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# Obesity phenotype and patient-reported outcomes in moderate and severe chronic kidney disease: a cross-sectional study from the CKD-REIN cohort study

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## Abstract

**Purpose** To evaluate the association between obesity phenotypes and health-related quality of life (HRQoL) in non-dialysis-dependent CKD patients.

**Methods** Data from the national CKD-REIN cohort which included 3033 patients with stage 3–4 CKD were used. Patients were divided into three groups: non-obese (NO) patients (BMI < 30 kg/m$^2$), metabolically healthy obese (MHO) (BMI ≥ 30 kg/m$^2$ and ≤ 1 criterion NCEP/ATP III), and metabolically unhealthy obese (MUO) (BMI ≥ 30 kg/m$^2$ and ≥ 2 criteria NCEP/ATP III). HRQoL was measured by the KDQOL-36™ which comprised three disease-specific dimensions: symptoms, effects, and burden and two summaries scores: physical (PCS) and mental (MCS). We used a mixed effect model with adjustment on sociodemographic characteristics and comorbidities.

**Results** A total of 2693 patients completed the self-administered questionnaires. MHO patients accounted for 3.4% of the cohort and for 12% of obese patients. In the NO group, average HRQoL scores were 77.2 ± 15.9 for symptoms, 83.5 ± 16.5 for effects, 76.8 ± 22.7 for burden, 43.5 ± 9.7 for PCS, and 47.9 ± 7.0 for MCS. In the multivariate analysis, scores were similar in MHO and NO patients, but significantly different with those in MUO patients: symptoms (−0.7; $p = 0.71$ vs. −3.0; $p = 0.0025$), effects (+1.2; $p = 0.57$ vs. −4.3; $p < 0.0001$), burden (+2.7; $p = 0.31$ vs. −3.6; $p = 0.0031$), and PCS (−0.6; $p = 0.58$ vs. −4.3; $p < 0.0001$). MCS was not associated with obesity phenotypes.

**Conclusions** This study demonstrated an association between obesity phenotypes and QoL in non-dialysis-dependent CKD patients. MUO patients had worse QoL than NO and MHO patients even after adjustment on comorbidities.

**Keywords** Chronic kidney disease · Patient-reported outcomes · Quality of life · Obesity · Metabolically healthy obesity

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## Background

Chronic kidney disease (CKD) is a common disease which affects 8–10% of the global population [1, 2]. In 2012, approximately three million French people suffered from it [3]. Inevitable progression to end-stage renal disease (ESRD) and predisposition to the development of metabolic and cardiovascular complications predict gloomy prognosis in CKD patients. CKD affects health-related quality of life (HRQoL), physical abilities, and sleep quality of patients [4–7]. HRQoL is an individual's perception of the impact of a disease on daily life. Studies have demonstrated that impairment of HRQoL in CKD patients is associated with an increased risk of hospitalization and death [8–11]. To help to improve HRQoL in CKD patients, strategies requiring careful assessments of HRQoL need to be developed in routine medical care [12]. Obesity is more frequent in CKD patients (24.7%) than in the French general population (15.7%) [13, 14] and is always associated with compromised quality of life (QoL) [15–17]. However, obesity is a complex, multifactorial disease and various clinical obesity phenotypes have been identified in the general population. The phenotype called metabolically healthy obesity (MHO) is characterized by the absence of metabolic abnormalities and a preserved insulin sensibility [18–21]. Individuals with a MHO phenotype are at a lower risk of developing type 2 diabetes than those with a metabolically unhealthy obesity (MUO) phenotype [22, 23]. There are studies with conflicting results about cardiovascular risk [24, 25]. The relative prevalence of MHO in moderate and advanced CKD and its impact on patient-reported outcomes, such as HRQoL, still remain unknown. Managing obesity is still considered as a second-line medical management in obese CKD patients in routine nephrology practice. In addition, obesity management does not take into account obesity phenotypes. In this study, we have hypothesized that the impact of patient QoL differs between obesity phenotypes, MHO patients being more likely to have a better QoL than MUO patients. Thus, it might be interesting to adapt medical care according to obesity phenotype in CKD patients. To our knowledge, most HRQoL data have been obtained among ESRD patients undertaking dialysis or kidney transplantation. Studies on HRQoL in non-dialysis-dependent CKD (NDD-CKD) patients, particularly those related to obesity phenotypes, are scarce.

In this study, we have assessed (1) QoL and (2) depressive symptomatology in NDD-CKD patients according to obesity phenotypes.

## Methods

### Study design and participants

We performed a cross-sectional study using baseline data from the French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study. The CKD-REIN study was conducted in 40 clinic sites with outpatient nephrology care, nationally representative (public hospitals, for-profit and non-profit hospitals) [26, 27]. Included patients were at least 18 years old, with a proven stage 3–4 CKD, and non-transplant recipients. We enrolled 3033 patients who had moved forth to stage 2 or back to stage 5 without starting renal replacement therapy (RRT) during the period between the census and the inclusion in the study, assuming that this would reduce selection bias due to kidney function variability.

### Data collection

Data were collected from patient interviews and medical records. Comorbidities and CKD history were collected from medical records. Interviews were conducted by trained clinical research associates. Patients were asked about their kidney disease, their comorbidities, their treatments, and their weight history. Blood pressure and anthropometric measurements were carried out by a nurse or a nephrologist.

Patient-reported outcome measures (PROMs) were collected via self-administered questionnaires:

– The level of HRQoL was measured by the validated kidney disease quality of life short form 36 (KDQoL-36™) [28, 29]. This instrument comprises five subscales, combining a disease-specific core exploring three dimensions of CKD (symptoms, effects, and burden) and a generic core corresponding to SF-12 (physical component summary: PCS and mental component summary: MCS). The symptom dimension assessed the degree of bother (not at all, somewhat, moderately, very much, extremely) in terms of issues, such as muscle soreness, pain, bruising, itchy skin, particularly relevant in CKD patients, during the last 30 days. In this study, the effects of CKD on daily life were assessed by the five-point response scale used for the symptom dimension and included restrictions on fluid and dietary intake, impact on self-image and on work productivity, as well as ability to play one's family role. The burden of CKD was assessed by perceived levels of frustration and impact on daily functioning using a Likert scale (ranging from definitely true to definitely

false). Scores of the different subscales were calculated according to the KDQoL-36™ scoring program [30]. Values for each item were normalized from 0 (worst QoL) to 100 (best QoL). PCS and MCS could not be calculated if only one answer to an item in SF-12 was missing. Score calculations for specific dimensions required that at least 50% of items were completed.

– Depressive symptomatology was evaluated by the validated shortened center for epidemiologic studies depression scale (CES-D10) [31, 32]. CES-D10 contains three items on depressed affect, five items on somatic symptoms, and two items on positive affect. This scale reports affects within the last 7 days. In this study, a Likert scale was used for responses and ranged from 0 to 3 (rarely or none of the time, some or a little of the time, occasionally or a moderate amount of time, all of the time). For the two items on positive affect (item 5 and 8), the Likert scale was reversed and ranged from 3 to 0 (rarely or none of the time, some or a little of the time, occasionally or a moderate amount of time, all of the time). Score was not calculated if more than two answers to items were missing. An adult score greater than a value of 10/30 was recognized as being in favor of depressive symptomatology.

Standard blood and urine tests were performed in all patients. GFR was estimated (eGFR) using the CKD Epidemiology Collaboration equation (CKD-EPI).

To define CKD stages, we used the current definition: stage 2 for eGFR ranged from 90 to 60 ml/min (mild CKD), stage 3 for eGFR ranged from 30 to 59 ml/min (moderate CKD), and stage 4 for eGFR ranged from 15 to 29 ml/min (severe CKD) [33].

## Obesity phenotypes

To determinate metabolic unhealthy status, we used the following criteria from the third report of the National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP III):

– Triglycerides $\geq 1.7$ mmol/l
– HDL-c $< 1.04$ mmol/l for men and $< 1.29$ mmol/l for women
– Random glycemia $\geq 6.1$ mmol/l or diabetes
– SBP $\geq 130$ and/or DBP $\geq 85$ mm Hg or hypertension history or antihypertensive treatment.

We did not use the waist circumference because of its important correlation with obesity [23].

We constituted three groups of patients according to obesity phenotypes [14, 23]:

– Non-obese patients defined as those having a body mass index (BMI) $< 30$ kg/m$^2$;
– MHO patients defined as those having a BMI $\geq 30$ kg/m$^2$ and meeting $\leq 1$ criterion of the metabolic unhealthy status;
– MUO patients defined as those having a BMI $\geq 30$ kg/m$^2$ and meeting at least two criteria of the metabolic unhealthy status.

## Statistical analyses

We first described patient baseline characteristics according to their obesity phenotypes. Characteristics of patients who answered the self-administrated questionnaire were compared to those who did not. We used $\chi^2$ test or $t$ test as appropriate. Scores were normally distributed with Skewness and Kurtosis between $-1$ and 1.

We then compared PCS, MCS, and the three disease-specific dimensions between obesity phenotypes using a mixed effect model. We took into account the aleatory effect of the multicenter design. We calculated intra-cluster correlation (ICC) to assess the center effect. We performed a mixed effect model per dimension or summary score, i.e., five models. The following adjustment variables were tested: sex, age, education level, occupational status, living alone, living below the poverty line (INSEE 2016), status of the institution (private/public), eGFR, anemia (hemoglobin $< 12$ g/dl in women and $< 13$ g/dl in men), sleep apnea syndrome, and other comorbidities. The variable "living below the poverty line" was related to the type of household. A monthly income of less than 60% of the national median defined a patient as poor. Income was weighted by the number of family members. We used thresholds available through INSEE in 2016 [34]. For comorbidities included in our models, we were inspired by the comorbidity index developed by Groll et al. [35] which contains comorbidities having an impact on QoL. As diabetes and overweight were related to obesity phenotypes, they were not selected as comorbidities in the model adjustment. In addition, some variables described in the Groll's comorbidity index were not used in our study due to a lack of data. Finally, we took into account the following variables in our models: arthropathy, osteoporosis, asthma, obstructive pulmonary disease, heart failure, myocardial infarction, neurological disease (multiple scleroses, Parkinson's disease), stroke, peripheral vascular disease, upper gastrointestinal tract disease (gastrointestinal bleeding), and depression. Comorbidities were included in our models one by one as dichotomous variables.

Assumptions of mixed effect model were tested by graphic methods. Suspected interactions were also assessed. The alpha risk was adjusted by the Tukey–Kramer method. The overall alpha risk was 5%.

We also performed two sensitivity analyses. In the first analysis, underweight patients (BMI < 18.5 kg/m$^2$) were removed because they got a lower QoL score than non-obese patients with a normal weight. In the second analysis, diabetic patients were removed in order to eliminate the impact of the difference in diabetic/non-diabetic status between obesity phenotypes. Diabetes status was then defined as follows: previously diagnosed diabetes reported in medical records, or glucose-lowering medication, or HbA1c ≥ 6.5%, or fasting glucose ≥ 7.0 mmol/l, or random glucose ≥ 11.0 mmol/l.

In order to meet the secondary objective, the proportion of patients with a score in favor of depressive symptomatology (> 10/30) on CES-D10 was compared between the three obesity phenotypes using a $\chi^2$ test. For multivariate analyses, we performed a logistic regression model adjusted on sociodemographic variables and comorbidities.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

## Results

### Population characteristics

Of the 3033 patients who were included, 2597 completed the self-administered questionnaires and were classified into different obesity phenotypes. Compared to respondents, non-respondents were younger (mean age: 63.9 ± 14.8 vs. 67.2 ± 12.5 years; $p < 0.0001$), were less likely to have diabetes (51.5% vs. 41.9%; $p = 0.0008$), and had a slightly higher HbA1c level (7.4% vs. 7.2%; $p = 0.03$). There was no statistically significant difference between the two groups with respect to other sociodemographic characteristics, comorbidities, and obesity phenotypes.

Among the 2597 patients, 885 were women (34.1%) and 1712 men (65.9%). The mean age was 67.2 ± 12.5 years. The main characteristics of the study population are shown in Table 1. They were 1724 non-obese patients (66.4%), 88 MHO (3.4%), and 785 MUO (30.2%). MHO accounted for 12% of obese patients. In obese patients (BMI ≥ 30), the abdominal perimeter was greater than 80 cm in women and 94 cm in men, in accordance with thresholds defined for abdominal obesity by the French National Authority for Health (HAS, Haute Autorité de Santé). As a result, a misclassification bias of patients with renal sodium retention that would artificially increase BMI was eliminated. BMI was significantly different between MHO and MUO patients (33.4 ± 3.1 vs. 35.2 ± 4.6 respectively; $p < 0.0001$). No MHO patients had abnormal carbohydrate and lipid metabolism according to NCEP/ATP III criteria. About 96% of patients had hypertension.

### Health-related quality of life (HRQoL)

The proportion of missing scores was low (< 2%), except for SF-12 summary scores (PCS and MCS: 11.7%). All scores, except MCS ($p = 0.42$), were associated with obesity phenotypes ($p < 0.0001$). Scores were generally lower in women than in men and lower in MUO patients than in MHO and non-obese patients (Fig. 1).

In bivariate analyses, the status of the institution (private/public) was associated with all QoL scores ($p < 0.0001$). These associations were no longer statistically significant after adjusting for the variable "living below the poverty line." The status of the institution was not included in multivariate models.

In multivariate analyses, scores for the CKD-specific dimensions and PCS were not significantly different in MHO patients and in non-obese patients. By contrast, scores for all dimensions, except for MCS, were significantly lower in MUO patients than in non-obese patients (Table 2).

Scores for the symptoms dimension were slightly lower, but not statistically significant, in MHO patients than in non-obese patients. By contrast, MUO patients got significantly lower scores than non-obese patients. Scores for the effects and burden dimensions were higher, but not statistically significant, in MHO patients than in non-obese patients, and significantly lower in MUO patients than in non-obese. PCS was lower, but not statistically significant, in MHO patients than in non-obese patients, and significantly lower in MUO patients than in non-obese patients. Differences in score according to phenotypes were less marked when the model was adjusted on comorbidities, especially in MUO patients.

When comparing the two groups of obese patients, scores in effect ($p = 0.027$), burden (0.024), and PCS ($p = 0.003$) were significantly worse in MUO than in MHO patients.

Obesity phenotypes were not associated with MCS. A few variables, such as gender ($p < 0.0001$) and living below the poverty line ($p < 0.0001$), were associated with MCS.

The ICC was greater than 0.9 for all models, corresponding to the absence of a center effect.

### Sensitivity analyses

The underweight patients got average scores of 7.5 points lower than those in non-obese patients with a normal weight for the CKD-specific dimensions ($p < 0.05$). By contrast, their PCS and MCS were not significantly different from those in non-obese patients with a normal weight. The results of the sensitivity analysis were unchanged after removing underweight patients (Table 3).

After removing diabetic patients, the total number of patients was 1491 (1211 non-obese, 88 MHO, and 192 MUO). Mean scores were increased by 1 to 3 points for non-obese and MUO patients. However, scores were significantly

**Table 1** Patient characteristics according to obesity phenotypes

| | All<br>*N* = 2597<br>%/m ± SD* | Non-obese<br>*N* = 1724 (66.4%)<br>%/m ± SD | MHO<br>*N* = 88 (3.4%)<br>%/m ± SD | MUO<br>*N* = 785 (30.2%)<br>%/m ± SD | *p*** |
|---|---|---|---|---|---|
| Age, years | 67.2 ± 12.5 | 66.6 ± 13.8 | 68.2 ± 10.0 | 68.5 ± 9.4 | 0.0014 |
| Sex | | | | | 0.0928 |
| Men | 65.9 | 67.0 | 56.8 | 64.6 | |
| Education, years | | | | | < 0.0001 |
| < 12 | 63.6 | 57.9 | 69.3 | 75.3 | |
| 12–14 | 23.0 | 25.4 | 18.2 | 18.2 | |
| > 14 | 13.4 | 16.6 | 12.5 | 6.5 | |
| Occupational status | 16.6 | 19.7 | 17.0 | 9.8 | < 0.0001 |
| Living below the poverty line, INSEE 2016 | 19.5 | 17.0 | 20.0 | 24.8 | 0.0003 |
| Living alone | 22.2 | 20.1 | 26.4 | 26.4 | 0.0014 |
| CKD stage at census time | | | | | 0.23 |
| Stage 3 | 55.1 | 56.4 | 48.9 | 53.0 | |
| Stage 4 | 44.9 | 43.6 | 51.1 | 47.0 | |
| Medical history | | | | | |
| Cardiovascular disease[a] | 52.2 | 48.6 | 44.3 | 61.0 | < 0.0001 |
| Hypertension | 90.9 | 87.9 | 92.0 | 97.3 | < 0.0001 |
| Diabetes[b] | 42.6 | 29.8 | 0.0 | 75.6 | < 0.0001 |
| Coronary heart disease | 20.5 | 17.9 | 11.7 | 27.0 | < 0.0001 |
| Heart failure | 11.0 | 9.4 | 5.7 | 15.2 | < 0.0001 |
| Stroke | 9.4 | 8.7 | 5.8 | 11.3 | 0.0664 |
| Peripheral vascular disease | 12.5 | 10.8 | 3.4 | 17.4 | < 0.0001 |
| Obstructive sleep apnea syndrome (OSA) | 14.1 | 6.4 | 19.5 | 30.1 | < 0.0001 |
| Respiratory diseases except OSA | 13.7 | 11.9 | 10.3 | 18.1 | 0.0001 |
| Epilepsy | 1.3 | 1.5 | 1.2 | 1.0 | 0.6643 |
| Multiple sclerosis | 0.2 | 0.2 | 0.0 | 0.1 | 0.8973 |
| Parkinson's disease | 0.3 | 0.3 | 1,1 | 0,3 | 0.3576 |
| Depression | 7.0 | 6.3 | 8.0 | 8.7 | 0.0885 |
| Osteoporosis | 4.2 | 4.7 | 4.5 | 2.9 | 0.1184 |
| Arthritis | 20.0 | 16.9 | 28.4 | 25.9 | < 0.0001 |
| Gastrointestinal bleeding | 3.8 | 3.4 | 1.1 | 5.0 | 0.0709 |
| Blood pressure (BP) | | | | | |
| Systolic BP, mm Hg | 142.5 ± 20.5 | 141.0 ± 20.4 | 141.9 ± 17.9 | 146.0 ± 20.7 | < 0.0001 |
| Diastolic BP, mm Hg | 78.2 ± 12.0 | 78.4 ± 11.7 | 81.9 ± 11.5 | 77.5 ± 12.8 | 0.0030 |
| SBP ≥ 130 and/or DBP ≥ 85 | 76.7 | 74.5 | 79.3 | 81.5 | 0.0005 |
| Classification criteria | | | | | |
| Waist circumference, cm | 102.1 ± 16.1 | 94.4 ± 11.6 | 110.9 ± 10.8 | 118.4 ± 12.2 | |
| BMI, kg/m$^2$ | 28.6 ± 5.8 | 25.3 ± 3.0 | 33.4 ± 3.1 | 35.2 ± 4.6 | |
| Blood pressure abnormalities[c] | 95.9 | 94.7 | 94.3 | 98.9 | < 0.0001 |
| Triglycerides ≥ 1.7 mmol/l | 43.4 | 33.7 | 0.0 | 69.0 | < 0.0001 |
| HDL-c abnormalities[d] | 34.3 | 26.5 | 1.1 | 54.5 | < 0.0001 |
| Carbohydrate disorder[e] | 51.8 | 38.9 | 0.0 | 84.3 | < 0.0001 |
| Laboratory variables | | | | | |
| CKD-EPI eGFR, ml/min/1.73 m$^2$ | 33.0 ± 12.1 | 33.4 ± 12.3 | 32.3 ± 11.5 | 32.2 ± 11.8 | 0.0506 |
| Anemia | 40.3 | 39.3 | 29.5 | 43.8 | 0.0126 |
| Quality of life | | | | | |
| In general, would you say your health is[f] | | | | | < 0.0001 |
| Excellent | 0.4 | 0.6 | 0.0 | 0.1 | |

**Table 1** (continued)

| | All<br>*N* = 2597<br>%/m ± SD* | Non-obese<br>*N* = 1724 (66.4%)<br>%/m ± SD | MHO<br>*N* = 88 (3.4%)<br>%/m ± SD | MUO<br>*N* = 785 (30.2%)<br>%/m ± SD | *p*** |
|---|---|---|---|---|---|
| Very good | 3.6 | 5.0 | 1.2 | 0.8 | |
| Good | 58.3 | 62.7 | 65.9 | 47.7 | |
| Fair | 31.6 | 26.9 | 23.2 | 42.9 | |
| Poor | 6.1 | 4.9 | 9.8 | 8.5 | |
| CES-D 10 (0–30) | 7.6 ± 5.2 | 7.0 ± 4.9 | 7.2 ± 5.5 | 8.8 ± 5.6 | < 0.0001 |

*% or means ± standard deviation

**$\chi^2$ test for qualitative variables, variance analysis for quantitative variables

[a]Coronary heart disease, stroke, peripheral vascular disease, heart failure, dysrhythmia, or valvular disease

[b]Diabetes reported in medical records or glucose-lowering medication or HbA1c ≥ 6.5% or fasting glucose ≥ 7.0 mmol/l or random glucose ≥ 11.0 mmol/l

[c]SBP ≥ 130 and/or DBP ≥ 85 mm Hg or hypertension history or antihypertensive treatment

[d]HDL-c < 1.04 mmol/l for men and < 1.29 mmol/l for women

[e]Random glycemia ≥ 6.1 mmol/l or diabetes

[f]Results from the 1st question of SF-12

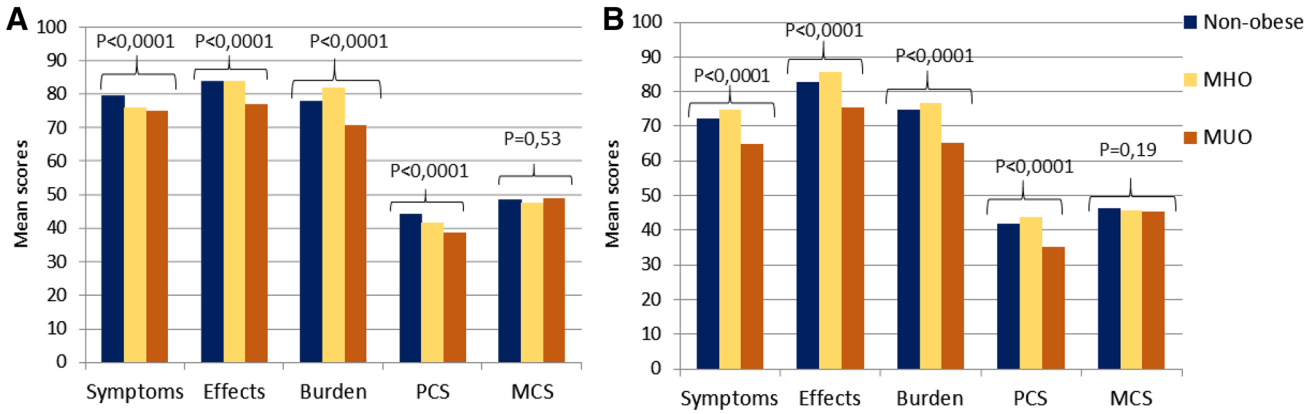


**Fig. 1** KDQoL-36™ score in men (**a**) and women (**b**) with stages 3–4 CKD

worse in MUO patients compared to those in non-obese patients. MHO patients got similar scores to those in non-obese patients (Table 4).

## Secondary objective

In total, 26.7% of patients got a score > 10/30 on CES-D10 indicating depressive symptomatology. When we considered obesity phenotypes, 21% of non-obese, 22.1% of MHO, and 29.8% of MUO patients got a score > 10/30 on CES-D10 ($p < 0.0001$).

Among the patients with depressive symptoms, 92 patients (14.7%) had a history of depression recorded in the medical record.

In the multivariate analysis, after adjustment for significant sociodemographic variables and comorbidities, there was no association between obesity phenotypes and the presence of depressive symptoms ($p = 0.43$). There was no significant difference in risk between MUO and non-obese patients (OR = 1.14, 95% CI [0.88–1.5]) and between MHO and non-obese patients (OR = 0.87; 95% CI [0.5–1.6]).

## Discussion

This study demonstrates an association between obesity phenotypes and QoL in NDD-CKD patients (stage 3–4 CKD). Compared to non-obese patients, MUO patients had a worse QoL on all CKD-specific dimensions of HRQoL and on PCS. The impact of CKD symptoms on QoL and on daily live was more harmful and levels of frustration were higher in MUO patients than in MHO and non-obese patients. In

**Table 2** Multivariate models of the association between obesity phenotypes and KDQOL-36 subscales

| | Non-obese | MHO | *p* | MUO | *p* |
|---|---|---|---|---|---|
| Symptoms | | | | | |
| Bivariate | Ref | −1.8 (−5.3 to 1.7) | 0.31 | −5.9 (−7.3 to −4.6) | <0.0001 |
| Sociodemographic adjusted model[a] | Ref | −0.2 (−3.8 to 3.3) | 0.89 | −4.2 (−5.8 to −2.7) | <0.0001 |
| Multivariate[b] | Ref | −0.7 (−4.3 to 2.9) | 0.71 | −3.0 (−4.0 to −0.9) | 0.0025 |
| Effect | | | | | |
| Bivariate | Ref | 0.9 (−2.8 to 4.7) | 0.61 | −7.3 (−8.8 to −5.8) | <0.0001 |
| Sociodemographic adjusted model[a] | Ref | 0.8 (−3.2 to 4.9) | 0.68 | −6.6 (−8.3 to −4.8) | <0.0001 |
| Multivariate[c] | Ref | 1.2 (−2.9 to 5.2) | 0.57 | −4.3 (−6.1 to −2.5) | <0.0001 |
| Burden | | | | | |
| Bivariate | Ref | 2.8 (−2.3 to 7.9) | 0.28 | −8.1 (−10.1 to −6.1) | <0.0001 |
| Sociodemographic adjusted model[a] | Ref | 3.3 (−2.0 to 8.7) | 0.22 | −5.3 (−7.6 to −3.0) | <0.0001 |
| Multivariate[d] | Ref | 2.7 (−2.7 to 8.0) | 0.31 | −3.6 (−6.0 to −1.2) | 0.0031 |
| PCS | | | | | |
| Bivariate | Ref | −1.0 (−3.1 to 1.1) | 0.37 | −6.0 (−6.8 to −5.1) | <0.0001 |
| Sociodemographic adjusted model[a] | Ref | 0.1 (−2.0 to 2.3) | 0.94 | −5.3 (−6.3 to −4.4) | <0.0001 |
| Multivariate[e] | Ref | −0.6 (−2.7 to 1.5) | 0.58 | −4.3 (−5.3 to −3.4) | <0.0001 |
| MCS | | | | | |
| Bivariate | Ref | −1.2 (−2.8 to 0.4) | 0.14 | −0.4 (−1.0 to 0.3) | 0.25 |
| Sociodemographic adjusted model[a] | Ref | −0.7 (−2.5 to 1.0) | 0.39 | 0.4 (−0.4 to 1.0) | 0.33 |
| Multivariate[f] | Ref | −0.8 (−2.5 to 0.9) | 0.37 | 0.6 (−0.2 to 1.3) | 0.12 |

[a]Mixed effect model adjusted for sex, age, education, occupational status, living below the poverty line, living alone

[b]Mixed effect model adjusted for sex, occupational status, living below the poverty line, anemia, sleep apnea syndrome, and comorbidities: arthropathy, osteoporosis, asthma, obstructive pulmonary disease, heart failure, myocardial infarction, neurological disease (multiple sclerosis, Parkinson's disease), stroke, peripheral vascular disease, upper gastrointestinal tract disease (gastrointestinal bleeding), and depression

[c]Mixed effect model adjusted for age, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[d]Mixed effect model adjusted for sex, age, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[e]Mixed effect model adjusted for sex, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[f]Mixed effect model adjusted for sex, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

**Table 3** Multivariate models of the association between obesity phenotypes and KDQOL-36™ subscales at inclusion after removing underweight ($n=2653$)—sensitivity analysis

| | Non-obese | MHO | *p* | MUO | *p* |
|---|---|---|---|---|---|
| Symptoms[a] | Ref | −0.7 (−4.3 to 2.9) | 0.71 | −2.5 (−4.1 to −0.9) | <0.0025 |
| Effect[b] | Ref | 1.0 (−2.9 to 5.0) | 0.60 | −4.5 (−6.3 to −2.7) | <0.0001 |
| Burden[c] | Ref | 2.7 (−2.6 to 8.0) | 0.31 | −3.7 (−6.1 to −1.3) | <0.0024 |
| PCS[d] | Ref | −0.6 (−2.7 to 1.5) | 0.59 | −4.3 (−5.3 to −3.4) | <0.0001 |
| MCS[e] | Ref | −0.8 (−2.5 to 0.9) | 0.38 | 0.6 (−0.2 to 1.4) | 0.12 |

[a]Mixed effect model adjusted for sex, occupational status, living below the poverty line, anemia, sleep apnea syndrome, and comorbidities: arthropathy, osteoporosis, asthma, obstructive pulmonary disease, heart failure, myocardial infarction, neurological disease (multiple sclerosis, Parkinson's disease), stroke, peripheral vascular disease, upper gastrointestinal tract disease (gastrointestinal bleeding), and depression

[b]Mixed effect model adjusted for age, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[c]Mixed effect model adjusted for sex, age, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[d]Mixed effect model adjusted for sex, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[e]Mixed effect model adjusted for sex, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

**Table 4** Multivariate models of the association between obesity phenotypes and KDQOL-36™ subscales at inclusion after removing diabetic patients ($n = 1491$)—sensitivity analysis

| | Non-obese | MHO | *p* | MUO | *p* |
|---|---|---|---|---|---|
| Symptoms[a] | Ref | −1.2 (−4.7 to 2.4) | 0.52 | −2.5 (−5 to −0.1) | < 0.046 |
| Effect[b] | Ref | 0.1 (−3.7 to −3.9) | 0.94 | −3.3 (−6.1 to −0.6) | < 0.016 |
| Burden[c] | Ref | 0.8 (−4.5 to 6.0) | 0.77 | −2.0 (−5.8 to 1.8) | < 0.31 |
| PCS[d] | Ref | −1.2 (−3.3 to 0.9) | 0.27 | −3.9 (−5.5 to −2.3) | < 0.0001 |
| MCS[e] | Ref | −0.8 (−2.5 to 1.0) | 0.39 | 1.0 (−0.3 to 2.3) | 0.11 |

[a]Mixed effect model adjusted for sex, occupational status, living below the poverty line, anemia, sleep apnea syndrome, and comorbidities: arthropathy, osteoporosis, asthma, obstructive pulmonary disease, heart failure, myocardial infarction, neurological disease (multiple sclerosis, Parkinson's disease), stroke, peripheral vascular disease, upper gastrointestinal tract disease (gastrointestinal bleeding), and depression

[b]Mixed effect model adjusted for age, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[c]Mixed effect model adjusted for sex, age, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[d]Mixed effect model adjusted for sex, occupational status, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

[e]Mixed effect model adjusted for sex, living below the poverty line, eGFR, anemia, sleep apnea syndrome, and comorbidities

our study, the frequency of MHO phenotype was low in CKD patients. Characteristics and QoL scores in MHO patients were close to those in non-obese patients. Multivariate analyses displayed in Table 2 highlight a significant impact of comorbidities on HRQoL in MUO patients. Despite this observation, we have shown that obesity phenotypes were associated with QoL in CKD patients, but independently from comorbidities. The differences in QoL between MHO and MUO patients can be explained by several factors. Firstly, the majority of MUO patients were diabetic patients with potential microvascular complications, such as peripheral neuropathies that could affect QoL. In the sensitivity analysis removing diabetic patients, there were moderate but persistent differences in QoL. Secondly, the differences observed may be explained by a difference in BMI between MHO and MUO patients. We found a significant quantitative interaction between BMI and obesity phenotype only in MUO patients suggesting that BMI had a greater impact on QoL in MUO than in other patients. Thirdly, physical abilities seemed to be stable in MHO patients as compared to MUO patients [36, 37]. In addition, fat distribution could also have an impact on physical capacities and, as a result, may also play a role in the impact of obesity on QoL. MCS was a very singular dimension for which a few variables seemed to influence it. However, obesity phenotypes were not associated with MCS.

HRQoL scores in disease-specific dimensions were relatively high in this population compared to those previously published in dialysis populations [38, 39]. The impact of CKD regarding burden of symptoms and impairment of QoL is differently perceived by dialysis and non-dialysis patients. The KDQoL-36 ™ was first of all developed to assess QoL in patients undergoing chronic dialysis. It has, however, been used in CKD patients without the need of renal replacement therapy, but it is not yet proven that questions asked in this questionnaire are well appropriate to assess the impact of CKD on QoL in the early stages of the disease. KDQoL-36™ is the abbreviated version of the KDQoL™ which French version has been validated. Although KDQoL-36™ has not been validated in a French population of CKD patients at early stages (3–4), it seems, however, reasonable to use it in non-dialysis patients as it is the abbreviated version of a validated instrument. In addition, its English version has been validated in the Chronic Renal Insufficiency Cohort (CRIC) study which included mild-to-moderate (stage 2–4) CKD patients [40]. Despite the significant number of detailed questions, this abbreviated version is easier to routinely administrate than the original version, especially in a large cohort such as the CKD-REIN.

In addition, there are many data on HRQoL in dialysis patients. Fukuhara et al. found very poor HRQoL scores in European dialysis patients included in the international DOPPS cohort [41]. These scores were lower than those found in our cohort. For instance, average score for the burden dimension was 35.5 in the DOPPS cohort vs. 74.4 in the CKD-REIN cohort. QoL scores for NDD-CKD patients were higher in the CRIC cohort than in the CKD-REIN cohort [11]. In the CRIC cohort, non-obese (BMI < 30) and obese patients (BMI ≥ 30) got higher scores than those in the CKD-REIN cohort. The average scores for non-obese and obese patients included in the CRIC cohort were 85.5 ± 13.9 and 81.8 ± 15.3 for symptoms, 90.7 ± 14.3 and 87.9 ± 16.5 for effects 83.2 ± 23.5 and 81.3 ± 24.0 for burden, 51.0 ± 10 and 49.9 ± 10.9 for MCS, and 44.1 ± 11 and 39.1 ± 11.4 for PCS, respectively. Such differences may be explained by a younger age of patients (average age of 58 years) and a

higher proportion of stage 2–3 CKD (80%) in the CRIC cohort, and by a cultural difference between the two cohorts. Mujais et al. found QoL scores close to ours in their CKD cohort [42].

QoL was associated with increased risk of hospitalization and death from any cause in the study conducted by Lopes et al. [43]. The authors showed that the mortality risk score increased by 11%, 7%, and 6% every loss of five points for PCS, MCS, and the disease-specific dimensions (symptoms, effects, and burden), respectively. In our study, differences in scores between obesity phenotypes appear to be clinically relevant.

Regarding obese population, Lopez-Garcia et al. [44] were interested in QoL in the general population according to obesity phenotypes using SF-12. They showed that having a metabolic syndrome or being obese worsened PCS. They found that compared to metabolically healthy non-obese individuals, MHO patients had as poor a PCS score as MUO patients. These results differed from our findings. This difference can be explained in part by a difference between the study populations: Lopez-Garcia et al. included younger individuals with less comorbidities than those included in our study. In addition, there were no CKD patients in their study population.

To our knowledge, this is the first study focusing on QoL according to obesity phenotypes in a population of stage 3–4 CKD patients. This study is based on a representative cohort of CKD patients (stage 3–4) monitored in a nephrology consultation. QoL questionnaires were self-administered which minimized social desirability response bias. The answer rate (89%) was very good in our study.

This study had several limitations. First, because of its cross-sectional design, proof of the causal link between obesity phenotype and QoL cannot be provided. During the follow-up, changes in the QoL could possibly have been different among obesity phenotypes. Second, criteria for poor metabolic health status were those used in the general population. CKD patients have a higher metabolic risk than the general population. More than 90% of patients in the CKD-REIN cohort had a history of high blood pressure or were receiving an antihypertensive therapy. As a result, we selected the most metabolically healthy obese in the MHO group. Some criteria used in the general population, such as the HOMA-IR index, are not validated in CKD patients. In addition, other data, such as body composition, were not collected in the CKD-REIN cohort. Body composition would have allowed us to refine the criteria for identification of groups.

Many variables were collected in our study. The 5-year planned follow-up for the CKD-REIN cohort will permit additional findings to support exploratory results presented in this article. There are still many unanswered questions: Is there a MHO/MUO continuum? What is the evolution of QoL according to obesity phenotypes? What is the fate of these patients in terms of CKD progression and complications (renal and non-renal)?

In conclusion, we performed a cross-sectional study which demonstrated that obesity phenotypes were associated with QoL in NDD-CKD patients. In this study, MUO patients had a worse QoL than non-obese and MHO patients independently of comorbidities.

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## Compliance with ethical standards

**Conflict of interest** CKD-REIN is supported by a public–private partnership with funding from 9 pharmaceutical companies as listed above. All authors declare that they have no relevant financial interests.

**Ethics approval** All legal authorizations were obtained including those from the *Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* (CCTIRS No 12.360), the *Commission nationale de l'informatique et des libertés* (CNIL No DR-2012-469), and the *Comité de protection des personnes* IDF VII (CPP No IDRCB 2012-A00902-41). CKD-REIN biological collection is registered in the management application of the *COnservation D'Eléments du COrps Humain* (CODECOCH No-2012-1624). The *Institut national de la santé et de la recherche médicale* (Inserm) Institutional Review Board approved the study protocol (IRB00003888).

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