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Obesity impairs general health-related quality of life (HR-QoL) in premenopausal women to a greater extent than the polycystic ovary syndrome (PCOS)

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Title: Obesity impairs **general** health-related quality of life (HR-QoL) in premenopausal women to a greater extent than the polycystic ovary syndrome (PCOS).

Short Title: Obesity, PCOS and HR-QoL

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STRUCTURED SUMMARY

Objective: Obesity is frequently associated with the polycystic ovary syndrome (PCOS), and both conditions may impact the health-related quality of life (HR-QoL) of affected patients. We aimed to estimate the relative impact of obesity and PCOS on the general HR-QoL of premenopausal women.

Design: Case-control study.

Patients: Consecutive overweight and obese premenopausal women seeking advice for weight loss, of whom 32 were diagnosed with PCOS and 72 had no evidence of androgen excess and were considered controls.

Measurements: Spanish versions of the Short Form 36 Health Survey (SF-36) questionnaire and the Nottingham Health Profile (NHP) were self-administered by the women.

Results: PCOS patients and controls had similar body mass index, yet controls were older. General HR-QoL mean scores were similar in both groups, yet PCOS patients scored worse in the role-emotional item of SF-36, and controls scored worse in the pain item of NHP. Increasing grades of obesity, on the contrary, were associated with worse scores in the NHP and SF-36 items related to general and physical aspects of HR-QoL. When compared with the standards established for the Spanish general population, both PCOS patients and controls frequently presented with abnormal scores, yet only increasing grades of obesity were associated with more frequent abnormal scoring.

Conclusions: Obesity impaired general HR-QoL to a greater extent than PCOS in overweight and obese premenopausal women.

Introduction

Health-related quality of life (HR-QoL) is a multidimensional concept that comprises physical, emotional and social concepts associated with a specific disease and its management.¹ The polycystic ovary syndrome (PCOS) is a life-time disorder that appears in up to 6.5% of Spanish premenopausal women.² The clinical signs and symptoms of PCOS, derived from the androgen excess and ovulatory dysfunction that define the syndrome^{3,4} include hirsutism, acne, menstrual irregularity and infertility and have a peripubertal onset. Therefore, these signs and symptoms exert a negative impact on mood and psychological function of affected women for decades. Not surprisingly, depression is frequent in PCOS patients and the presence of hirsutism has been described in association with anxiety and psychological complaints.⁵⁻¹⁰

Moreover, PCOS is frequently associated with insulin resistance, obesity and related metabolic disorders.¹¹ Obesity in particular is present in almost 50% of PCOS patients in clinical series¹¹ and may impair by itself the HR-QoL of women.¹²⁻¹⁵ However, to date it is unclear whether PCOS by itself,¹⁶ or its associations with obesity and other metabolic derangements,¹⁷⁻¹⁹ are the major contributors to the impaired HR-QoL previously reported women in whom both conditions, PCOS and weight excess, coexist.

We aimed to delineate the specific contributions of PCOS and of weight excess to the impairment in the general HR-QoL of premenopausal women seeking advice for weight loss.

Material and Methods

Patients

The present study derived from an earlier report addressing the prevalence of PCOS among otherwise healthy premenopausal women seeking medical advice for weight loss.²⁰ In brief, all the premenopausal women referred by their general physicians to the Department of Endocrinology of Hospital Universitario Ramón y Cajal, for weight loss from May 1, 2002, through December 31, 2005, were prospectively evaluated. All the women were referred from the primary care facilities attending a

specific suburb of Madrid which has a medium-low socio-economic status. Inclusion criteria required being referred exclusively for weight loss as the main complaint, having a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) above 25, being younger than 50 years, and not having classic menopausal symptoms such as hot flushes. Women taking medications that might interfere with hormone profiles, such as contraceptives or insulin sensitizers, were also excluded.

The diagnosis of PCOS used the criteria derived from the 1990 conference sponsored by the National Institute of Child and Human Development: clinical and/or biochemical hyperandrogenism together with ovulatory dysfunction, after excluding secondary aetiologies such as non-classic adrenal hyperplasia, hyperprolactinaemia and androgen-secreting tumours.²¹ Having both hyperandrogenism and ovulatory dysfunction, and although an ovarian ultrasound scan was not obtained, the PCOS patients diagnosed here also fulfilled more recent definitions of PCOS.^{3,4,22} The assays and specific methods used to establish these criteria have been described in detail elsewhere.^{20,23,24} The study was approved by the local ethics committee and all participants gave written informed consent.

From a total of 113 consecutive women recruited, 32 had PCOS, 3 had hyperandrogenemia without evidence of oligoovulation, 2 had idiopathic hirsutism, 2 had isolated chronic oligomenorrhea without clinical or biochemical hyperandrogenism, and 2 had oligomenorrhea and hyperprolactinemia, precluding the diagnosis of PCOS. The remaining 72 women had no evidence of hyperandrogenism or reproductive abnormalities and were considered as the nonhyperandrogenic control group for further comparisons.²⁰ Because none of the control women had clinical or biochemical hyperandrogenism or menstrual disturbances or ovulatory dysfunction, the presence of PCOS according to recent definitions^{3,4,22} was ruled out reliably in all of them even in the absence of an ovarian ultrasound scan. The present study focuses on the comparison of general HR-QoL among the 32 PCOS patients with the 72 controls.

HR-QoL questionnaires

We measured **general** HR-QoL using the Spanish versions of the Short Form 36 Health Survey (SF-36) questionnaire²⁵ and the Nottingham Health Profile (NHP).²⁶

The SF-36 questionnaire uses 36 questions to estimate HR-QoL in eight scaled scores, which are the weighted sums of the questions in their section. Four scores measure physical health (physical functioning, role-physical, bodily pain and general health) and four measure mental health (vitality, social functioning, role-emotional and mental health).²⁷ Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The higher the score, the better the result for the particular item.

The NHP is an auto-administered test of 45 questions distributed into two parts. Part I includes 38 questions grouped into six sections: physical ability (8 questions), pain (8 questions), sleep (5 questions), social isolation (5 questions), emotional reactions (9 questions), and energy level (3 questions). Part II consists of 7 general questions that may not be applicable and is seldom used nowadays. Each question has to be answered as ‘yes’ or ‘no’. Each scale is weighted, and the weights are transformed to yield scores from 0 (no distress) to 100 (maximum distress). Scores are obtained for each section and combined in order to obtain a total score.

The SF-36 and NHP questionnaires were self-administered by the women **early in the morning and 3 to 8 days after a spontaneous or progesterone-induced withdrawal menstrual bleeding**. We compared the results of the PCOS patients with those of the controls, and we also compared the results of both groups with the reference percentiles established for the Spanish general population of the same age-range and sex.^{28,29} Values above the 95th percentile were considered abnormal for the NHP, and values below the 5th percentile were considered abnormal for the SF-36.

Statistical analysis

We express results as means \pm SD unless stated otherwise. We used the Kolmogorov-Smirnov test to estimate the distribution of continuous variables, and we applied logarithmic or square root transformations as needed to ensure normality. We submitted normally distributed variables to a general linear model that included having PCOS or being a control as the independent variable, and

included age as a covariate to correct for the difference in age among PCOS patients and controls. Variables that remained skewed even after mathematical transformation were submitted to Mann-Whitney U tests and, for variables showing statistically significant differences, the possible impact of the difference in age between patients and controls was explored by analyzing Spearman's correlation of these variables with age in the whole population.

The impact of the grade of obesity on HR-QoL indexes was explored considering PCOS patients and controls as a whole. We used the Kruskal-Wallis non-parametric ANOVA and, when this test resulted in statistically significant differences, we identified which grades of obesity caused these differences by using repeated Mann-Whitney U tests in which the Bonferroni correction was applied to the level of significance. For nominal and ordinal variables we applied Pearson's χ^2 or Fisher's exact tests, as appropriate.

We used the PASW Statistics 18 software (SPSS Inc. Chicago, Illinois) to compute statistic analyses. A $\alpha = 0.05$ level of significance was used for all analyses except when Bonferroni adjustments were needed in order to correct for multiple comparisons among subgroups of women.

Results

Clinical characteristics of overweight and obese premenopausal women depending on the presence or absence of PCOS

The comparisons of the clinical and biochemical characteristics of PCOS patients and controls are included in Table 1. We introduced age as a covariate in the general linear model because PCOS patients were younger compared with controls. PCOS patients presented with increased hirsutism scores, androgen, triglycerides and luteinizing hormone concentrations, and reduced sex hormone-binding globulin and estradiol levels. PCOS patients were insulin resistant compared with the controls, and therefore had increased fasting insulin levels and homeostasis model assessment insulin resistance and β -cell function indexes, and reduced insulin sensitivity index as calculated from the results of an oral glucose tolerance test.³⁰ The number of pregnancies and deliveries was reduced in PCOS patients when compared with the controls.

Impact of PCOS on the HR-QoL of overweight and obese premenopausal women

The only statistically significant difference among PCOS women and controls in the NHP consisted of a reduced score in the bodily pain item of PCOS patients compared with the controls, whereas no difference was observed in any other item (Figure 1). Because this variable was skewed even after mathematical transformations we used nonparametric correlation to estimate a possible influence of the older age of the controls in their higher bodily pain scores. These scores showed a statistically significant yet **very** weak correlation with age ($r^2 = 0.065$, $P = 0.009$).

Similarly, PCOS was associated only with a worse score in the role-emotional item of the SF-36 test even after correcting for the difference in age, whereas no difference was observed in any other item (Figure 1).

When compared with the reference values established for the Spanish population, the percentages of subjects with abnormal scores in the NHP **were** not different in PCOS patients and controls, yet both groups showed a large percentage of women showing abnormally increased scores in the energy and mobility items and in the total score (Table 2). The percentage of women with scores abnormally reduced with respect to the reference populational data was higher in PCOS patients compared with the controls in the role-emotional item of SF-36, and there was a large percentage of women in both groups presenting with abnormal scores in the general health, physical functioning, role-emotional and social functioning items of the SF-36 test (Table 2).

Impact of the grade of obesity on the HR-QoL of overweight and obese premenopausal women

For these analyses we considered PCOS patients and controls as a whole, and we classified them according to their BMI into overweight (BMI 25.0 – 29.9 kg/m²), grade 1 obesity (BMI 30.0 – 34.9 kg/m²), grade 2 obesity (BMI 35.0 – 39.9 kg/m²) and grade 3 obesity (BMI equal or above 40.0 kg/m²) subgroups.

The pain item of the NHP showed abnormally higher scores in women presenting with grade 1, 2 and 3 obesity compared with overweight women (Table 3), and the physical ability item was also

worse in grade 3 obese women compared with overweight women (Table 3). No other differences among grades of obesity were observed in other NHP items (Table 3).

Regarding SF-36, women presenting with grade 2 and 3 obesity had abnormally reduced scores compared with overweight women in the physical functioning item (Table 3), and the general health item was also reduced in women with grade 3 obesity compared with the overweight subgroup (Table 3).

Finally, the number of women presenting with scores above the 95th percentile of the NHP scores of the Spanish general population was higher for the physical ability item in obese women compared with overweight women (Table 4), and there was a large percentage of obese presenting with abnormal scores also in the energy and total score of the NHP although not showing differences among grades of obesity (Table 4). Similarly, the number of women presenting with scores below the 5th percentile of the SF-36 scores of the Spanish general population was higher for the general health item in obese women compared with overweight women (Table 4), and there was a large percentage of obese presenting with abnormal scores also in the physical functioning, role-emotional and social functioning items, although not showing differences among grades of obesity (Table 4).

Discussion

Our present results suggest that, when adequately paired for weight, there are very few differences among premenopausal women with or without PCOS in their HR-QoL. Our PCOS patients showed worse results compared with the controls only for the role-emotional item of the SF-36 questionnaire. This item evaluates emotional problems that interfere with aspects pertaining to daily life and their laboral sphere. Also, PCOS patients scored lower, and therefore better, in the pain item of the NHP compared with the controls, yet the older age of the latter might explain this particular difference because HR-QoL worsens with age.³¹

In contrast with the minimal impact of PCOS on HR-QoL, obesity was associated with a broad worsening of many aspects evaluated by the HR-QoL scales used here, in conceptual agreement with previous studies in children and adults.^{32,33}

213 Compared with overweightness, obesity associated in our series worse scores in the pain and
214 physical ability items of the NHP and in the physical functioning and general health items of the SF-
215 36. The results regarding the pain and phsysical ability item of NHP may be related to the well-known
216 association of obesity with osteomuscular disorders and with the obvious difficulties that weight
217 excess impose of mobility.³⁴ Similarly, obesity exerted a negative impact of the SF-36 items related to
218 daily life activities, including mobility and personal care, influencing the general health perception of
219 these women.

220 Moreover, when compared with the standards derived from the general population, obese women
221 frequently scored abnormally in the energy, physical ability and total score items of the NHP, and in
222 the general health and physical functioning items of SF-36. Also, the frequencies of abnormal scores
223 tended to be higher with increasing grades of obesity, reaching statistical significance compared with
224 the overweight subgroup for the physical ability item of NHP and the general health item of SF-36.
225 Although quite frequent, the abnormal scores in the role-emotional and social functioning items of SF-
226 36 were similarly distributed in oveweight and obese women. Considering that PCOS was equally
227 prevalent in overweight and obese women in the present series of premenopausal women²⁰ this finding
228 possibly reflected the specific impact of PCOS on the emotional aspects of HR-QoL.

229 The negative impact of obesity may explain the worsening of **general** HR-QoL of PCOS patients
230 in previous studies **by others**, considering that obesity is frequently associated with PCOS.³⁵ The
231 impairment of HR-QoL, psychological well-being and sexual satisfaction in PCOS patients reported in
232 an earlier **study conducted in Germany**^{36,37} might have been influenced by the fact that this series of
233 **German** PCOS patients were much heavier compared with their controls and, **in sharp contrast with**
234 **our present study, the German series included many PCOS patients referred for the treatment of**
235 **infertility, a trait that may impair HR-QoL by itself.**

236 **In conceptual agreement with our present results, previous studies showed** that the differences in
237 HR-QoL among adolescents with or without PCOS dissapeared when controlling for the influece of
238 body mass index,³⁸ and no differences in the SF-36 questionnaire were found among PCOS patients
239 and controls in adults when adjusting for weight.¹⁶ Similarly, body mass index was a significant
240 modifier of the differences in the SF-36 found among Australian PCOS patient and controls,¹⁸ **and a**

recent systematic review highlighted the importance that weight concerns plays in the impairment of HR-QoL in PCOS patients.³⁹ The contribution of obesity to the impairment of HR-QoL in PCOS patients was highlighted by the improvement observed after successful dietary restriction and life-style modification.⁴⁰

However, our present results do not indicate, by any means, that PCOS does not impair HR-QoL by itself. This has been demonstrated in several studies^{7,16,18} by using a disease-specific HR-QoL instrument termed the Polycystic Ovary Syndrome Questionnaire (PCOSQ) that considered 5 domains related to this disorder: emotions, body hair, weight, infertility, and menstrual problems.^{41,42} Our study was, on the contrary, designed to estimate the impact of obesity and PCOS on general HR-QoL instruments, and therefore did not consider disease-specific dimensions that could not be answered by the controls. In fact, many PCOS patients scored abnormally in several items of the NHP and SF-36 when compared with the standards derived from the general population.

Moreover, the fact that the PCOS patients in our series were younger compared with the controls must be considered when interpreting our present results. As stated above, HR-QoL clearly worsens with age.³¹ Therefore, the age difference in among our PCOS patients and controls might have obscured any difference in general HR-QoL attributable to PCOS. Furthermore, as a whole PCOS patients showed a general HR-QoL similar to non-PCOS women who were several years older, possibility reflecting that their HR-QoL may be inadequately impaired for their younger age.

In summary, obesity impaired general HR-QoL to a greater extent than PCOS in overweight and obese premenopausal women. Given the frequent association among both disorders, this finding should be considered when designing therapeutic strategies directed towards the improvement of the quality of life of these women.

References

- 1 Guyatt, G.H., Feeny, D.H. & Patrick, D.L. (1993) Measuring health-related quality of life. *Annals of Internal Medicine*, **118**, 622-629.

1
2
3 268 2 Asuncion, M., Calvo, R.M., San Millan, J.L., Sancho, J., Avila, S. & Escobar-Morreale, H.F.
4
5 269 (2000) A prospective study of the prevalence of the polycystic ovary syndrome in unselected
6
7 270 Caucasian women from Spain. *Journal of Clinical Endocrinology and Metabolism*, **85**, 2434-
8
9 271 2438.
10
11 272 3 Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H.F.,
12
13 273 Futterweit, W., Janssen, O.E., Legro, R.S., Norman, R.J., Taylor, A.E. & Witchel, S.F. (2006)
14
15 274 Position statement: criteria for defining polycystic ovary syndrome as a predominantly
16
17 275 hyperandrogenic syndrome: an Androgen Excess Society guideline. *Journal of Clinical*
18
19 276 *Endocrinology and Metabolism*, **91**, 4237-4245.
20
21 277 4 Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H.F.,
22
23 278 Futterweit, W., Janssen, O.E., Legro, R.S., Norman, R.J., Taylor, A.E. & Witchel, S.F. (2009) The
24
25 279 Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task
26
27 280 force report. *Fertility and Sterility*, **91**, 456-488.
28
29 281 5 Barth, J., Catalan, J., Cherry, C. & Day, A. (1993) Psychological morbidity in women referred for
30
31 282 treatment of hirsutism. *Journal of Psychosomatic Research*, **37**, 615-619.
32
33 283 6 Sonino, N., Fava, G., Mani, E., Belluardo, P. & Boscaro, M. (1993) Quality of life of hirsute
34
35 284 women. *Postgraduate Medicine*, **69**, 186-189.
36
37 285 7 Barnard, L., Ferriday, D., Guenther, N., Strauss, B., Balen, A. & Dye, L. (2007) Quality of life and
38
39 286 psychological well being in polycystic ovary syndrome. *Human Reproduction*, **22**, 2279-2286.
40
41 287 8 Benson, S., Hahn, S., Tan, S., Mann, K., Janssen, O.E., Schedlowski, M. & Elsenbruch, S. (2009)
42
43 288 Prevalence and implications of anxiety in polycystic ovary syndrome: results of an internet-based
44
45 289 survey in Germany. *Human Reproduction*, **24**, 1446-1451.
46
47 290 9 Deeks, A.A., Gibson-Helm, M.E. & Teede, H.J. (2010) Anxiety and depression in polycystic
48
49 291 ovary syndrome: a comprehensive investigation. *Fertility and Sterility*, **93**, 2421-2423.
50
51 292 10 Jedel, E., Waern, M., Gustafson, D., Landen, M., Eriksson, E., Holm, G., Nilsson, L., Lind, A.K.,
52
53 293 Janson, P.O. & Stener-Victorin, E. (2010) Anxiety and depression symptoms in women with
54
55 294 polycystic ovary syndrome compared with controls matched for body mass index. *Human*
56
57 295 *Reproduction*, **25**, 450-456.
58
59
60

- 1
2
3 296 11 Gambineri, A. & Pasquali, R. (2006) Insulin resistance, obesity and metabolic syndrome in
4
5 297 polycystic ovary syndrome. *Endocrinologia y Nutrición*, **53**(Suppl 1), 49-55.
6
7 298 12 Sarlio-Lahteenkorva, S., Stunkard, A. & Rissanen, A. (1995) Psychosocial factors and quality of
8
9 299 life in obesity. *International Journal of Obesity and Related Metabolic Disorders*, **19** Suppl 6, S1-
10
11 300 5.
12
13 301 13 Lean, M., Han, T. & Seidell, J. (1999) Impairment of health and quality of life using new US
14
15 302 federal guidelines for the identification of obesity. *Archives of Internal Medicine*, **159**, 837-843.
16
17 303 14 Doll, H., Petersen, S. & Stewart-Brown, S. (2000) Obesity and physical and emotional well-being:
18
19 304 Associations between body mass index, chronic illness, and the physical and mental components
20
21 305 of the SF-36 questionnaire. *Obesity Research*, **8**, 160-170.
22
23 306 15 Kolotkin, R.L., Meter, K. & Williams, G.R. (2001) Quality of life and obesity. *Obesity Reviews*, **2**,
24
25 307 219-229.
26
27 308 16 Coffey, S., Bano, G. & Mason, H.D. (2006) Health-related quality of life in women with
28
29 309 polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary
30
31 310 Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). *Gynecological Endocrinology*,
32
33 311 **22**, 80-86.
34
35 312 17 Elsenbruch, S., Benson, S., Hahn, S., Tan, S., Mann, K., Pleger, K., Kimmig, R. & Janssen, O.E.
36
37 313 (2006) Determinants of emotional distress in women with polycystic ovary syndrome. *Human*
38
39 314 *Reproduction*, **21**, 1092-1099.
40
41 315 18 Ching, H.L., Burke, V. & Stuckey, B.G. (2007) Quality of life and psychological morbidity in
42
43 316 women with polycystic ovary syndrome: body mass index, age and the provision of patient
44
45 317 information are significant modifiers. *Clinical Endocrinology*, **66**, 373-379.
46
47 318 19 Jones, G.L., Balen, A.H. & Ledger, W.L. (2008) Health-related quality of life in PCOS and related
48
49 319 infertility: how can we assess this? *Human Fertility (Cambridge)*, **11**, 173-185.
50
51 320 20 Alvarez-Blasco, F., Botella-Carretero, J., San Millan, J. & Escobar-Morreale, H. (2006)
52
53 321 Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women.
54
55 322 *Archives of Internal Medicine*, **166**, 2081-2086.
56
57
58
59
60

1
2
3 323 21 Zawadzki, J.K. & Dunaif, A. (1992) Diagnostic criteria for polycystic ovary syndrome: Towards a
4 324 rational approach. In: *Polycystic ovary syndrome*, Vol. 4. Blackwell Scientific Publications,
5 325 Boston, 377-384.
6
7
8
9 326 22 The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. (2004) Revised
10 327 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary
11 328 syndrome (PCOS). *Human Reproduction*, **19**, 41-47.
12
13
14
15
16 329 23 Escobar-Morreale, H.F., Lasuncion, M.A. & Sancho, J. (2000) Treatment of hirsutism with ethinyl
17 330 estradiol-desogestrel contraceptive pills has beneficial effects on the lipid profile and improves
18 331 insulin sensitivity. *Fertility and Sterility*, **74**, 816-819.
19
20
21
22 332 24 Escobar-Morreale, H.F., Sanchon, R. & San Millan, J.L. (2008) A prospective study of the
23 333 prevalence of nonclassical congenital adrenal hyperplasia among women presenting with
24 334 hyperandrogenic symptoms and signs. *Journal of Clinical Endocrinology and Metabolism*, **93**,
25 335 527-533.
26
27
28
29
30
31 336 25 Alonso, J., Prieto, L. & Anto, J.M. (1995) [The Spanish version of the SF-36 Health Survey (the
32 337 SF-36 health questionnaire): an instrument for measuring clinical results]. *Medicina Clínica*, **104**,
33 338 771-776.
34
35
36
37 339 26 Alonso, J., Prieto, L. & Anto, J.M. (1994) The Spanish version of the Nottingham Health Profile:
38 340 a review of adaptation and instrument characteristics. *Quality of Life Research*, **3**, 385-393.
39
40
41 341 27 Ware, J., Snow, K., Kosinski, M. & Gandek, B. (1993) *SF-36 Health Survey. Manual and*
42 342 *interpretation guide*. The Health Institute, Boston.
43
44
45
46 343 28 Alonso, J., Regidor, E., Barrio, G., Prieto, L., Rodriguez, C. & De la Fuente, L. (1998) Population
47 344 reference values of the Spanish version of the Health Questionnaire SF-36. *Medicina Clínica*, **111**,
48 345 410-416.
49
50
51
52 346 29 Alonso, J., Anto, J. & Moreno, C. (1990) Spanish version of the Nottingham Health Profile:
53 347 translation and preliminary validity. *American Journal of Public Health*, **80**, 704-708.
54
55
56
57 348 30 Matsuda, M. & DeFronzo, R.A. (1999) Insulin sensitivity indices obtained from oral glucose
58 349 tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*, **22**, 1462-1470.
59
60

- 350 31 Lopez-Garcia, E., Banegas, J., Graciani Perez-Regadera, A., Gutierrez-Fisac, J., Alonso, J. &
351 Rodriguez-Artalejo, F. (2003) Population-based reference values for the Spanish version of the
352 SF-36 Health Survey in the elderly. *Medicina Clínica*, **27**, 701-709.
- 353 32 Staffieri, J. (1967) A study of social stereotype of body image in children. *Journal of Personality*
354 *and Social Psychology*, **7**, 101-104.
- 355 33 Anandacoomarasamy, A., Caterson, I., Leibman, S., Smith, G., Sambrook, P., Fransen, M. &
356 March, L. (2009) Influence of BMI on health-related quality of life: comparison between and
357 obese adult cohort and age-matched population norms. *Obesity*, **17**, 2114-2118.
- 358 34 Bray, G. (2004) Medical consequences of obesity. *Journal of Clinical Endocrinology and*
359 *Metabolism*, **89**, 2583-2589.
- 360 35 Gambineri, A., Pelusi, C., Vicennati, V., Pagotto, U. & Pasquali, R. (2002) Obesity and the
361 polycystic ovary syndrome. *International Journal of Obesity and Related Metabolic Disorders*,
362 **26**, 883-896.
- 363 36 Elsenbruch, S., Hahn, S., Kowalsky, D., Offner, A.H., Schedlowski, M., Mann, K. & Janssen,
364 O.E. (2003) Quality of life, psychosocial well-being, and sexual satisfaction in women with
365 polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism*, **88**, 5801-5807.
- 366 37 Hahn, S., Janssen, O.E., Tan, S., Pleger, K., Mann, K., Schedlowski, M., Kimmig, R., Benson, S.,
367 Balamitsa, E. & Elsenbruch, S. (2005) Clinical and psychological correlates of quality-of-life in
368 polycystic ovary syndrome. *European Journal of Endocrinology*, **153**, 853-860.
- 369 38 Trent, M., Austin, S., Rich, M. & Gordon, C. (2005) Overweight status of adolescent girls with
370 polycystic ovary syndrome: body mass index as mediator of quality of life. *Ambulatory Pediatrics*,
371 **5**, 107-111.
- 372 39 Jones, G.L., Hall, J.M., Balen, A.H. & Ledger, W.L. (2008) Health-related quality of life
373 measurement in women with polycystic ovary syndrome: a systematic review. *Human*
374 *Reproduction Update*, **14**, 15-25.
- 375 40 Thomson, R., Buckley, J., Lim, S., Noakes, M., Clifton, P., Norman, R. & Brinkworth, G. (2009)
376 Lifestyle management improves quality of life and depression in overweight and obese women
377 with polycystic ovary syndrome. *Fertility and Sterility*, December 11 [Epub ahead of print].

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378 41 Cronin, L., Guyatt, G., Griffith, L., Wong, E., Azziz, R., Futterweit, W., Cook, D. & Dunaif, A.
379 (1998) Development of a health-related quality-of-life questionnaire (PCOSQ) for women with
380 polycystic ovary syndrome (PCOS). *Journal of Clinical Endocrinology and Metabolism*, **83**,
381 1976-1987.

382 42 Jones, G.L., Benes, K., Clark, T.L., Denham, R., Holder, M.G., Haynes, T.J., Mulgrew, N.C.,
383 Shepherd, K.E., Wilkinson, V.H., Singh, M., Balen, A., Lashen, H. & Ledger, W.L. (2004) The
384 Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ): a validation.
385 *Human Reproduction*, **19**, 371-377.

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Table 1. Clinical and biochemical characteristics in PCOS patients and controls

	Patients (n = 32)		Controls (n = 72)		P value
Age (yr)	26.1	± 7.2	32.5	± 7.9	<0.001
Body mass index (kg/m ²)	35.7	± 8	35.3	± 6.2	0.41
Waist-hip ratio	0.82	± 0.09	0.80	± 0.07	0.06
Abdominal circumference (cm)	95	± 15	94	± 13	0.11
Total body fat (kg)	35.7	± 12.2	35.8	± 11.1	0.52
Relative body fat (%)	38.2	± 6.9	39.5	± 5.6	0.84
Systolic blood pressure (mmHg)	116	± 12	122	± 19	0.26
Diastolic blood pressure (mmHg)	69	± 8	72	± 12	0.19
Hirsutism score	7.3	± 5.5	1.0	± 1.6	<0.001
Total testosterone (nmol/litre)	2.2	± 1.0	1.4	± 0.5	<0.001
Free testosterone (pmol/litre)	45	± 21	24	± 10	<0.001
Sex hormone-binding globulin (nmol/litre)	28	± 14	37	± 19	0.08
17-hydroxyprogesterone (nmol/litre)	3.0	± 1.5	1.8	± 1.2	0.007
Androstenedione (nmol/litre)	12	± 6	8	± 3	0.002
Dehydroepiandrosterone-sulphate (µmol/litre)	5.4	± 2.0	4.2	± 0.2	0.25
Luteinizing hormone (U/litre)	6.1	± 3.7	4.4	± 2.0	0.003
Follicle-stimulating hormone (U/litre)	5.8	± 2.9	5.9	± 1.8	0.74
Estradiol (pmol/litre)	169	± 139	195	± 143	0.27
Fasting glucose (mmol/litre)	5.1	± 0.6	5.3	± 0.7	0.96
Fasting insulin (pmol/litre)	104	± 69	76	± 49	0.02
Homeostasis model assessment-insulin resistance	3.5	± 2.5	2.7	± 1.8	0.04
Homeostasis model assessment-β	229	± 192	128	± 64	0.01
Insulin sensitivity index	3.9	± 2.6	5.2	± 3.4	0.03
Total cholesterol (mmol/litre)	4.7	± 1.0	4.8	± 1.0	0.39
High-density lipoprotein-cholesterol (mmol/litre)	1.2	± 0.2	1.2	± 0.3	0.41
Low-density lipoprotein-cholesterol (mmol/litre)	3.0	± 0.8	3.0	± 0.8	0.49
Triglycerides (mmol/litre)	1.3	± 1.0	1.1	± 0.6	0.011
Pregnancies (n)	0.4	± 0.8	1.2	± 1.4	0.001
Deliveries (n)	0.3	± 0.5	0.9	± 1.1	0.002
Abortions (n)	0.1	± 0.4	0.3	± 0.6	0.08

Data are means ± SD. Data were analysed using a general linear model in which age was introduced as a covariate to correct for the difference in age observed between patients and controls. Reproduced from Álvarez-Blasco et al.,²⁰ with permission.

Table 2. Women presenting with abnormal scores in tests of HR-QoL among PCOS patients and controls.

	PCOS patients (n = 32)	Controls (n = 72)	χ^2	P value
Nottingham Health Profile ^a				
Emotional reactions	2 (6%)	8 (11%)	0.602	0.72
Sleep	0 (0%)	1 (1%)	0.449	0.99
Energy	5 (16%)	7 (10%)	0.756	0.51
Pain	0 (0%)	0 (0%)		
Physical ability	3 (9%)	12 (17%)	0.954	0.38
Social isolation	2 (6%)	3 (4%)	0.210	0.64
Total score	3 (9%)	8 (11%)	0.071	0.99
SF-36 questionnaire ^b				
General health	6 (19%)	10 (14%)	0.402	0.56
Mental Health	2 (6%)	5 (7%)	0.017	0.99
Physical functioning	8 (26%)	15 (21%)	0.223	0.64
Role-physical	0 (0%)	3 (4%)	1.373	0.55
Role-emotional	12 (38%)	12 (17%)	5.417	0.02
Social functioning	7 (22%)	10 (14%)	1.033	0.31
Bodily pain	0 (0%)	6 (8%)	2.830	0.17
Vitality	2 (6%)	6 (8%)	0.135	0.99

^a Data are counts (percentage) of women presenting with scores above the 95th percentile of the Spanish general population.

^b Data are counts (percentage) of women presenting with scores below the 5th percentile of the Spanish general population.

Table 3. Influence of the grade of obesity on HR-QoL scores considering PCOS patients and controls as a whole.

	Overweight (25.0 – 29.9 kg/m ²) n = 25	Grade 1 obesity (30.0 – 34.9 kg/m ²) n = 35	Grade 2 obesity (35.0 – 39.9 kg/m ²) n = 30	Grade 3 obesity (> 40.0 kg/m ²) n = 23	χ^2	P value
Nottingham Health Profile						
Emotional reactions	31 ± 26	29 ± 29	24 ± 22	34 ± 30	1.490	0.69
Sleep	22 ± 31	24 ± 32	23 ± 28	20 ± 28	0.356	0.95
Energy	13 ± 25	27 ± 37	22 ± 30	39 ± 42	5.668	0.13
Pain	4 ± 8	16 ± 21 ^a	19 ± 22 ^a	26 ± 25 ^a	14.644	0.01
Physical ability	14 ± 14	28 ± 23	26 ± 25	36 ± 27 ^a	9.940	0.02
Social isolation	10 ± 17	8 ± 16	5 ± 14	11 ± 22	2.634	0.45
Total score	16 ± 15	22 ± 19	20 ± 16	28 ± 21	4.303	0.23
SF-36 questionnaire						
General health	69 ± 15	66 ± 17	56 ± 23	54 ± 21 ^a	9.947	0.02
Mental Health	66 ± 16	68 ± 17	70 ± 19	66 ± 23	0.717	0.87
Physical functioning	90 ± 15	81 ± 20	79 ± 19 ^a	71 ± 22 ^a	16.347	0.001
Role-physical	92 ± 21	88 ± 26	85 ± 27	88 ± 24	2.090	0.55
Role-emotional	65 ± 41	63 ± 46	68 ± 40	65 ± 43	0.111	0.99
Social functioning	80 ± 19	79 ± 27	80 ± 23	72 ± 31	0.876	0.69
Bodily pain	68 ± 22	64 ± 20	65 ± 26	55 ± 23	0.137	0.53
Vitality	58 ± 16	57 ± 19	60 ± 21	57 ± 23	0.558	0.91

Data are means ± SD.

^a $p < 0.05$ compared with overweight women according to Kruskal-Wallis tests, followed by repeated Mann-Whitney tests as *post hoc* analysis, applying Bonferroni correction to the level of significance.

Table 4. Women presenting with abnormal scores in tests of HR-QoL depending on their grade of obesity, considering PCOS patients and controls as a whole

	Overweight (25.0 – 29.9 kg/m ²) n = 25	Grade 1 obesity (30.0 – 34.9 kg/m ²) n = 35	Grade 2 obesity (35.0 – 39.9 kg/m ²) n = 30	Grade 3 obesity (> 40.0 kg/m ²) n = 23	χ^2 ^c	P value ^c
Nottingham Health Profile^a						
Emotional reactions	3 (13%)	4 (13%)	1 (4%)	2 (9%)	0.299	0.69
Sleep	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0.303	1.00
Energy	1 (4%)	4 (12%)	1 (3%)	6 (26%)	1.661	0.29
Pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Physical ability	0 (0%)	4 (13%)	4 (15%)	7 (32%)	5.258	0.02
Social isolation	1 (4%)	1 (3%)	1 (4%)	2 (9%)	0.028	1.00
Total score	1 (4%)	4 (13%)	2 (7%)	4 (18%)	1.355	0.45
SF-36 questionnaire^b						
General health	0 (0%)	3 (10%)	6 (22%)	7 (32%)	5.673	0.02
Mental Health	1 (4%)	1 (3%)	2 (7%)	3 (13%)	0.327	1.00
Physical functioning	1 (4%)	8 (26%)	6 (22%)	7 (36%)	7.327	0.06
Role-physical	0 (0%)	1 (3%)	1 (4%)	1 (5%)	0.927	1.00
Role-emotional	5 (21%)	10 (32%)	5 (19%)	4 (18%)	2.153	0.54
Social functioning	2 (8%)	5 (16%)	4 (15%)	6 (27%)	1.465	0.35
Bodily pain	2 (8%)	1 (3%)	2 (7%)	1 (5%)	0.377	0.62
Vitality	1 (4%)	2 (7%)	2 (7%)	3 (14%)	0.546	0.68

^a Data are counts (percentage) of women presenting with scores above the 95th percentile of the Spanish general population.

^b Data are counts (percentage) of women presenting with scores below the 5th percentile of the Spanish general population.

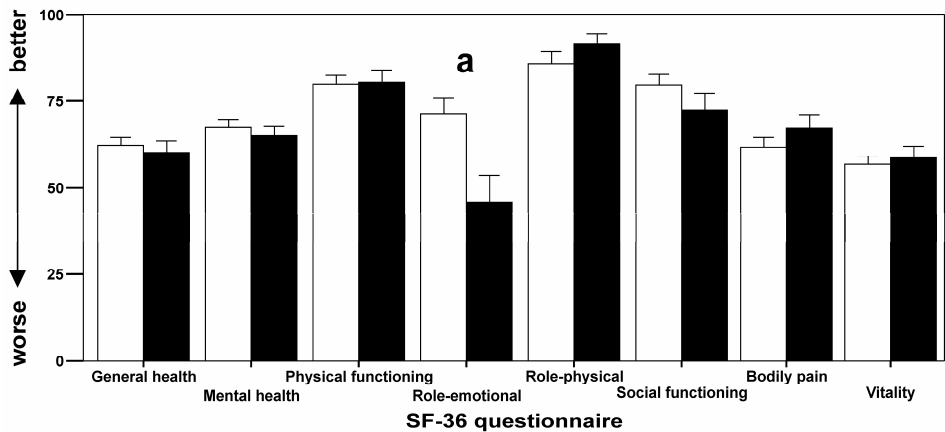
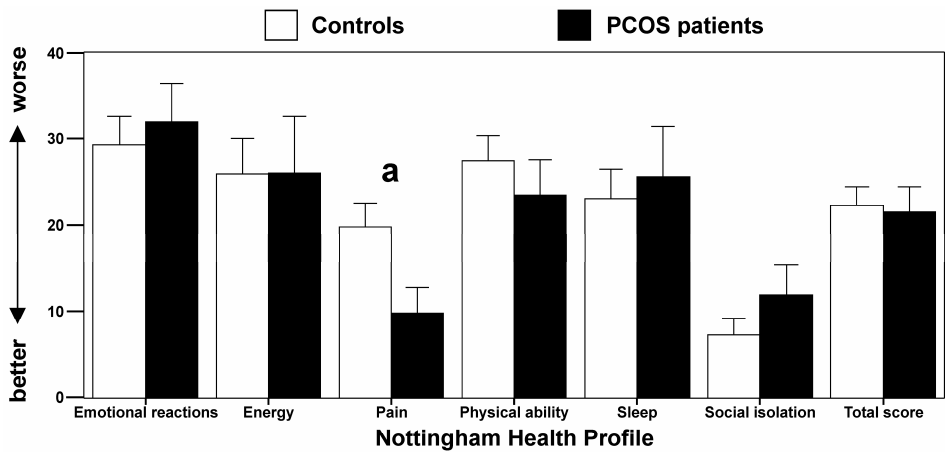
^c Data were submitted to Fisher’s exact test. The grade 1, 2 and 3 obesity categories were merged into an obesity category that was compared with the overweight category because, with the exception of physical functioning and role-emotional, for all HR-QoL items there were more than 20% of cells with expected frequencies below 5 and/or cells with expected categories below 2, not matching the requirements of the χ^2 test.

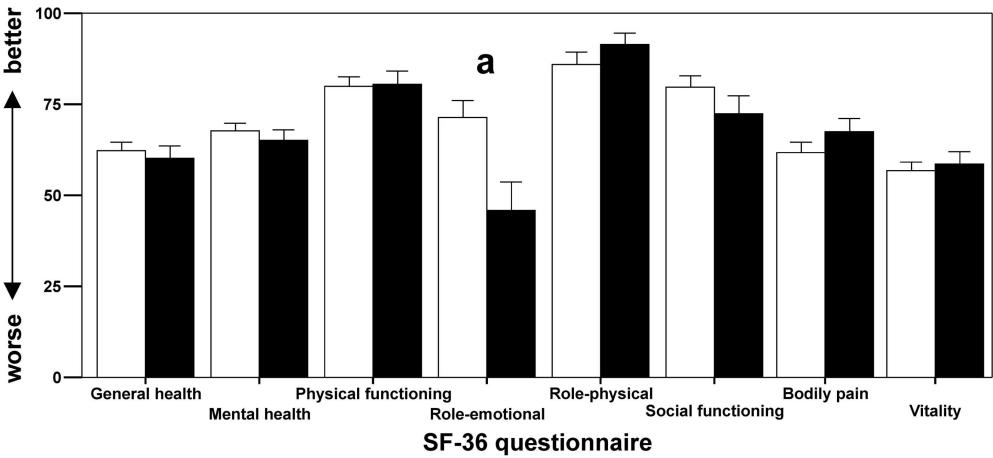
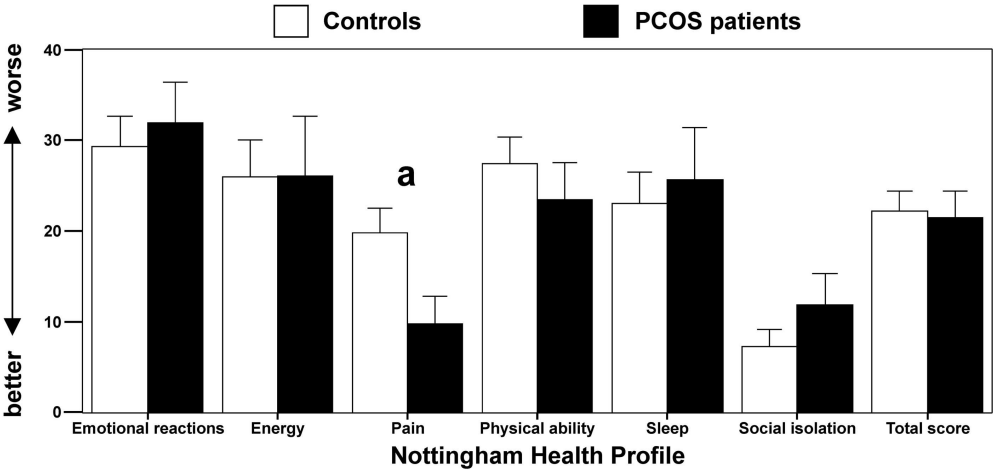
Legend to Figure

Figure 1. Health-related quality of life scores in PCOS patients and controls. Data are means \pm SEM.

^a $p < 0.05$ for the comparison of PCOS patients and controls after controlling for a difference in age among them.

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