

# Lifestyle factors and reversion to normoglycaemia by prediabetes type in PREDAPS study.

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## Research article

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# Abstract

**Background** There is little evidence on how healthy lifestyle factors can explain the variation in the proportion of patients reverting to normal glucose regulation according to type of prediabetes

**Aims** To study the role of lifestyle factors on the reversion to normal glucose regulation according to type of prediabetes. **Design and Setting** Observational prospective cohort study. The Cohort study in Primary Health Care on the Evolution of Patients with Prediabetes from 2012-2015

**Methods** Participants were classified, according to the definition established by ADA using either fasting plasma glucose (FPG) levels between 100-125 mg/dL or HbA1c between 39-47 mmol/mol (5.7%–6.4%), in three groups. Reversion to normal glucose regulation was calculated at third year of follow-up. Relationship of lifestyle factor and type of prediabetes with reversion was estimated by means of Odds Ratios (OR) using three sequential models. **Results** Proportion of reversion rates were 31% for FPG group, 31% for HbA1c group and 7.9% for both altered parameters group, respectively. BMI < 25 kg/m<sup>2</sup> [OR (95% CI): 1.90 (1.20-3.01)], high adherence to Mediterranean diet 1.78 (1.21-2.63) and absence of abdominal obesity 1.70 (1.19-2.43) were the strongest lifestyle predictors for reversion. Compared with those with both altered parameters, OR of reversion of prediabetes was 4.87 (3.10-7.65) for FPG group and 3.72 (2.39-5.78) for HbA1c group. These estimates remained almost the same after further adjustment for biochemical parameters and lifestyle factors.

**Conclusions** Although optimal lifestyle factors showed to be a positive predictor, those do not seem to explain the differences according to the type of prediabetes.

## Background

The global prevalence of diabetes among adults aged 18 and beyond, has risen from 4.7% in 1980 to 8.5% in 2014, representing almost 422 million people by 2014 [1]. Together with this trend, mortality of diabetes has scaled up to be positioned in the eight causes of death rank worldwide [2]. Risk factors for developing diabetes type 2 have been well established and characterized [3–5], therefore interventions towards controlling some of them have been spread.

Prediabetes status has been associated with a higher risk of developing diabetes type 2. This stage is characterized by either an impaired fasting plasma glucose (IFG) or impaired glucose tolerance (IGT), or elevated glycated haemoglobin A1c (HbA1c) depending on the established diagnostic criteria [6]. Prior research on this topic highlights optimal lifestyle factors and drug therapies (majority oral antidiabetic medications) implementations as effective predictive positive factors to conversion to normal glucose regulation in subjects with prediabetes [4, 7–8]. However, those interventions do not seem to play the same role depending on the type of prediabetes. For example, some studies have found a better response to glucose regulation after applying lifestyle modifications only in individuals with IGT [9]. In addition, a recent study observed how individuals with HbA1c levels in range of prediabetes were less likely to revert to normal glycaemia after physical activity recommendations [10].

This apparent heterogeneous association, between optimal lifestyles and reversion to normal glycaemia regulation according prediabetes type, could be the cornerstone for individualized prevention strategies in subjects with prediabetes. However, there is little evidence on how healthy lifestyle factors can explain the variation in the proportion of patients reverting to normal glucose regulation according to type of prediabetes. In order to understand better the restore to normal glycaemia in individuals with prediabetes, this study aims to evaluate the key role of lifestyle factors on predicting reversion to normal glycaemia by type of prediabetes using a prospective cohort of individuals with prediabetes followed up by primary care physicians in Spain.

## Methods

### Study design

The Cohort study in Primary Health Care on the Evolution of Patients with Prediabetes (PREDAPS Study) is a prospective study encompassing two cohorts of patients: those with prediabetes status and those free of prediabetes and diabetes. Details on information and design have been published elsewhere [11]. Briefly, this prospective study conducted at the primary care setting, started in 2012. To be member of the prediabetes cohort individuals aged 30 to 74 years old were included when meeting the following prediabetes criteria based on the definition established by American Diabetes Association [12] using FPG and HbA1c parameters. First group, namely i) both altered parameters group, included all individuals with HbA1c 39–47 mmol/mol (5.7–6.4%) and FPG 100–125 mg/dl; second group, ii) isolated elevated HbA1c group, included all individuals with HbA1c 39–47 mmol/mol (5.7–6.4%) and FPG < 100 mg/dl; and third group, iii) isolated IFG group, included all individuals with HbA1c < 39 mmol/mol (< 5.7%) and FPG 100–125 mg/dl. Individuals aged 30 to 74 years old with HbA1c < 39 mmol/mol (< 5.7%) and FPG < 100 mg/dl were assigned to the normoglycaemia cohort. Individuals with the following criteria were excluded to be members of the study cohort: if they had diabetes, terminal disease, pregnancy, surgery, or hospital admission in the previous 3 months at study entry, or any hematologic disease, which could alter HbA1c values. The study was classified by the Spanish Drug and Health Product Agency as a Non-Interventional (Observational) Post-Authorization Study, and the protocol was approved by the Parc de Salut Mar Clinical Research Ethics Committee in Barcelona. A total of 2022 individuals gave their written informed consent for participation: 1184 subjects with prediabetes and 838 without impaired glucose metabolism.

The present study analysed the relationship between lifestyle and other variables measured at baseline and the situation of reversion to normal glycaemia in the third year of follow-up among the cohort of subjects with prediabetes. Thus, out of 1184 subjects with prediabetes, a total of 948 (80.1%) attended their third follow up visit and were retained to be members of the final cohort, therefore remaining patients were excluded.

### Covariates

At baseline, information on biographical data, family and personal history of diabetes, smoking, alcohol consumption, diet, physical activity, drug treatment, social support and socio-economic position was

obtained from each participant's clinical history and from the personal interview conducted by the physician at their practices. During the medical visit a physical examination was performed, which included anthropometry and determination of blood pressure. Similarly, blood and urine analyses were requested to determine FPG, HbA1c, lipid profile, transaminases, blood count, iron levels and renal function.

Smoking habit was classified into three mutually exclusive categories: current smoker, former smoker, and never smoker. Individuals were asked to state which of the following alternatives best reflected their alcohol consumption frequency: never drinker, former drinker, occasional drinker, or daily drinker. For the present analysis individuals were classified into non-drinkers, occasional drinkers and daily drinkers. Physical activity data were collected based on the frequency –number of times in the last two weeks- and amount –mean time in minutes for each session- of different types of physical activity, and, on the basis of the data collected, the minutes per week of physical activity performed by each participant were estimated. Subjects were classified into two categories according to if they had followed or not the World Health Organization (WHO) physical activity recommendations -accumulate at least 150 minutes per week of moderate aerobic activity or 75 minutes per week of vigorous aerobic activity-, or an equivalent combination of moderate and vigorous activity [13].

Adherence to the diet was estimated through an adaptation of the score used by Panagiotakos in the ATTICA study [14]. In each of the 20 types of food investigated, research subjects were asked about the following frequency consumption options: daily consumption,  $\geq 3$  times / week, 1–2 times / week,  $< 1$  time / week, never or almost never. A score of 0 was assigned to a less healthy consumption and 4 to the healthiest consumption of each food. A score of 0 is considered minimum adherence, compared to 80, which would be maximum adherence. Adherence to the Mediterranean diet was grouped into three categories low (0–53 points), medium (54–59 points) and high (60–80 points).

Overweight and general obesity was defined as a Body Mass Index (BMI)  $\geq 25$  g/m<sup>2</sup>, and abdominal obesity as a waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $\geq 90$  mmHg, or current use of antihypertensive treatment or having a personal history of hypertension. Hypercholesterolemia was defined as total serum cholesterol  $\geq 250$  mg/dl, low high-density cholesterol (HDL-C) as  $< 40$  mg/dl in men and  $< 50$  mg/dl in women, and hypertriglyceridemia as serum level of triglycerides  $\geq 200$  mg/dl

## **Statistical analysis**

Distribution of demographic characteristics, lifestyle variables, obesity, and hypertension and biochemical parameters according to type of prediabetes was compared using the chi-square test. Then it was calculated the percentage of subjects who reverted to normal glycaemia according to these variables and type of prediabetes. Reversion to normal glucose regulation, was considered if FPG and HbA1c values were FPG  $< 100$  mg /dl and HbA1c  $< 39$  mmol/mol ( $< 5.7\%$ ), respectively, at third year of follow up. The relationship between demographic characteristics, lifestyle variables, obesity, hypertension and biochemical parameters and the reversion to normal glycaemia was estimated by odds ratio (OR)

adjusted for age and sex. Relationship between type of prediabetes and the reversion to normal glycaemia was estimated using three sequential models: adjusting for age and sex (Model A); hypertension, hypercholesterolemia, HDL levels and triglycerides (Model B), and alcohol consumption, smoking, BMI, abdominal obesity, physical activity, adherence to Mediterranean diet (Model C). Each successive model included the factors from the previous model. Finally, the criteria diagnostic of prediabetes was subdivided using as cut-off levels FPG < 110 and  $\geq$  110 mg/dl and HbA1c < 42 and  $\geq$  42 mmol/mol (< 6 and  $\geq$  6%), respectively, and the relationship between subtype of prediabetes and the reversion to normal glycaemia was also estimated by models A, B y C. Statistical analyses were performed using the STATA package version 12.0 (StataCorp LP, College Station, TX, USA).

## Results

### Baseline characteristics

Among our cohort of prediabetes, mean age was 58.7 years (median: 60 years). Out of them, 21% of patients were classified as having isolated IFG, 27.6% as isolated elevated HbA1c levels and 50.9% as both altered parameters. Table 1 shows the baseline characteristics of study cohort according to type of prediabetes. There was an inverse proportion of men and women according to each prediabetes criteria, while 61% of those with isolated IFG were men, corresponding percentages by isolated elevated HbA1c and both parameters were 38.9% and 50.3%, respectively ( $p < 0.001$ ). Distribution of age was similar within groups, although those with isolated IFG tended to be younger. In terms of alcohol consumption, the proportion of daily drinkers were 29% among those with both altered parameters compared to 19.5% among those with isolated elevated HbA1c and 34% among those with isolated IFP. Those with both altered parameters had higher proportions of BMI > 25 kg/m<sup>2</sup> and abdominal obesity. There were no differences in distribution of remaining lifestyle factors as smoking, physical activity and adherence to diet. Those with both altered parameters had a higher frequency of hypertension and triglycerides levels and there were no differences in distribution of hypercholesterolemia or HDL levels.

Table 1  
Baseline  
characteristics  
of study  
cohort  
individuals  
according  
type of  
prediabetes.

Table 1

Baseline characteristics of study cohort individuals according type of prediabetes.

Characteristics	Both altered parameters FPG:100–125 mg/dl and HbA1c:39–47 mmol/mol		Isolated elevated HbA1c FPG: <100 mg/dl and HbA1c:39–47 mmol/mol		Isolated IFG FPG:100–125 mg/dl and HbA1c: <39 mmol/mol		p value*
	N	%	N	%	N	%	
Sex							< 0.001
Women	240	49.7	160	61.1	79	38.9	
Men	243	50.3	102	38.9	124	61.1	
Age							0.003
30–49 years	60	12.4	43	16.4	46	22.7	
50–64 years	241	49.9	137	52.3	104	51.2	
65+ years	182	37.7	82	31.3	53	26.1	
Smoking							0.053
Current smoker	77	15.9	52	19.8	28	13.8	
Former smoker	180	37.3	94	35.9	96	47.3	
Never smoker	229	46.8	116	44.3	79	38.9	
Alcohol consumption							0.003
Daily drinker	140	29	51	19.5	69	34	
Occasionally drinker	187	38.7	116	44.3	84	41.4	
Never drinker	156	32.3	95	36.3	50	24.6	
BMI							< 0.001
Overweight/Obese (> 25 kg/m <sup>2</sup> )	169	92.8	212	80.9	448	83.3	
Normal weight (up to 25 kg/m <sup>2</sup> )	34	7.2	50	19.1	35	16.7	

Characteristics	Both altered parameters FPG:100–125 mg/dl and HbA1c:39–47 mmol/mol		Isolated elevated HbA1c FPG: <100 mg/dl and HbA1c:39–47 mmol/mol		Isolated IFG FPG:100–125 mg/dl and HbA1c: <39 mmol/mol		p value*
Obesity abdominal							< 0.001
Waist ≥ 88/102 cm	362	74.9	161	61.5	119	58.6	
Waist < 88/102 cm	121	25.1	101	38.5	84	41.4	
Physical Activity							0.500
Do not follow OMS recommendations	112	52.0	146	56.2	251	55.2	
Follow OMS recommendations	232	48	114	43.8	91	44.8	
Adherence to Mediterranean diet							0.794
Low/Medium	361	74.7	190	72.5	149	73.4	
High	122	25.2	72	27.5	54	26.6	
Hypertension							< 0.001
Yes	359	74.3	151	57.6	130	64.0	
No	124	25.7	111	42.4	73	36.0	
Hypercholesterolemia							0.172
Yes	292	60.5	167	63.7	112	55.2	
No	191	39.5	95	36.3	91	44.8	
Low HDL levels							0.064
Yes	125	25.9	53	20.2	38	18.7	
No	358	74.1	209	79.8	165	81.3	
Hypertriglyceridemia							0.001
Yes	161	33.3	59	22.5	47	23.2	

Characteristics	Both altered parameters FPG:100–125 mg/dl and HbA1c:39–47 mmol/mol	Isolated elevated HbA1c FPG: <100 mg/dl and HbA1c:39–47 mmol/mol	Isolated IFG FPG:100–125 mg/dl and HbA1c: <39 mmol/mol	p value*
No	322 66.7	203 77.5	156 76.8	
*Chi square of heterogeneity				

## Reversion rates according to type of prediabetes

At third year of follow up, there were a total of 165 (17.4%) patients who reverted to normal glucose regulation. When stratifying by type of prediabetes, the proportion of patients reverting to normal glycaemia defined by both -HbA1c and FPG- criteria had the lowest proportion of reversion (7.9%) compared with those defined with isolated IFG (31.0%) or isolated elevated HbA1c (24.4%), respectively (Fig. 1). We subdivided the diagnostic criteria of prediabetes using as cut-off levels FPG < 110 and > 110 mg/dl and HbA1c < 42 and  $\geq$  42 mmol/mol (< 6% and  $\geq$  6%), respectively. Individuals with HbA1c levels  $\geq$  42 mmol/mol (< 6%) had the lowest reversion rates (3.2% for those with FPG: 100–125 mg/dl and 8.7% with FPG < 100 mg/dl), while those with isolated FPG < 110 mg/dl and isolated HbA1c < 42 mmol/mol (< 6%) obtained the highest reversion rates (40.7% and 32.9%) (Fig. 2).

## Factors associated with the reversion to normoglycemia

Table 2 shows the percentage of reversion according to each baseline characteristic factor as well as the OR of reversion. We did not observe any association with sex. There was a trend towards a decreased likelihood of reversion with the increase in age. Lifestyle factors such as BMI < 25 kg/m<sup>2</sup> [OR 1.90 (95% CI:1.20–3.01)], absence of abdominal obesity [OR 1.70 (95% CI 1.19–2.43)], adherence to Mediterranean diet [OR 1.78 (95% CI 1.21–2.63)] and physical activity [OR 1.48 (95% CI:1.04–2.10)] showed to be positive predictive factors associated with reversion to normal glycaemia. Not having hypertension shown to be associated with reversion to normoglycaemia, and there was no association with biochemical parameters such as hypercholesterolemia, HDL low levels or hypertriglyceridemia

Table 2  
Percentage  
of  
reversion  
to normal  
glucose  
regulation  
and odds  
ratio (OR)  
according  
to the

Table 2

Percentage of reversion to normal glucose regulation and odds ratio (OR) according to the characteristics of the subjects

Characteristics	Percentage of reversion	Odds ratio (95% confidence interval)*
Sex		
Women	16.7	1.00
Men	18.1	1.06 (0.75–1.49)
Age		
30–49 years	31.5	2.92 (1.82–4.69)
50–64 years	15.6	1.17 (0.78–1.76)
65 + years	13.6	1.00
Smoking		
Current smoker	17.2	1.00
Former smoker	17.8	1.23 (0.74–2.04)
Never smoker	17.1	1.19 (0.71–1.99)
Alcohol consumption		
Daily drinker	14.6	1.00
Occasionally drinker	19.9	1.33 (0.85–2.07)
Never drinker	16.6	1.10 (0.66–1.82)
BMI		
Overweight/Obese (> 25 kg/m <sup>2</sup> )	16.2	1.00
Normal weight (up to 25 kg/m <sup>2</sup> )	26.1	1.90 (1.20–3.01)
Physical Activity		
Do not follow OMS recommendations	14.9	1.00
Follow OMS recommendations	19.4	1.48 (1.04–2.10)
Adherence to Mediterranean diet		
Low/Medium	17.9	1.00
High	17.2	1.78 (1.21–2.63)

Characteristics	Percentage of reversion	Odds ratio (95% confidence interval)*
Obesity abdominal		
Waist > = 88/102 cm	14.8	1.00
Waist < 88/102 cm	22.9	1.70 (1.19–2.43)
Hypertension		
Yes	14.7	1.00
No	23.1	1.53 (1.06–2.19)
Hypercholesterolemia		
Yes	17.3	1.00
No	17.5	1.02 (0.72–1.45)
Low HDL levels		
Yes	18.5	1.00
No	17.1	0.98 (0.65–1.47)
Hypertriglyceridemia		
Yes	14.6	1.00
No	18.5	1.38 (0.93–2.05)
* Sex and age adjusted odds ratio, except the odds ratios according sex and age		

## Role of Lifestyle factors on reversion according to type of prediabetes

Compared with participants with both FPG and HbA1c criteria, when adjusting by age and sex, the OR of reversion of prediabetes was 4.87 (95% CI: 3.10–7.65) among those with isolated IFG and 3.72 (95% CI: 2.39–5.78) for those with isolated elevated HbA1c. When adding biochemical parameters as well as hypertension (Model B), OR remained almost constant: 4.78 (95% CI: 3.03–7.55) and 3.59 (95% CI: 2.30–5.60), respectively. Finally, when including lifestyle factors (Model C), OR did remain almost the same: 4.52 (95% CI: 2.84–7.18) for isolated IFG group and 3.43 (95% CI: 2.17–5.42) for isolated elevated HbA1c group (Table 3). Also, when subdividing prediabetes cohort according to levels of FPG and HbA1c, the OR in de Model C was similar to OR in the Model B. Taking as reference those with HbA1c levels  $\geq$  42 mmol/mol ( $\geq$  6%) and FPG 100–125 mg/dl, the OR for reversion after adjusting for all factors (Model C) were as follows: isolated FPG < 110 mg/dl: 18.21 (95% CI: 8.08–41.06), isolated FPG  $\geq$  110 mg/dl: 5.75 (95% CI: 2.30–14.37), isolated HbA1c < 42 mmol/mol (< 6%): 13.34 (95% CI: 6.03–29.52), isolated

HbA1c  $\geq$  42 mmol/mol ( $\geq$  6%): 2.70 (95% CI: 0.97–7.51), and HbA1c < 42 mmol/mol (< 6%) and FPG 100–125 mg/dl: 4.36 (95% CI: 1.94–9.80).

Table 3  
Reversion  
to normal  
glucose  
regulation.  
Odds ratio  
(and 95%  
confidence  
interval)  
according  
prediabetes  
type and  
according  
prediabetes  
subtype.

Table 3

Reversion to normal glucose regulation. Odds ratio (and 95% confidence interval) according prediabetes type and according prediabetes subtype.

	Model A	Model B	Model C
<b>Prediabetes type</b>			
Both altered parameters	1,00	1,00	1,00
Isolated elevated HbA1c	3.72 (2.39–5.78)	3.59 (2.30–5.60)	3.43 (2.17–5.42)
Isolated IFG	4.87 (3.10–7.65)	4.78 (3.03–7.55)	4.52 (2.84–7.18)
<b>Prediabetes subtype</b>			
HbA1C $\geq$ 42 mmol/mol and FPG 100–125 mg/dl	1,00	1,00	1,00
HbA1c < 42 mmol/mol and FPG 100–125 mg/dl	4.54 (2.03–10.17)	4.46 (1.99–9.99)	4.36 (1.94–9.80)
Isolated HbA1c $\geq$ 42 mmol/mol	2.81 (1.02–7.74)	2.75 (0.99–7.61)	2.70 (0.97–7.51)
Isolated HbA1c < 42 mmol/mol	14.65 (6.73–31.91)	14.11 (6.44–30.94)	13.34 (6.03–29.52)
Isolated FPG $\geq$ 110 mg/dl	6.18 (2.50–15.30)	6.03 (2.43–14.98)	5.75 (2.30–14.37)
Isolated FPG < 110 mg/dl	19.76 (8.84–44.15)	19.28 (8.60–43.25)	18.21 (8.08–41.06)
Model A: Adjusted by sex and age			
Model B: Model A plus hypertension, hypercholesterolemia, HDL levels and Triglycerides			
Model C: Model B plus alcohol consumption, smoking, BMI, abdominal obesity, physical activity, adherence to			

## Summary

The current prospective cohort study included a total of 948 individuals with a prediabetes status. At the third year of follow-up, compared with the group of subjects with both altered parameters, FPG and HbA1c, the reversion to normal glucose regulation was almost four times higher in subjects with isolated elevated HbA1c and almost five times higher in subjects with isolated IFG.

## Strengths and limitations

This study has several strengths and limitations that deserve some comment. To best of our knowledge, this is the first study evaluating the role of optimal lifestyle factors in the reversion to normal glucose regulation according type of prediabetes. Our study highlights the feasibility of conducting a prospective observational study, with data collected nation-wide by primary care physicians during routine clinical practice. Regarding to lab data, analytical determinations of FPG, HbA1c and covariates were performed at different laboratories. This fact could result in some source of misclassification. Of note, since 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, as it is unlikely that the reversion could be related to the methods employed by specific laboratories. Finally, the percentage of dropout was 21% in subjects with prediabetes defined by both HbA1c and FPG criteria, 16% in subjects defined by only HbA1c and 19% in subjects defined by only FGP. If reversion were lower in the subjects who dropped out than in the subjects who followed, the differences found in the reversion according to the type of prediabetes would be underestimated.

## Comparison with existing literature

Despite there are prior studies evaluating the proportion of reversion to normoglycaemia, all them were heterogeneous in design, duration of follow-up and criteria definition yielding a broad range of reversion rates [15–19], and only few did it according to prediabetes status criteria [10, 20]. The latter, a Japanese study [20] using four prediabetes subgroups according to elevated HbA1c and/or IFG, observed a greater proportion of reversion rates among those with elevated HbA1c levels. In contrast, our results showed an opposite trend resulting in lower rates for individuals with HbA1c levels above 42 mmol/mol (6.0%) regardless FPG levels, similar to the results provided by a British study [10].

A potential source of misclassification when classifying patients according to FPG levels cannot be ruled out. While FPG is subjected to not only intra-individual variability but also daily variation levels [21], HbA1c reflects average plasma glucose over the previous eight to 12 weeks [22] acting as a more established parameter. In the current study, among those classified with isolated FPG levels, more than half had FPG levels < 110 mg/dl presenting the highest reversion rate, and 2.3-fold times higher likelihood of reversion compared with those with FPG ranging from 110–125 mg/dl, respectively. If any substantial impact of misclassification, we would not be able to see this difference.

A recent study, that applied the same prediabetes criteria than ours, observed how individuals who reverted to normal glycaemia regulation after five years of follow up, had a low insulin resistance and optimal beta-cell function at baseline [23]. Following this reasoning, is probable, that in our study population, individuals with HbA1c  $\geq$  42 mmol/mol ( $\geq$  6%) at baseline had an increased insulin resistance and/or a decreased beta cell function, based on the lowest reversion rates found regardless FPG levels. However, we were not able to measure such physiological markers.

In the present study, baseline characteristics such as age less than 50 years, normal weight, absence of abdominal obesity, physical activity, adherence to Mediterranean diet and absence of hypertension have been associated with a higher likelihood to normal glucose regulation. There are prior studies evaluating

reversion to glucose regulation using an interventional design mainly focus on optimal lifestyle actions in a prediabetes population. However, only few are focused on this relationship using a fixed period (i.e. baseline levels). The vast majority, although not all [10, 24], draw similar conclusions than ours [3, 15–16, 18–19, 25]. Both, obesity and body fat distribution, are critical factors to decrease insulin sensitivity and B cells function [26]. In contrast, physical activity causes increased glucose uptake into active muscles balanced by hepatic glucose production and it improves insulin action resulting in preventing insulin resistance [27]. In addition, there is evidence that a low-glycaemic-index diet, such as Mediterranean, improves insulin sensitivity and prevents from diabetes [28]. It is therefore probable that individuals reverting to normal glucose regulation followed an optimal lifestyle behaviour long time before baseline state.

## **Implications for research and/or practice**

There is a gap in knowledge about the extent to which healthy lifestyles explain the reversion to normal glucose regulation, according to the type of prediabetes. The current study found that adjustment for lifestyles did not modify markedly the magnitude of association between type of prediabetes and reversion, which suggests that the excess restore to normal glucose in individuals with isolated IFG or isolated elevated HbA1c cannot be explained via these factors. Therefore, our findings suggest that beyond optimal lifestyles, FPG and HbA1c could be in themselves key markers to revert to normal glycaemia in subjects with prediabetes, especially the FPG level below 110 mg/dl and the HbA1c level below 42 mmol/mol (6.0%).

The criteria of prediabetes are still a controversial topic, based on multiple changes in its definition. Controversy especially lies on the cut-off value levels to define IFG levels < 110 mg/dl [29, 30]. Keeping in mind that almost half of the subjects with those IFG levels reverted to normal glycaemia, this might lead into an overestimation of the true prevalence of this status. Of note, those patients would not be the specific target for intensification of optimising lifestyle factors and other actions such as initiating antidiabetic therapy. In addition to existing doubts about the adequacy of FPG levels below 110 mg/dl to define prediabetes, our findings add new arguments to this controversy given the limited role of optimal lifestyles in the differences to the reversion according to the type of prediabetes. Further studies evaluating reversion to normal glucose regulation and the role of optimal lifestyle factors, together with, clinical outcomes associated to prediabetes diagnostic criteria, are warranted to not only harmonize definitions on prediabetes but also to better identify specific subjects with a low probability of normalizing glycaemia levels.

In conclusion, optimal lifestyle factors showed to be a positive factor to reversion to normoglycaemia after three years of follow up in our prediabetes cohort however, they do not seem to explain differences in the reversion to normal glucose regulation according type of prediabetes.

## **Declarations**

### **Declaration of interest**

The authors declare that they have no conflict of interest.

### **Author contribution statement**

CG-G and LC-S originated and designed the study, contributed to the analysis of the data and to the drafting of the paper. FJ-N, MM, FJS, JD-ES, SA and RS collected data of the study and contributed to the interpretation of the results and to the drafting of the paper. FJGS and RS collected data of the study and coordinated the writing of the article. RA, and ER contributed to the analysis of the data and to the drafting of the paper. All authors contributed to the final version of the article. All authors have seen and approved the final version. ER is the guarantor of the study.

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