Pre-transplant weight but not weight gain is associated with new-onset diabetes after transplantation: a multi-centre cohort Spanish study

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Abstract

Background. New-onset diabetes after transplantation (NODAT) is associated with poorer outcomes in kidney transplantation (KT). Thus, identification of modifiable risk factors may be crucial for ameliorating the impact of this entity on transplant outcomes. We assessed the relationships between the weight, body mass index (BMI) and weight gain with NODAT.

Methods. We retrospectively analysed 2168 KT performed in Spain during 1990, 1994, 1998 and 2002, with a functioning graft after the first year. At 1 year after KT, three groups were considered: (i) NODAT group (n = 215); (ii) impaired fasting glucose (IFG) group (n = 389); (iii) control group (n = 1564).

Results. The incidence of NODAT was 10.8%, 9.9% and 10.0% at 3, 12 and 24 months post-transplantation, respectively. Older recipient age (P < 0.0001) and greater use of tacrolimus (P < 0.0001) were observed in NODAT group. Obesity was more frequent in NODAT group (P < 0.0001), but patients with NODAT had a lower weight gain during the first year after KT (P = 0.038). On multivariate analysis, independent risk factors associated with the development of NODAT were: recipient age [odds ratio (OR): 1.060, P = 0.0001], tacrolimus (OR: 1.611, P = 0.005), triglycerides (OR: 1.511, P = 0.018), positive hepatitis C virus (HCV) status (OR: 1.969, P = 0.001) and pre-transplant body mass index (BMI) (OR: 1.135, P = 0.0001), but not the weight gain.

Conclusions. BMI, but not the weight gain at 1 year after transplant, is an independent risk factor for NODAT. Tailoring clinical strategies may minimize the impact of this complication.

Keywords: diabetes post-transplant; kidney transplantation; NODAT; weight gain

Introduction

New-onset diabetes after transplant (NODAT) is a frequent entity in kidney transplant recipients [1], and it is associated with poor outcomes. Prospective and retrospective studies have concluded that NODAT is an independent predictor of global mortality, graft failure and death-censored graft failure [1–4]. Identification of those potentially modifiable risk factors may help to create strategies in order to improve transplant outcomes.

NODAT has been related to both non-modifiable and modifiable risk factors such as age, ethnic, genetic background, gender, family history of diabetes, hepatitis C virus infection, cytomegalovirus (CMV) infection, immunosuppressive drugs and overweight [1,5–9]. In particular, body weight and body mass index (BMI) have been shown to be associated with post-transplant diabetes in most studies [4,7]. Moreover, the weight gain after kidney transplantation (KT) is common and is attributable mainly to inappropriate dietary habits, decreased physical activity and steroid use [10]. Because weight gain is a risk factor for an insulin-resistant state in general population, it is plausible to think that this risk factor could be associated with NODAT. However, the relationship between NODAT and weight gain during the first post-transplant year remains undetermined. While some investigators have reported a significant association between NODAT and weight gain, others have not [1,11–17].

The aim of the present study was to assess the relationships between anthropometric parameters such as pre-transplant weight, BMI and weight gain at the first post-transplant year with NODAT at 12 months post-transplantation in a large cohort of KT recipients.
Table 1. Baseline characteristics and the follow-up data of NODAT, IFG and control patients at the time of transplantation

| All          | NODAT          | IFG           | Control        | P-value* |
|--------------|----------------|---------------|----------------|----------|
| Number of patients | 2168           | 215           | 389            | 1564     |
| Donor characteristics |                |               |                |          |
| Age (year)   | 42 ± 17        | 46 ± 17       | 45 ± 17        | 41 ± 17  |
| Gender (% male) | 66.3           | 65.1          | 69.9           | 65.5     |
| Living donors (%) | 2.0            | 1.9           | 1.6            | 2.1      |
| Recipient characteristics |            |               |                |          |
| Age (year)   | 46 ± 13        | 55 ± 9        | 50 ± 12        | 44 ± 13  |
| Gender (% male) | 63.1           | 57.7          | 70.7           | 61.9     |
| Primary cause of ESRD (%) | 23.7           | 12.1          | 21.1           | 25.9     |
| Glomerulonephritis | 13.5           | 16.3          | 15.7           | 12.6     |
| Polycystic    | 62.8           | 71.6          | 63.2           | 61.5     |
| Other/unknown | 29.0           | 41.4          | 33.1           | 26.3     |
| Time on dialysis (months) | 42.7 ± 47.1    | 38.8 ± 41.7   | 39.0 ± 42.5    | 44.1 ± 48.8 |
| HCV antibodies (% positive) | 14.2           | 17.7          | 9.8            | 14.8     |
| Year of transplant 2002 (%) | 29.0           | 41.4          | 33.1           | 26.3     |
| HLA mismatches | 3.1 ± 1.2      | 3.3 ± 1.2     | 3.1 ± 1.2      | 3.1 ± 1.2 |
| Cold ischaemia time (h) | 18.8 ± 6.2     | 18.7 ± 6.0    | 19.0 ± 6.3     | 18.7 ± 6.3 |
| Immunosuppression (%) |                |               |                |          |
| Cyclosporine-based | 72.4           | 63.2          | 63.3           | 76.0     |
| Tacrolimus-based | 24.3           | 33.0          | 33.2           | 20.8     |
| Anti-mTOR-based | 3.3            | 6.6           | 3.7            | 2.8      |
| Delayed graft function (%) | 28.3           | 27.4          | 29.3           | 28.2     |
| Acute rejection (%) | 29.2           | 25.4          | 24.1           | 31.8     |
| Scr at 1 year (mg/dL) | 1.6 ± 0.6      | 1.5 ± 0.5     | 1.6 ± 0.6      | 1.6 ± 0.6 |
| Proteinuria at 1 year (g/day) | 1.1 ± 0.5      | 1.2 ± 0.5     | 1.1 ± 0.4      | 1.1 ± 0.5 |
| TGD >200 mg/dL (%) | 20.6           | 28.4          | 24.3           | 18.6     |
| Steroid withdrawal at 1 year (%) | 5.3            | 7.4           | 10.3           | 3.7      |

NODAT, new-onset diabetes after transplantation; IFG, impaired fasting glucose; BMI, body mass index; ESRD, end-stage renal disease; HCV, hepatitis C virus; PRA, panel-reactive antibodies; HLA, human lymphocyte antigen; mTOR, mammalian target of rapamycin; Scr, serum creatinine; TGD, triglycerides.

*Significant differences compared with IFG.
+aKruskal–Wallis or ANOVA (continuous variables), chi-square (categorical variables).

Materials and methods

Study design

We conducted a retrospective cohort study with patients receiving a kidney allograft in 34 Spanish centres during four different years (1990, 1994, 1998 and 2002), with a last follow-up in December 2005. The study design has been previously reported [18]. Patients with age under 18 years, those with graft loss during the first year, patients who had a diagnosis of diabetes mellitus prior to transplant and those for whom data were not available were excluded for this study.

Clinical variables

The following variables were evaluated at time of transplantation: source of the organ (living or deceased), cause of donor death, age and gender of the donor and of recipient, presence of hepatitis B surface antigen and hepatitis C virus (HVC) antibodies in the donor and recipient, cause of end-stage renal disease (ESRD), time on dialysis, panel-reactive antibodies, number of human lymphocyte antigen (HLA) mismatches, and cold ischaemia time. After transplantation, the following variables were recorded: immunosuppressive treatment by intention to treat, presence of delayed graft function (defined as haemodialysis requirement after the first week of surgery once rejection, vascular complications or urinary obstruction were ruled out) and acute rejection. At 3 months and yearly thereafter, the following variables were recorded: serum creatinine, glycaemia, total cholesterol, triglycerides, 24-h proteinuria, weight and blood pressure. The use of hypoglycaemic therapy was also recorded.

Medical record review was performed according to Spanish law with reference to clinical data confidentiality protection. The study was approved by each of the participating hospitals and was conducted in accordance with the provisions of the Declaration of Helsinki.

Definition of variables

NODAT was diagnosed according to the 2003 international consensus guidelines for new-onset diabetes after transplantation [5]: fasting plasma glucose ≥126 mg/dL on two separate occasions or casual plasma glucose ≥200 mg/dL with symptoms, or the need for insulin/oral hypoglycaemic agents treatment. Glucose levels between 100 and 125 mg/dL were diagnostic of impaired fasting glycaemia (IFG). Glucose levels lower than 100 without treatment were considered as normal or normoglycaemia. The total sample was subdivided into three groups that take account the glucose metabolism alterations at 1 year after transplantation: (i) patients with NODAT (NODAT group); (ii) patients with IFG (IFG group); and (iii) normoglycaemic patients (control group or normoglycaemic group).

BMI was calculated as body weight in kilograms divided by square of their height in metres. Obesity was defined as a BMI ≥30 kg/m², and overweight as a BMI between 25 and 30 kg/m². A BMI <25 was defined as control BMI.

The weight gain at 12 months after transplantation was calculated as the difference between the weight at 12 months and the weight at time of transplantation (basal weight). Similarly, the percentage increase (delta) at the first year was calculated as the difference between the weight at 12 months and the basal weight, divided by the basal weight and multiplied by 100.

Statistical analysis

Descriptive results are expressed as mean ± SD for continuous variables. Frequency and contingency tables were used to describe categorical and ordinal variables. Comparison between groups was performed by chi-square test for categorical data. For numeric data, ANOVA or Kruskal–Wallis for normal or non-normal distribution was employed, respectively, with Bonferroni adjustments for pairwise. Multiple logistic regression analyses were carried out to identify risk factors for NODAT at the first
year after transplantation as dependent variable, including those factors found to be significant in previous univariate analyses and those potential confounder variables. Finally, we analysed the effect of potential interactions between weight gain during the first year and the BMI at time of transplantation (basal BMI). Statistical analyses were performed with SPSS software version 16.0 (SPSS, Inc., Chicago, IL). A P-value <0.05 was considered significant.

Results

A total of 5060 patients, who received a KT in 34 Spanish centres during 1990, 1994, 1998 and 2002, were initially considered. We excluded those with age lower than 18 years (n = 131), those with graft loss or death with functioning graft during the first year (n = 427), those with diabetes mellitus prior to KT (n = 268) and those for whom data for BMI calculation were not fully available (n = 2066). Finally, 2168 renal transplant patients fulfilling the inclusion criteria were studied. Of these patients, at 1 year after KT, there were 215 patients in NODAT group (9.9%), 389 in IFG group (17.9%) and 1564 in control group (72.1%). The median of follow-up was 6.8 years (interquartile range: 4.1–8.6 years).

The baseline characteristics and the follow-up data of donor and recipients, in the three groups, are provided in Table 1. In the control group, donor and recipients were younger and had a lower proportion of patients transplanted in 2002 compared with the other years. A higher incidence of acute rejection with a lower proportion of tacrolimus-based therapy and a lower proportion of steroids withdrawal at 1 year were also observed in this group. A lower percentage of glomerulonephritis as primary disease and a higher proportion of HCV antibodies positive were found in the NODAT group, while hypertriglyceridaemia (>200 mg/dL) at 3 months after transplant was more frequently seen in NODAT and IFG groups.

Frequency of NODAT and IFG

Figure 1 shows the prevalence of IFG and NODAT at 3, 12 and 24 months after transplantation. NODAT was observed in 234 (10.8%), 215 (9.9%) and 209 (10.0%) recipients at 3, 12 and 24 months post-transplantation, respectively. Likewise, IFG was found in 414 (19.1%), 389 (17.9%) and 388 (18.6%) recipients at 3, 12 and 24 months, respectively.

Figure 1 also shows the clinical changes of each group during the first 2 years after transplantation. The majority of recipients, 88% of control (normoglycaemic patients), 41% of IFG and 63% of NODAT, remained in the same group from 3 to 12 months. However, a total of 24% of patients with NODAT at 3 months after transplant became IFG patients at 12 months after transplant, whereas 13% normalized to control patients at 1 year after transplantation.

Similarly, a large percentage of patients in the IFG group at 3 months experienced changes during the follow-up, either to NODAT or to control group. More specifically, 47% of patients with IFG at 3 months became control patients at 12 months after transplant. Nevertheless, 12% of patients with IFG at 3 months evolved to NODAT at 12 months. Finally, only 1% of patients from control group at 3 months developed NODAT at 12 months, and up to 11% patients in control group at 3 months had IFG at 12 months.

The same results were shown when the clinical changes between 12 and 24 months were taken into account. Interestingly, the percentage of patients that recovered NODAT or IFG was higher between 3 and 12 months post-transplantation than between the first and second year.

Of note, the patients that improved from NODAT group at 3 months, either to IFG or control group at 12 months, had a lower age at transplantation (52.6 ± 11.1 vs. 55.6 ±
9.1 years, \( P < 0.001 \) compared to those who did not change. In the same way, the patients that, at 12 months, returned to control group from IFG at 3 months after transplantation were younger (46.2 ± 11.0 versus 52.1 ± 13.5 years at transplantation, \( P < 0.001 \)) than the patient who did not recover.

**BMI and weight gain**

Mean BMI was 24.4 ± 4.0 kg/m\(^2\) at the time of transplant, 25.2 ± 3.8 kg/m\(^2\) at 3 months after transplantation and 26.3 ± 4.2 kg/m\(^2\) at 1 year after KT. At the time of transplant, 60.1% patients had a normal BMI, with 30.9% overweight, and 9% were obese. At 1 year after transplantation, the percentage of patients with a normal BMI had decreased to 41.6%, and the percentage of patients with overweight or with obesity had increased to 40.9% and 17.5%, respectively.

During the first year post-transplantation, 1691 (78.8%) patients gained weight, while 477 (21.2%) had weight loss. The mean weight gain was 5.0 ± 6.3 kg (range between −29 and 37 kg), and the mean weight gain delta was 8.2 ± 7.4% (range between −36% and 61%). Excluding those patients who have lost weight, the mean of gain weight and weight gain delta were 7.2 ± 4.9 kg and 11.6 ± 8.2%, respectively. Furthermore, 39.7% of the patients gained between 0% and 10%, and 39.1% gained >10% of their baseline weight. The weight gain was inversely associated with baseline BMI; that is, the patients with normal BMI at transplantation showed a higher weight gain at 1 year after transplantation compared with patients with overweight and obesity (6.0 ± 5.7; 4.3 ± 6.5; and 1.7 ± 8.4 kg, respectively, \( P < 0.001 \)). These differences remained significant when the weight gain delta was analysed (10.2 ± 9.9% for control BMI, 6.1 ± 8.8% for overweight and 2.1 ± 10.0% for obese patients; \( P < 0.001 \)).

**Figure 2 and Table 2** show the relationship between BMI, weight, and weight gain with NODAT, IFG or control status. NODAT group had a higher BMI, at time of KT, than IFG or control groups. Notably, the percentage of patients with obesity was higher in NODAT group with respect to IFG and control group (24.2%, 10.8% and 6.5%, respectively).

At the first post-transplant year, the patients with NODAT had a weight gain of 6.4 ± 10 compared with 8.5 ± 9.9 and 8.4 ± 10 in the IFG or control group, respectively (\( P = 0.038 \)). In other words, the percentage of patients who had a weight loss during the first year of transplantation was lower in control and IFG groups compared to NODAT group, but these differences were not significant.

**Table 2.** Weight and BMI changes of NODAT, IFG and control patients during the first year after transplantation

|                     | NODAT   | IFG     | Control | \( P \)-value\(^a\) |
|---------------------|---------|---------|---------|---------------------|
| Number of patients  | 215     | 389     | 1564    |                     |
| Basal weight (kg)   | 70.6 ± 12.8 | 69.6 ± 12.4 | 65.0 ± 12.0 \(^{b,c}\) | 0.0001               |
| Basal BMI (kg/m\(^2\)) | 27.0 ± 4.7 | 25.2 ± 3.7 \(^b\) | 23.9 ± 3.8 \(^{b,c}\) | 0.0001               |
| BMI <25 kg/m\(^2\) (%) | 38.6     | 49.1 \(^b\) | 65.8 \(^{b,c}\) | 0.0001               |
| BMI 25–30 kg/m\(^2\) (%) | 37.2     | 40.1     | 27.7 \(^c\) | 0.0001               |
| BMI >30 kg/m\(^2\) (%) | 24.2     | 10.8 \(^b\) | 6.5 \(^c\) | 0.0001               |
| Weight at 1 year (kg) | 74.6 ± 13.7 | 75.0 ± 12.6 | 70.2 ± \(^{b,c}\) | 0.0001               |
| BMI at 1 year (kg/m\(^2\)) | 28.5 ± 5.1 | 27.2 ± 3.8 \(^b\) | 25.8 ± 4.0 \(^{b,c}\) | 0.0001               |
| BMI <25 kg/m\(^2\) (%) | 28.8     | 29.5     | 46.3 \(^c\) | 0.0001               |
| BMI 25–30 kg/m\(^2\) (%) | 38.4     | 47.8 \(^b\) | 39.5 \(^c\) | 0.005                |
| BMI >30 kg/m\(^2\) (%) | 32.8     | 22.7 \(^b\) | 14.2 \(^{b,c}\) | 0.0001               |
| Weight gain at 1 year (kg) | 4.2 ± 6.9 | 5.4 ± 6.5 \(^b\) | 5.1 ± 6.1 | NS                   |
| Weight gain >10 kg (%) | 19.4     | 21.1     | 18      | NS                   |
| Weight gain 0–10 kg (%) | 53.9     | 58.3     | 61.4    | NS                   |
| Weight gain <0 kg (%) | 26.7     | 20.6     | 20.6    | NS                   |
| Delta weight gain at 1 year | 6.4 ± 10.0 | 8.5 ± 9.9 \(^b\) | 8.4 ± 10.0 \(^b\) | 0.038                |
| Delta weight gain >25% (%) | 3.9       | 6.6      | 5.4     | NS                   |
| Delta weight gain >10% (%) | 34.0      | 39.8     | 39.6    | NS                   |
| Delta weight gain 0–10% (%) | 39.3      | 39.6     | 39.8    | NS                   |
| Delta weight gain <0% (%) | 26.7      | 20.6     | 20.6    | NS                   |

NODAT, new-onset diabetes after transplantation; IFG, impaired fasting glucose; BMI, body mass index.

\(^a\)Kruskal–Wallis or ANOVA (continuous variables), chi-square (categorical variables).

\(^b\)Significant differences compared with NODAT.

\(^c\)Significant differences compared with IFG.
The patients who changed from NODAT to other groups at 1 year after KT had a lower percentage of obesity at transplantation (7.1% vs. 26.9%, P = 0.012) compared with those who did not recover. Similarly, the patients that, at 12 months after KT, returned to control group from IFG at 3 months after transplant were thinner (BMI: 24.1 ± 3.9 versus 25.7 ± 3.9 kg/m² at transplantation, P < 0.001) than the patient who did not recover. No association between weight gain during the first year after transplantation and recovery of NODAT or IFG was observed.

Variables associated with NODAT

Results of the multivariate logistic regression analysis, using NODAT at 1 year after transplantation as dependent variable, are provided in Table 3. Independent clinical risk factors associated with the development of NODAT were: recipient age, pre-transplant BMI, use of tacrolimus, triglyceride levels at 3 months (>200 mg/dL) and HCV status.

However, the weight gain during the first post-transplant year was not associated with NODAT in the multivariate analysis. No changes were observed in the odds ratio when weight gain was eliminated from the model. Therefore, no interaction between BMI and weight gain was demonstrated.

Discussion

In the present study, we showed that pre-transplant BMI, but not weight gain during the first post-transplant year, makes up an important risk factor for the development of NODAT. Additionally, other risk factors for this entity were age, use of tacrolimus, triglycerides and HCV status as reported previously [1,4,19–21]. To our knowledge, this is one of the largest observational multi-centre studies assessing the influence of weight gain and baseline BMI on the development of diabetes post-transplantation.

Like other studies, we have demonstrated the relationship between weight and body mass index with NODAT [1,4,6]. Up to 24% of patients who developed NODAT were obese at the time of transplantation, and the risk of NODAT increased 13% for each increase of one unit of BMI, after adjusting for other confounder variables. It is also well known about the relation between weight gain and renal transplantation. Patients who received a KT experience weight gain after the transplantation. In our study, there was an increase of 8.2% of basal weight at 1 year after transplantation, which is similar to other studies [10,22]. We found a trend towards lower weight gain in the NODAT group. However, weight gain was not an independent predictor for NODAT in multivariate analysis.

In agreement with our results, Cosio et al. found a significant correlation between pre-transplant weight and NODAT, but not with weight gain, in patients who received cyclosporine-based immunosuppression [1]. In addition, previous reports have documented a significantly lower weight gain during the first post-transplant year in patients who developed NODAT [12,13]. The reasons for a lower weight gain in patients with NODAT are not entirely clear. It is possible that patients with NODAT may have underlying metabolic disorders which prevent weight increase. At the same time, it is possible that a strict dietary control or a more rapid reduction of steroids was performed in NODAT group. Unfortunately, we did not record further clinical data, such as dose of steroids, or data of starting diabetes for supporting this hypothesis.

In contrast, several other studies have reported that weight gain is associated with NODAT [15–17]. Methodological differences may explain, at least in part, the apparent result disparity. Many of these studies used an increased post-transplant BMI as a surrogate for weight gain, which may lead to misleading results. We calculated for each patient the weight gain as an independent variable that allowed us accurately to estimate weight gain. In addition, some of these investigations did not include patients under tacrolimus-based immunosuppression.

The results of our study also differ from those found in non-transplantation population [11]. In fact, lifestyle modification and reduction of weight have been shown to reduce the risk for type 2 diabetes in the general population [23]. Some reasons may account for these controversial findings. The negative effect of weight gain may be masked by other risk factors for NODAT inherent to KT, such as immunosuppression or HCV status. Accordingly, use of tacrolimus, triglycerides levels and HCV status were associated with the risk for NODAT in our study. In addition, it is plausible that the effect of weight gain for developing diabetes requires a longer term. As a matter of fact, in the general population, an association has been observed between duration of obesity and risk of non-insulin-dependent diabetes mellitus [24].

In agreement with previous reports, we found that the changes from NODAT to IFG or normal status were not uncommon [25,26]. Although most patients remained in the same group, 37% of NODAT patients at 3 months after KT became IFG or normoglycaemic (control patients) at 12 months. Interestingly, in our study, this change was related to younger and lower BMI patients. These findings reinforce the hypothesis that, in predisposed patients, further factors such as immunosuppression would favour the

| Table 3. Multivariate analysis for NODAT at 1 year after transplantation |
|-----------------------------|-------------|-----------------|
| OR (95% CI) | P         |
|-----------------------------|-------------|-----------------|
| Model with weight gain |             |                 |
| BMI (kg/m²) | 1.135 (1.093–1.178) | 0.0001 |
| Recipient age (years) | 1.060 (1.045–1.075) | 0.0001 |
| Triglycerides (vs. <200 mg/dL) | 1.511 (1.072–2.131) | 0.018 |
| Tacrolimus (vs. cyclosporine) | 1.611 (1.156–2.246) | 0.005 |
| Hepatitis C antibody positive | 1.969 (1.309–2.961) | 0.001 |
| Delta weight gain (%) | 1.012 (0.996–1.029) | 0.145 |
| Model without weight gain |             |                 |
| BMI (kg/m²) | 1.130 (1.091–1.170) | 0.0001 |
| Recipient age (years) | 1.059 (1.044–1.073) | 0.0001 |
| Triglycerides (vs. <200 mg/dL) | 1.507 (1.075–2.112) | 0.017 |
| Tacrolimus (vs. cyclosporine) | 1.623 (1.174–2.245) | 0.003 |
| Hepatitis C antibody positive | 1.923 (1.287–2.873) | 0.001 |

Also adjusted for: gender, primary cause of ESRD, year of transplantation, HLA mismatches, acute rejection, anti-mTOR-based therapy, steroids withdrawal at 1 year after kidney transplant, renal function. NODAT, new-onset diabetes after transplantation; BMI, body mass index at transplantation.
development of NODAT and, in the same way, in those patients with lesser predisposition at time of transplant, as younger and thinner, the action of those additional factors could be recovered.

This study has some limitations. It is a retrospective study. All retrospective studies have the potential for recall bias. However, the case selection and data collection were rigorous and complete. Because we believe that the BMI is a better marker of obesity than weight, we preferred to include in the study only those patients with this value. In the present study, the incidence of NODAT at 1 year of transplant was 10%, using the 2003 international consensus guidelines for this metabolic alteration. In addition, we did not perform in our patients an oral glucose tolerance test for unmasking metabolic disorders. Thus, this approach may underestimate the true incidence of this disorder, and prospective studies are needed to clarify these aspects.

We conclude that the baseline BMI, but not the weight gain in the first year after transplant, is an independent risk factor for the development of NODAT. If reduction in weight prior to transplantation or the use of a particular approach may underestimate the true incidence of this disorder, and prospective studies are needed to clarify these aspects.

Conflict of interest statement. None declared.

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