $\geq$ 100 mg/dL [$\geq$5.6 mmol/L]). The *group 2* was composed by subjects with isolated impaired HbA_{1c} ($\geq$5.7% [$\geq$39 mmol/mol]). The *group 3* included subjects with both impaired parameters (FPG and HbA_{1c}).

In order to further evaluate the influence of each parameter separately, we subdivided each of the afore-mentioned groups as follows: *group 1* was subdivided in: isolated FPG 100–109 mg/dL and isolated FPG $\geq$ 110 mg/dL; *group 2* was subdivided in: isolated HbA_{1c} 5.7–5.9% and isolated HbA_{1c} - $\geq$ 6.0%; and, *group 3* was subdivided in four subgroups: FPG 100–109 mg/dL and HbA_{1c} 5.7–5.9%; FPG 100–109 mg/dL and $HbA_{1c} \geq 6.0\%$; FPG $\geq$ 110 mg/dL and HbA_{1c} 5.7–5.9% and FPG $\geq$ 110 mg/dL and $HbA_{1c} \geq 6.0\%$.

2.3. Study variables and data-collection

Data were collected at the first visit (baseline period) and at third annual visit. Information on biographical data, family history, personal history, lifestyle, drug treatment, social support and socio-economic position were obtained from clinical records of study subjects and personal interview was conducted by the physician. The values of FPG and HbA1c were obtained annually in each subject to know if he had developed diabetes or not.

Hypertension (HTN) was defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg, being treated by antihypertensive drugs or previous diagnosis of HTN. Hypercholesterolemia was defined as serum total cholesterol $\geq$ 250 mg/dL, HDL-C as <40 mg/dL in men or <50 mg/dL in women, and hypertriglyceridemia (HTG) as serum triglycerides $\geq$ 200 mg/dL. Overweight was defined as BMI between 25.0 and 29.9 kg/m^2, general obesity was defined as BMI $\geq$ 30 kg/m^2, and abdominal obesity as waist circumference $\geq$102 cm in men and $\geq$88 cm in women [6].

The adherence to Mediterranean diet was measure according to the study ATTICA and its score *Panagiotakos* [15]. For each twenty types of studied food, subjects had to respond

if their consumption was every day, more than three times a week, two times each week, once a week, less than once a week, never or rarely. Zero as a score in each meal ~~is~~ was considered as the subject is having a less healthy diet meanwhile 4 was considered the subject as having a very healthy one. The general score of 0 was considered as low adherence to diet and 80 was considered the maximum one. The adherence to Mediterranean diet was classified in three categories: low (0–53 points), medium (54–59 points) and high (60–80 points). Moreover, subjects were asked about frequency of meals (i.e. at least three meals per day and less than three meals).

Smoking consumption was classified as: smokers, ex-smokers and non-smokers. Alcohol consumption was classified as: daily drinkers, occasional drinkers, and non-drinkers (never or former) which included ex-drinkers and teetotalers. Physical activity was classified according to WHO recommendations. Subjects followed the recommendations if they practiced more than 150 min per week of moderate aerobic physical activity, more than 75 min each week of vigorous aerobic physical activity or an equivalent combination [16].

2.4. *Statistical analysis*

A descriptive analysis was performed describing the baseline characteristics (demographic distribution, lifestyle variables, obesity, HTN and biochemical parameters) according to prediabetes groups using chi-square test (categorical variables) and Student *t* test (continuous variables). From baseline period to the third annual visit, we estimated the cumulative incidence of newly diagnosed T2DM per sub-cohort as well as incidence rates per 100 person-years (95%, confidence interval [CI]). Diabetes was considered when a patient presented either FPG $\geq$ 126 mg/dL ($\geq$7.0 mmol/L) or $HbA_{1c} \geq 6.5\%$ ($\geq$48 mmol/-mol). The association between demographic characteristics, lifestyle variables, obesity, HTN and biochemical parameters and onset was performed using a COX regression. To evaluate the role of lifestyle factors on T2DM onset according to prediabetic status, we used three consecutive models: the first one (*model 1*) was sex- and age-adjusted; the second one (*model 2*) was sex- and age-adjusted and also by HTN, hypercholesterolemia, low HDL-C and HTG; the third one (*model 3*) was adjusted by the ones in *model 2* and also by alcohol consumption, smoking, BMI, abdominal obesity, adherence to diet, physical activity and eat three meals/ day. Hazard ratios (HR) of T2DM onset as well as risk reduction expressed in percentages were calculated. Statistical analyses were performed using the STATA package version 12.0 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. *Baseline characteristics*

The mean age of prediabetic cohort was 58.7 (standard deviation [SD]: 9.3) years. According to ADA criteria, 21.5% (95% CI: 19.11–23.8) of study population had isolated IFG (FPG $\geq$ 100 mg/dL, *group 1*), 26.7% (95% CI: 24.2–29.2) had isolated impaired HbA_{1c} ($HbA_{1c} \geq 5.7\%$, *group 2*) and 51.9% (CI: 49.0–54.7) had both impaired parameters (FPG $\geq$ 100 mg/dL ~~y~~ and $HbA_{1c} \geq 5.7\%$, *group 3*). Table 1 shows the baseline characteristics according to the three subgroups. Proportion of males were 60% for *group 1* (isolated impaired FPG), 40% for *group 2* (only impaired HbA_{1c}), and 49% for *group 3* (both impaired parameters). Ap proximately 40% of subjects, regardless the group, were aged between 60 and 69 years old, although *group 1* had a higher proportion of individuals aged over 50 years. Most of the population (>80%), regardless the group, had BMI > 25 kg/m^2 although the proportion of abdominal obesity was higher in *group 3* (corresponding proportions for the latter: 74% for *group 3*, 61.4% for *group 2 and* 58.3% for *group 1*). More than half of study subjects presented HTN, hyperlipidemia and low HDL-C. There were no differences in distribution of remaining lifestyle factors as smoking, physical activity and adherence to diet.

3.2. *Cumulative incidence and incidence rate of diabetes type 2 onset*

At third follow-up, 143 study subjects (12.1%) developed T2DM. Fig. 1 shows a graphical representation of cumulative incidence according to three criteria of prediabetes. The highest cumulative incidence was 18.7% in *group 3* (impaired FPG and HbA_{1c}), followed by 6.7% in *group 1* (only impaired FPG).

When subdividing prediabetic cohort in eight subgroups according to FPG and HbA_{1c} levels (Fig. 2), subjects with only FPG < 110 mg/dL and the subjects with isolated $HbA_{1c} < 6.0\%$ had the lower cumulative incidence of T2DM (1.40% and 2.10%, respectively). In contrast those with both impaired parameters (FPG $\geq$ 110 mg/dL and $HbA_{1c} \geq 6\%$) showed the highest cumulative incidence (28.8%), corresponding cumulative incidences were 1.3% and 1.5%, respectively.

Likewise, the incidence rate of T2DM was 4.26 (95% CI: 3.61–5.01) cases per 100 person-years (Suppl Table 1), although those results are based on small absolute numbers. The incidence rate of T2DM was 6.86 (95% CI: 5.71–8.23) cases per 100 person-years for *group 3* and 2.3 (95% CI: 1.4–3.6) cases per 100 person-years for *group 1*. Finally, the incidence rate of T2DM among subjects with only FPG 100–110 mg/dL and those with only $HbA_{1c} < 6\%$ was 0.44 cases (95% CI: 0.11–1.78) per 100 person-years and 0.49 cases (95% CI: 0.16–1.53) per 100 person-years, respectively.

3.3. *Multivariate regression age- and sex-adjusted*

Table 2 shows the percentage of prediabetic patients who developed T2DM according to different baseline characteristics as well as the HRs of T2DM (adjusted by *model 1*). There was no association with sex or age.

Regarding lifestyle factors, the most important risk factor for T2DM onset was low-medium adherence to diet (1.98 (95% CI: 1.25–3.12)). In contrast, eating three meals per day showed to be a protective factor (0.56 (95% CI: 0.32–0.96)). There was no association with physical activity or tobacco consumption.

Following comorbidities were associated about twofold times higher of developing T2DM: HTN (2.16 (95% CI: 1.41–3.30)), abdominal obesity (2.29 (95% CI: 1.49–3.52)), BMI > 25 kg/m^2 (1.79 (95% CI: 1.28–2.50)), low HDL-C levels

Table 1 – Baseline individual characteristics from study cohort according to prediabetes type.

Characteristics	PREDIABETES TYPE						*p value group1 vs. group 2*	*p value group1 vs. group 3*	*p value group 2 vs. group 3*
	Group 1 Only impaired FPG (100–125 mg/dL)		Group 2 Only impaired HbA_{1c} (5.7–6.4%)		Group 3 Both parameters (FPG: 100–125 mg/dL & HbA_{1c}: 5.7–6.4%)				
	N	%	N	%	N	%			
Sex									
Male	156	61.4	126	39.9	313	51	<0.001	0.005	0.001
Female	98	38.6	190	60.1	301	49			
Age (years), N, mean (SD)	254	57.5 (9.5)	316	58.9 (9.8)	614	60.4 (8.8)	0.0892	<0.001	0.0164
Hypertension									
No	89	35	137	43.4	165	26.9	0.044	0.016	<0.001
Yes	165	65	179	56.7	449	73.1			
Hyperlipidemia									
No	107	42.1	132	41.8	244	39.7	0.932	0.515	0.550
Yes	147	57.9	184	58.2	370	60.3			
HDL levels (mg/dl) N, mean (SD)	254	53.5 (14.0)	316	55.4 (14.2)	614	(53.9 14.5)	0.1003	0.6753	0.1290
Hypertriglyceridemia									
No	186	73.2	248	78.5	418	68.1	0.144	0.133	0.001
Yes	68	26.8	68	21.5	196	31.9			
Waist circumference (cm) N, mean (SD)	254	98.4 (11.8)	316	97.2 (12.6)	614	102(12)	0.2253	<0.001	<0.001
BMI (kg/m^2), N, mean (SD)	254	29.0 (4.5)	316	28.9 (5.0)	614	30.7 (4.8)	0.6987	<0.001	<0.001
Adherence to diet									
Low-medium	186	73.2	226	71.5	454	73.9	0.037	0.766	0.004
High	68	26.8	90	28.5	160	26.1			
Physical activity									
Follow recommendations	104	40.9	134	42.7	291	47.4	0.678	0.083	0.172
Do not follow recommendations	150	59.1	180	57.3	323	52.6			
Following at least 3 meals/day									
No	23	9.1	15	4.8	40	6.5	0.040	0.189	0.279
Yes	231	90.9	301	95.3	574	93.5			
Smoking									
Non-smoker	97	38.2	138	43.7	297	48.4	0.039	0.016	0.087
Ex-smoker	117	46.1	113	35.8	225	36.6			
Smoker	40	15.8	65	20.6	92	15			
Alcohol consumption									
Non-drinkers (never/former)	19	7.5	32	10.1	49	8	0.007	0.026	0.442
Occasional drinker	44	17.3	85	26.9	157	25.6			
Daily drinker	191	75.2	199	63	408	66.5			

No.: Cases number. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin A_{1c}. HTN: Hypertension. HDL-C: High-density lipoproteins cholesterol. HTG: Hypertriglyceridemia. BMI: Body mass index.

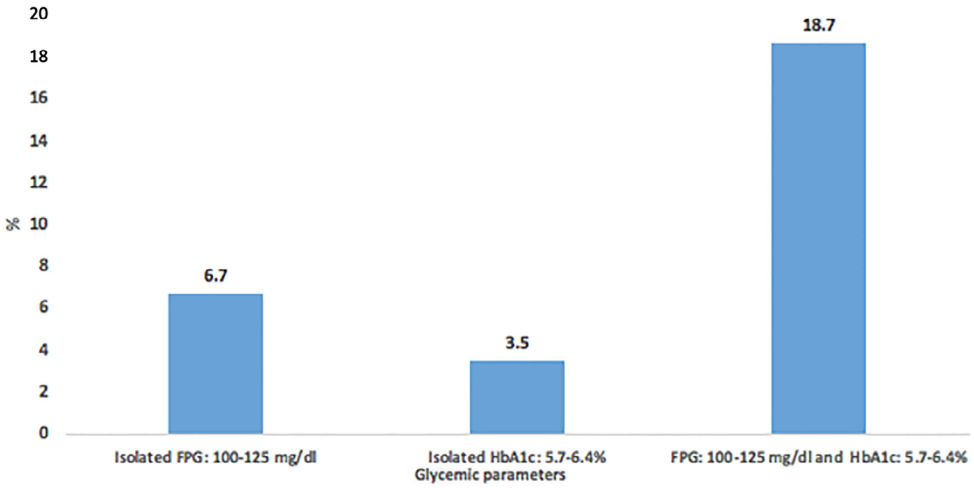

Fig. 1 – Cumulative incidence (%) of diabetes type 2 stratified by type of prediabetes. T2DM: Type 2 diabetes mellitus. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin A_{1c}.

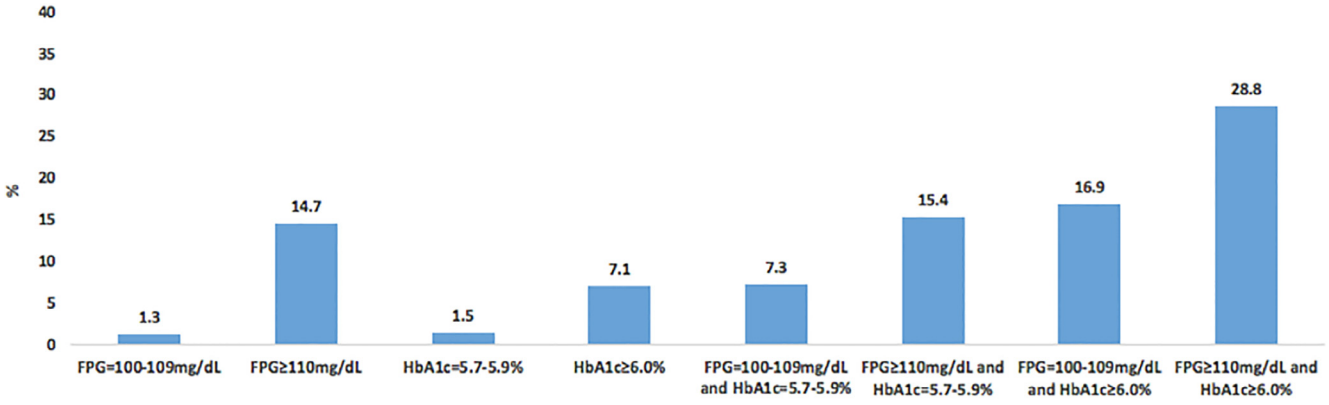

Fig. 2 – Cumulative incidence (%) of diabetes type 2 stratified by eight categories of prediabetes. T2DM: Type 2 diabetes mellitus. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin A_{1c}.

(1.81 (95% CI: 1.27–2.58)) and hypertriglyceridemia (1.65 (95% CI: 1.17–2.32)).

There was no association with hyperlipidemia.

3.4. *Role of lifestyle factors in diabetes T2DM*

Adjusting by sex and age (*model 1*) and using as reference *group 2* (only impaired HbA_{1c}), HR of developing T2DM for each prediabetic group (Table 3) were 1.83 (95% CI: 0.85–3.93) for *group 1* (only impaired FPG) and 5.82 (95% CI: 3.13–10.82) for *group 3* (both impaired parameters). When adding biochemical parameters (*model 2*), estimates decreased by 10.7% (1.75 (95% CI: 0.82–3.76)) for *group 1* and 17.6% (5.10 (95% CI: 2.73–9.51) for *group 3*, respectively. Of note, compared to *model 2*, estimates remained almost constant when we added lifestyle factors (*model 3*): risk reduction of 2.7% (1.73 (95% CI: 0.80–3.73) and 7.3% (4.82 (95% CI: 2.57–9.04), respectively.

Assessing the eight groups of prediabetes (Table 4) and using as reference isolated HbA_{1c} 5.7–5.9% (*model 3*), there was no association among subjects with FPG 100–110 mg/dL (0.80 (95% CI: 0.13–4.78). Contrary to these results, patients with both highly impaired parameters (FPG $\geq$ 110 mg/dL and $HbA_{1c} \geq 6\%$) had a higher risk (20.11 (95% CI: 6.27–64.55)), with a risk reduction of 8.5% comparing *model 3* with *model 2*. Finally, the risk of developing T2DM was similar in subjects with isolated FPG $\geq$ 110 mg/dL (8.35 (95% CI: 2.39–29.09)) and subjects with FPG $\geq$ 110 mg/dL and HbA_{1c} 5.7–5.9% (8.59 (95% CI: 2.54–29.08)).

4. Discussion

This prospective cohort included a total of 1184 prediabetic subjects. The three categories of this cohort showed similar baseline characteristics. The global incidence rate of T2DM at the end of the third follow-up was 4.26 (95% CI: 3.61–5.01) cases per 100 person-years. Subjects with both impaired parameters (FPG and HbA_{1c}) had the highest probability of T2DM onset. More precisely, if we take 100 participants of this category, 6 of them will develop T2DM per year of follow-up. The incidence rate in subjects with isolated impaired FPG or isolated impaired HbA_{1c} were: 2.27 (95% CI: 1.41–3.65) and 1.18 (95% CI: 0.65–2.13) cases per 100 person-years, respectively. In line with the current results,

Table 2 – Percentage of diabetes type 2 development and Hazard Ratio (HR) according to lifestyle factors and comorbidities.

		% Diabetes type 2	HR (95% CI)
Sex	Male	11.93	1.00
	Female	12.22	1.04 (0.75–14.5)
Age (years old)	30–49	12.83	1.16 (0.63–2.15)
	50–59	11.63	1.05 (0.61–1.84)
	60–69	12.45	1.20 (0.71–2.04)
	>70 (70–75)	11.11	1.00
Prediabetes type	Impaired FPG	6.69	1.83 (0.85–3.93)
	Impaired HbA_{1c}	3.48	1.00
	Both	18.73	5.82 (3.13–10.82)
Hypertension	No	7.16	1.00
	Yes	14.50	2.16 (1.41–3.30)
Hyperlipemia	No	12.42	1.00
	Yes	11.84	0.92 (0.66–1.28)
Low HDL-C levels	No	10.58	1.00
	Yes	16.78	1.81 (1.27–2.58)
Hypertriglyceridemia	No	10.45	1.00
	Yes	16.27	1.65 (1.17–2.32)
Abdominal obesity	<88/102 cm	6.70	1.00
	≥88/102 cm	14.80	2.29 (1.49–3.52)
BMI (kg/m^2)	<25	4.50	1.00
	>25	13.20	1.79 (1.28–2.50)
Adherence to diet	Low-medium	13.90	1.98 (1.25–3.12)
	High	7.20	1.00
Physical activity	Yes	14.37	1.00
	No	10.26	0.74 (0.53–1.03)
Eating more than three times a day	No	19.23	1.00
	Yes	11.57	0.56 (0.32–0.96)
Tobacco consumption	Smoker	9.64	1.00
	Ex-smoker	14.29	1.51 (0.90–2.54)
	Non-smoker	11.09	1.11 (0.65–1.90)
Alcohol consumption	**Daily drinker**	11.28	1.00
	Occasional drinker	12.24	1.13 (0.73–1.74)
	Non-drinker (Never/former)	18.00	1.76 (1.06–2.93)

*Hazard ratio adjusted by sex and age.

T2DM: Type 2 diabetes mellitus. HR: Hazard ratio sex- and age-adjusted. CI: 95%, confidence interval. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin A_{1c}. HTN: Hypertension. HDL-C: High-density lipoproteins cholesterol. HTG: Hypertriglyceridemia. BMI: Body mass index.

Table 3 – Hazard Ratio (95% confidence interval) of diabetes type 2 according to type of prediabetes.

	HR (95% CI)		
Prediabetes criteria	Model 1	Model 2	Model 3
Only impaired FPG (100–125 mg/dL)	1.83 (0.85–3.93)	1.75 (0.82–3.76)	1.73 (0.80–3.73)
Only impaired HbA_{1c} (5.7–6.4%)	1.00	1.00	1.00
Both parameters (FPG: 100–125 mg/dL & HbA_{1c}: 5.7–6.4%)	5.82 (3.13–10.82)	5.10 (2.73–9.51)	4.82 (2.57–9.04)

T2DM: Type 2 diabetes mellitus. HR: Hazard ratio. CI: 95%, confidence interval. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin A_{1c}.
Model 1: Adjusted by sex and age.
Model 2: Model 1 adjusted by hypertension, hypercholesterolemia, low HDL levels and hypertriglyceridemia.
Model 3: Model 2 adjusted by alcohol consumption, tobacco consumption, BMI, abdominal obesity, adherence to diet, physical activity and eating more than three times a day.

prior studies [17,18], which used the same diagnostic criteria, observed how the incidence rate of subjects with both impaired parameters ranged between 3 and 5-fold times higher compared with individuals with only one impaired parameter. Of note, in the present study, prediabetic patients with isolated FPG < 110 mg/dL and isolated HbA_{1c} < 6% showed the lowest incidence rates and no statistical increase risk of T2DM onset.

In the present study, metabolic factors such as hypertension [19,20], impaired lipid metabolism (low HDL levels and hypertriglyceridemia [19–22], BMI > 25 kg/m^2, abdominal obesity [19,22–24] showed to be positive predictors for T2DM, in line with prior research studies. In this study, having a low/medium adherence to diet was a protective factor against T2DM. Other authors [22] did not find this association. It could be possible that those patients had a higher perception and

Table 4 – Hazard Ratio of T2DM according prediabetes criteria using a narrow cut-off points.

Prediabetes criteria	HR (CI) of T2DM		
	Model 1	Model 2	Model 3
Only FPG 100–109 mg/dL	0.87 (0.14–5.21)	0.82 (0.14–4.93)	0.80 (0.13–4.78)
Only FPG ≥ 110 mg/dL	9.26 (2.67–32.07)	8.66 (2.50–30.05)	8.35 (2.39–29.09)
Only HbA_{1c} = 5.7–5.9%	1.00	1.00	1.00
Only HbA_{1c} ≥ 6.0%	5.20 (1.38–19.62)	4.84 (1.28–18.32)	4.50 (1.19–17.06)
FPG 100–109 mg/dL & HbA_{1c} 5.7–5.9%	4.83 (1.33–17.57)	4.18 (1.15–15.25)	3.90 (1.06–14.29)
FPG ≥ 110 mg/dL & HbA_{1c} 5.7–5.9%	10.39 (3.08–35.07)	9.33 (2.76–31.53)	8.59 (2.54–29.08)
FPG 100–109 mg/dL & HbA_{1c} ≥ 6.0%	12.70 (3.77–42.78)	10.78 (3.19–36.40)	9.49 (2.80–32-17)
FPG ≥ 110 mg/dL & HbA_{1c} ≥ 6.0%	25.61 (8.03–81.64)	21.74 (6.79–69.57)	20.11(6.27–64.55)

T2DM: Type 2 diabetes mellitus. HR: Hazard ratio. CI: 95%, confidence interval. FPG: Fasting plasma glucose. HbA_{1c}: Glycated hemoglobin A_{1c}.
Model 1: Adjusted by sex and age.
Model 2: Model 1 adjusted by hypertension, hypercholesterolemia, low HDL-C levels and hypertriglyceridemia.
Model 3: Model 2 adjusted by alcohol consumption, tobacco consumption, BMI, abdominal obesity, adherence to diet, physical activity and eating more than three times a day.

concern of its health and therefore lower risk of T2DM onset. When interpreting the role of BMI in T2DM onset, one cannot rule out some source of residual confounding which could affect the magnitude of the association, being therefore the abdominal obesity a more valid independent predictor. Contrary to these risk factors, eating three meals per day shown to be a protective factor against T2DM. Finally, alcohol consumption and its possible association with T2DM still remains unclear. The present study observed a higher risk among occasionally and non-drinkers than among daily drinkers. Some authors describe the relation between alcohol consumption and the risk of T2DM onset by a J-form [25] and others by a U-form [22,26].

According to groups of prediabetes, patients with both impaired parameters had a higher risk of T2DM onset, followed by subjects with isolated impaired FPG. It is worth noting that when adjusting by biochemical parameters and lifestyle ones (*model 3*), the association remained constant respective to adjusting by biochemical parameters (*model 2*), specifically the risk reduction was around or below 10% for all categories with the exception of those with FPG 100–109 mg/dL & HbA_{1c} ≥ 6% (risk reduction: 15%). Based on the small risk reduction comparing *model 3 vs. model 2*, lifestyle factors do not seem to explain differences in T2DM onset. ADA has modified the criteria for prediabetes considering cut-off points, adding FPG: 100–109 mg/dL and HbA_{1c}: 5.7%–6%. Yet, diagnostic criteria of prediabetes are still controversial. For example, other definitions as the one proposed by the organization defines prediabetes as FPG (110 to 125 mg/dL) and IGT defined as 2-h plasma glucose 140–199 mg/dL after OGTT or a combination of the two based on a 2-h OGTT, not considering HbA_{1c} levels [27]. When stratifying in eight groups, approximately 1% of subjects with isolated FPG < 110 mg/dL and those isolated HbA_{1c} < 6% developed T2DM at the third year of follow-up compared to 29% in individuals with FPG > 110 mg/dL and HbA_{1c} > 6%. Based on our results, the latest inclusion criterion advised by the ADA (i.e. FPG < 110 mg/dL) might lead into an overestimation of prediabetes status leading a high proportion of false positives [9,28–30]. Following this reasoning, it appears that combining various parameters might be a more valid tool and accurate predictor to classify prediabetic status [31] and doubt about the validity of using isolated FPG 100–110 mg/dL as a prediabetes criterion. Keeping in mind the challenges of prediabetes criteria, future studies are warranted to quantify not only the proportion of individuals with FPG < 110 mg/dL developing T2DM and its prognosis, but also to evaluate which cut-off points in FPG and HbA_{1c} are precise parameters for public health decision making.

4.1. *Strengths and limitations*

This population-based cohort study highlights the representativeness based not only on the universal health system implanted in Spain but also on the high response rate of patients during each follow-up visit. However, there are several limitations that deserve some comments. First, although this is a prospective cohort study with an extensive data collection which allows for multiple adjustment of confounders, these data were collected at baseline period being unable to measure changes on time (i.e. time dependent variables). However, some of the factors considered in the present study are chronic conditions or long-term lifestyle factors not susceptible to a fast variation within the follow-up during the study period. Second, although we used ADA criteria, other studies have used also Impaired Glucose Tolerance IGT which might have limited the comparison with prior studies. Third, although several laboratories were used across the country, each patient was assigned to the same laboratory during the follow-up. This limitation should be minor and expected to be non-differential in relation to the outcome. Fourth, when subdividing each type of prediabetes into different categories, the number of subjects in some of them is very small and, therefore, chance variation cannot be excluded in the differences found between some of them. Finally, it should be noted that the present study did not evaluate the impact of interventions but the role of those factors by type of prediabetes thus a direct comparison with other studies cannot be made.

In conclusion, lifestyle factors and metabolic conditions showed to be important risk factors for T2DM onset. Results from randomized trials and other observational studies have

shown how promoting new life style factors and psychical activity might decrease notably the incidence of diabetes type 2. However, the increased risk of T2DM onset according type of prediabetes observed in the current study cannot be explained via lifestyle factors. Future studies are essential to clarify which is the adequate cut-off point for each impaired glycemic parameter in order to fully monitor and identify high risk individuals for T2DM development. Other studies are needed in order to evaluate if the combination of both parameters is a better criterium of prediabetes screening.

Funding

Sanofi and Novartis gave financial support for the development of the data collection platform, the meetings of researchers, and the monitoring of information collected at baseline. Sanofi and Novartis had no role in the study design, analysis and interpretation of data, writing of the manuscript, nor the decision to submit the manuscript for publication.

Author contributions

IEL and LCS and ER originated and designed the study, contributed to the analysis of the data and to the drafting of the paper. CVG, AR, JFN, JDE, PN, FC and FJS collected data of the study and contributed to the interpretation of the results and to the drafting of the paper. LCS coordinated the writing of the article. All authors contributed to the final version of the article. All authors have seen and approved the final version. LCS is the guarantor of the study.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.05.033.

REFERENCES

[1] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
[2] Heltberg A, Andersen JS, Sandholdt H, Siersma V, Kragstrup J, Ellervik C. Predictors of undiagnosed prevalent type 2 diabetes – The Danish general suburban population study. Prim Care Diabetes 2018;12(1):13–22.
[3] Beagley Jessica, Guariguata Leonor, Weil Clara, Motala Ayesha A. Global estimates of undiagnosed diabetes in adults. Diabetes Res Clin Pract 2014 Feb;103(2):150–60.
[4] American diabetes association. Screening for diabetes. Diabetes Care Jan 2002, 25 (suppl 1) s21–s24.
[5] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41(Suppl. 1):S13–S27.
[6] Serrano R, García-Soidán FJ, Díaz-Redondo A, et al. Grupo de Estudio PREDADS. Estudio de cohortes en atención primaria sobre la evolución de sujetos con prediabetes (PREDAPS): fundamentos y metodología. Rev Esp Salud Publica 2013;87:121–35.
[7] World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. World Health Organization, Geneva; 1999.
[8] Punthakee Z, Goldenberg R, Katz P. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada: definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes 2018;42(Suppl 1):S10–5.
[9] Yudkin JS, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. BMJ 2014;349:g4485.
[10] Barry E, Roberts S, Oke J, et al. Efficacy and effectiveness of screen and treat politics in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. BMJ 2017;356:i6538.
[11] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393–403.
[12] Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013 Oct 15;159(8):543–51.
[13] Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J. Finnish diabetes prevention study group. The finnish diabetes prevention study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003;26(12):3230–6.
[14] Morris DH, Khunti K, Achana F, Srinivasan B, Gray LJ, Davies MJ, et al. Progression rates from HbA1c 6.0–6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia 2013 Jul;56(7):1489–93.
[15] Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutr Metab Cardiovasc Dis 2006;16:559–68.
[16] World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010.
[17] Heianza Y, Hara S, Arase Y, et al. HbA1c 5.7-6.4 % and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort studmatty. Lancet 2011;378:147–55.
[18] Inoue K, Matsumoto M, Akimoto K. Fasting plasma glucose and HbA1c as risk factors for type 2 diabetes. Diabet Med 2008;25:1157–63.
[19] Giráldez-García C, Ávila L, Carramiñana F, Torres JL, Bedoya MJ, Mancera J, et al. Evolución de pacientes con prediabetes en Atención Primaria de Salud (PREDAPS): resultados del segundo año de seguimiento. DiabetesPráctica 2015;5:49–96.
[20] Soriguer F, Rojo-Martínez G, Almaraz MC, Esteva I, Ruiz de Adana MS, Morcillo S, et al. Incidence of type 2 diabetes in southern Spain (Pizarra Study). Eur J Clin Invest 2008;38:126–33.
[21] Bardenheier BH, Bullard KM, Caspersen CJ, Cheng YJ, Gregg EW, Geiss LS. A novel use of structural equation models to examine factors associated with prediabetes among adults aged 50 years and older: National Health and Nutrition Examination Survey 2001–2006. Diabetes Care 2013;36:2655–62.
[22] Díaz-Redondo Alicia et al. Modifiable risk factors associated with prediabetes in men and women: a cross-sectional analysis of the cohort study in primary health care on the evolution of patients with prediabetes (PREDAPS-Study). BMC Family Practice 2015.
[23] Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and

impaired glucose regulation in Spain: theDi@bet.es Study. Diabetologia 2012;55(1):88–93.
[24] Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett- Connor EL, Dowse GK, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 1997;46:701–10.
[25] Liu C, Yu Z, Li H, Wang J, Sun L, Qi Q, et al. Associations of alcohol consumption with diabetes mellitus and impaired fasting glycemia among middle-aged and elderly Chinese. BMC Public Health 2010;10:713.
[26] Koppes Lando LJ, Dekker Jacqueline M, Hendriks Henk FJ, Bouter Lex M, Heine Robert J. Moderate alcohol consumption lowers the risk of type 2 diabetes. A meta-analysis of prospective observational studies. Diabetes Care 2005;28 (3):719–25.
[27] World Health Organization, World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva: World Health Organization, 2006: 1–50.
[28] Van den Bruel A. The triumph of medicine: how overdiagnosis is turning healthy people into patients. Fam Pract 2015;32:127–8.
[29] Yudkin JS. "Prediabetes": Are there problems with this label? Yes, the label creates further problems! Diabetes Care 2016;39:1468–71.
[30] Cefalu WT. "Prediabetes": Are there problems with this label? Yes, the label creates further problems! Diabetes Care 2016;39:1472–7.
[31] Bansal Nidhi. Prediabetes diagnosis and treatment: A review. World J Diabetes 2015 March 15;6(2):296–303.