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Short-term evaluation of renal markers in overweight adult cats

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Abstract

Background: Obesity has been proposed as an independently risk factor for chronic kidney disease (CKD) in people, but its role in feline kidney function is unknown.

Objective: Obesity has been proposed as an independent risk factor for chronic kidney disease (CKD) in people, but its role in feline kidney function is unknown. This study prospectively evaluated the effect of overweight on the concentration of symmetric dimethylarginine (SDMA) and creatinine in a cohort of healthy cats.

Methods: Forty healthy adult cats were included, 14 with a body condition score (BCS) = 5 and 26 with a BCS > 5. Cats were examined every 6 months, for up to 12 months. SDMA and creatinine were measured at baseline and follow-up.

Results: No effect was found for time of follow-up ($p = 0.072$), overweight ($p = 0.9442$) or their interaction ($p = 0.902$) on SDMA, though a significant effect was found for age ($p < 0.001$) [older cats showing higher SDMA] and sex ($p = 0.007$) [male cats showing higher SDMA]. Regarding creatinine, no effect for time ($p = 0.671$), age ($p = 0.061$), overweight ($p = 0.319$) or the latter's interaction ($p = 0.386$) were found.

Conclusions: In the short term, markers of renal function did not show an association with overweight. The role of obesity in feline kidney function still warrants further evaluation.

KEYWORDS
chronic kidney disease, creatinine, obesity, symmetric dimethylarginine

1 | INTRODUCTION

Obesity has risen to epidemic proportions in people and companion animals. Approximately 39% of the adult population is overweight and 13% is obese (World Health Organization, 2021). In a similar manner, 30.5–50% of domestic cats are estimated to be overweight or obese (Hoenig, 2012; Öhlund et al., 2018; Wall et al., 2019). Furthermore, obese cats show similar complications to people with obesity, such as dyslipidaemia and insulin resistance. Obesity and physical inactivity are the main risk factors for the development of type 2 diabetes in both humans and cats (Gilor et al., 2016; Hoenig, 2012). In addition, in humans, diabetes is the first cause of chronic kidney disease (CKD); and different studies have suggested that obesity and metabolic syndrome could also be independently associated with CKD (de Vries et al., 2014; Denic et al., 2017; Foster et al., 2011; Stefansson et al., 2016; Wahba et al., 2007). Glomerular hyperfiltration and albuminuria, which are common findings in early diabetic nephropathy, have been detected in non-diabetic obese patients (Chagnac et al., 2000; Denic et al., 2017; Stefansson et al., 2016), and people with higher body mass index could be at higher risk of CKD (Denic et al., 2017; Hsu et al., 2006). In addition, structural kidney changes have been observed in obese patients in association to ectopic lipid accumulation or fatty kidney (de Vries et al., 2014).

In cats, disorders associated with CKD include diseases of the lower urinary tract, renal lymphoma, infections, hyperthyroidism, nephrotoxic drugs and genetic kidney diseases, although the cause of CKD

is often unknown (Reynolds et al., 2013). The role of obesity on the development of CKD has been considered to be minor. Recently, one study showed that neither concentrations of SDMA nor other serum or urinary renal markers were different between cats with normal body condition score (BCS) and cats with a BCS > 5 (1–9), suggesting that obesity might not have an effect on CKD (Pérez-López et al., 2019). Similarly, one retrospective epidemiological study reported that, after ruling out dehydration, cats with greater body weight were less likely to develop CKD (Greene et al., 2014). In addition, body weight was significantly associated with survival time in cats with CKD in another study. However, a U-shaped relationship was also described, both the lowest and highest body weights being associated with shorter survival times (Freeman et al., 2016). Since association between obesity and CKD has hardly been studied in cats, further evaluation may shed light on this topic.

The aim of this study was to prospectively assess the effect of overweight on SDMA and creatinine, two established markers of kidney function, in a cohort of healthy cats.

2 | MATERIAL AND METHODS

A longitudinal study was performed at the Veterinary Teaching Hospital of the University of Las Palmas de Gran Canaria. Clinically healthy cats, aged five years or more, were consecutively included. The owners participated voluntarily after signing an informed consent form. Exclusion and inclusion criteria were the same as described previously in a cross-sectional study undertaken with the same animals (Pérez-López et al., 2019). Briefly, cats with CKD, diabetes or other disorders were excluded. CKD was defined as serum creatinine ≥1.6 mg/dl plus urinary specific gravity (USG) < 1.035 or a urinary protein-creatinine ratio (UPC) > 0.4 (International Renal Interest Society, 2019). Cats were classified according to their BCS (1–9) as normal-weight (BCS = 5), overweight (BCS = 6–7) or obese (BCS > 7). Overweight and obese cats were combined into the overweight group (BCS > 5), to simplify the interpretation of the results.

The study lasted 12 months; during this period, cats were examined every 6 months. They were assessed after a minimum of 12 h of fasting (without water deprivation), and underwent physical examination, blood and urine sampling (cystocentesis or home collection).

2.1 | This study was approved by the Animal Welfare Ethics Committee of the University of Las Palmas de Gran Canaria; Reference number 10/2018

2.1.1 | Analytical procedures

Blood samples were obtained in serum separator tubes, which were centrifuged and aliquoted within 20 min. Some of those aliquots were frozen and kept at −80°C until processed. Creatinine, urea, glucose, alkaline phosphatase activity, alanine aminotransferase activity, total proteins, globulins, albumin and glucose were measured in fresh or refrigerated serum samples within 24 h. Cholesterol, triglycerides and SDMA were measured in refrigerated serum samples within 24 h in 12 cats at baseline, and in frozen serum samples in the rest of cats and consecutives visits. All analytes were measured by spectrophotometry.

USG, urinary dipstick, and urinary sediment examination were performed within 24 h after urine collection. Urine samples were aliquoted and frozen (−80°C) for later measurement of urinary protein and creatinine by colorimetry (Animal Lab, Las Palmas de Gran Canaria).

2.2 | Statistical analysis

This study is the continuation of a previous cross-sectional study. For the latter, a minimal sample size of 16 cats per group was estimated to be needed to detect a difference of 10 μg/dl in SDMA between groups, with a 90% probability and a two-sided significance level of 0.05, after assuming a standard deviation of 8.3 μg/dl (Hall et al., 2014a; Massachusetts General Hospital Biostatistics Center, 2019). The mentioned study included 17 cats with BCS = 5 and 37 with BCS > 5. After that, two more cats were included adding up to 18 cats with BCS = 5 and 38 cats with BCS > 5. All these cats were attempted to be followed every 6 months for a maximum period of 12 months. Only cats with a minimum follow-up of 6 months were included in the statistical analysis.

Categorical variables are expressed as number of cats and percentages. Distribution of quantitative variables was assessed using the Shapiro–Wilk test. Normally distributed quantitative variables are shown as mean and standard deviation. Non normal quantitative variables are presented as medians and interquartile ranges (IQR). Crude differences between variables at different visits (0, 6, 12 months) were evaluated through a one-way repeated measures ANOVA for normally distributed variables, or through Skilling-Mack test (Skillings & Mack, 1981) for non-normally distributed variables (due to the presence of missing values). Student's *t*-test or Mann Whitney's *U* test were used for comparing variables at baseline between overweight and not overweight cats.

Statistical analysis was performed with the R software version 3.6.1 (R Development Core Team). Package tidyverse was used for figures and tables, and package nlme version 3.1–141 for fitting the linear mixed models (Pinheiro et al., 2020; R Core Team, 2020; Wickham et al., 2019).

3 | RESULTS

A total of 56 cats were included for a baseline visit, though 16 did not return for follow-up, despite several attempts to reschedule their appointments. Thus, 40 cats were included: 18 neutered males and 22 (21 neutered) females and their median age was 6.8 (5.3–10) years.

TABLE 1 Main baseline features of the 40 cats included in the study

Variable	BCS = 5 *N* = 14	BCS > 5 *N* = 26	*p*
Age (years)	5.92 (5.38–8.69)	7.17 (5.33–9.90)	0.58
Albumin (g/dl)	2.98 (0.32)	3.23 (0.28)	0.02
ALKP (U/L)	34.00 (14.25–39.75)	26.50 (18.00–34.00)	0.90
ALT (U/L)	43.00 (39.50–63.25)	54.50 (43.75–68.75)	0.27
Cholesterol (mg/dl)	160.85 (64.62)	167.64 (38.00)	0.73
Creatinine (mg/dl)	1.61 (0.33)	1.76 (0.30)	0.18
Globulin (g/dl)	4.15 (3.95–4.30)	4.30 (3.82–4.47)	0.94
Glucose (mg/dl)	113.00 (98.00–189.50)	130.50 (107.25–196.00)	0.60
SDMA (μg/dl)	9.00 (7.00–12.00)	9.50 (8.00–11.00)	0.49
Total proteins (g/dl)	7.26 (0.62)	7.43 (0.54)	0.41
Triglycerides (mg/dl)	46.00 (38.50–73.00)	85.50 (65.25–99.00)	0.002
UPC	0.14 (0.09–0.21)	0.10 (0.09–0.18)	0.45
Urea (mg/dl)	46.57 (13.98)	45.65 (7.33)	0.82
USG	1050.00 (1044.00–1051.00)	1050.00 (1045.75–1052.75)	0.33
Weight (kg)	3.90 (0.87)	5.84 (1.23)	<0.0001

Note. At baseline SDMA was missing in one cat with BCS = 5 and two cats with BCS > 5. Cholesterol was missing in one cat with BCS = 5 and one cat with BCS > 5. Triglycerides were missing in one cat with BCS = 5 and two cats with BCS > 5. Ratio UPC was missing in six cats with BCS = 5 and five cats with BCS > 5. USG was missing in five cats with BCS = 5 and four cats with BCS > 5. The other variables were measured in the total of 40 cats.
Abbreviations: BCS: body condition score; ALT: alanine aminotransferase; ALKP: alkaline phosphatase activity; SDMA: symmetric dimethylarginine; UPC: urine protein/creatinine ratio; USG: urinary specific gravity.

Breed distribution was as follows: domestic short hair (31), Siamese (3), mixed Persian (3), domestic long hair (1), Persian (1), and Angora (1). In total, 14 cats had a BCS = 5 (5 males, 9 females) and 26 cats a BCS > 5 (13 males, 13 females). Among cats with BCS > 5, 19 had a BCS between 6 and 7 and 7 cats had a BCS > 7. The median follow-up of the cats was 6 (0–12) months. Their baseline features are displayed in Table 1, and the main results during follow-up are displayed in Table 2.

3.1 | Effect of overweight

3.1.1 | SDMA

SDMA was measured in 37 cats (13 cats with BCS = 5 and 24 cats with BCS > 5). The linear mixed model showed no effect of overweight (p = 0.944), follow-up time (p = 0.072) or their interaction (p = 0.902) on SDMA. However, there was a significant effect for sex (male) [1.88 (95% CI: 0.62, 3.15); p = 0.007] and for age; SDMA increased on average 0.048 (95% CI: 0.03–0.07) μg/dl per month of age (p < 0.001) (see Figure 1),

3.2 | Creatinine

This variable was measured in all of the 40 cats (14 cats with BCS = 5 and 26 cats with BCS > 5). The linear mixed model did not show any effect of overweight (p = 0.319), follow-up time (p = 0.671), age (p = 0.061), sex (0.072) or their interaction (p = 0.386) on creatinine (see Figure 2).

4 | DISCUSSION

In this small sample of clinically healthy cats, SDMA and creatinine, which are established markers of renal function (International Renal Interest Society, 2019), did not show a significant change after a median follow-up of 6 months. Neither did these markers differ between cats with BCS = 5 and cats with BCS > 5. Therefore, the results of this prospective study add to previous reports that suggest that overweight does not have a relevant influence on kidney function in healthy cats (Greene et al., 2014; Pérez-López et al., 2019). A retrospective, epidemiological study reported that, after ruling out dehydration, cats with greater body weight were less likely to develop CKD (Greene et al., 2014). A cross-sectional study showed similar concentrations of SDMA and other renal markers in cats with normal and high BCS (Pérez-López et al., 2019).

These findings are opposed to those observed in people, since higher body mass index has been found to be an independent risk factor for the decline in glomerular filtration rate (GFR) (CKD Prognosis Consortium [CKD-PC], 2019; Denic et al., 2017), and structural kidney changes have been reported in obese patients due to ectopic lipid accumulation (de Vries et al., 2014). The latter can cause renal compression, which may lead to activation of the renin angiotensin aldosterone

TABLE 2 Variables measured at baseline and follow up visits (6 and 12 months)

Variable	Time = 0	Time = 6	Time = 12	*p*
Albumin (g/dl)	3.15 (0.32) [40]	3.11 (0.24) [35]	3.15 (0.29) [31]	0.469
ALKP (U/L)	28.50 (17.75–39.25) [40]	25.00 (16.00–37.50) [35]	31.00 (22.00–42.50) [31]	0.656
ALT (U/L)	50.00 (41.00–68.25) [40]	52.00 (41.50–65.00) [35]	51.00 (40.50–70.00) [31]	0.696
Cholesterol (mg/dl)	162.50 (125.50–195.50) [38]	177.50 (123.50–201.75) [26]	166.00 (148.25–191.50) [26]	0.287
Creatinine (mg/dl)	1.71 (0.32) [40]	1.73 (0.41) [36]	1.70 (0.35) [31]	0.905
Globulin (g/dl)	4.20 (3.90–4.43) [40]	4.00 (3.90–4.20) [35]	4.00 (3.80–4.30) [31]	0.226
Glucose (mg/dl)	26.50 (104.25–168.25) [38]	117.00 (102.00–160.00) [29]	104.50 (88.50–171.75) [24]	0.416
SDMA (μg/dl)	9.00 (8.00–11.00) [37]	9.00 (7.50–12.00) [23]	10.00 (9.00–12.00) [23]	0.206
Total proteins (g/dl)	7.35 (6.90–7.73) [40]	7.20 (6.80–7.45) [35]	7.10 (6.95–7.80) [31]	0.055
Triglycerides (mg/dl)	73.00 (48.50–93.00) [35]	76.00 (54.00–110.00) [21]	75.00 (61.50–92.25) [20]	0.423
UPC	0.10 (0.09–0.19) [29]	0.14 (0.11–0.17) [24]	0.12 (0.10–0.18) [22]	0.202
Urea (mg/dl)	45.00 (40.50–51.25) [40]	43.00 (39.00–47.00) [35]	43.00 (39.00–47.00) [30]	0.222
USG	1050.00 (1045.00–1052.00) [31]	1047.00 (1041.25–1051.00) [30]	1047.00 (1042.00–1048.75) [26]	0.282
Weight (kg)	5.16 (1.45) [40]	5.30 (1.59) [36]	5.11 (1.67) [30]	0.325

Note. The number of cats for each measurement at each time point is shown in square brackets. Normally distributed data are given as mean and standard deviation, whereas non-normally distributed data are given as median and IQR (25th–75th percentile).
Abbreviations: ALT, alanine aminotransferase; ALKP, alkaline phosphatase activity; SDMA, symmetric dimethylarginine; UPC, urine protein/creatinine ratio; USG, urinary specific gravity.

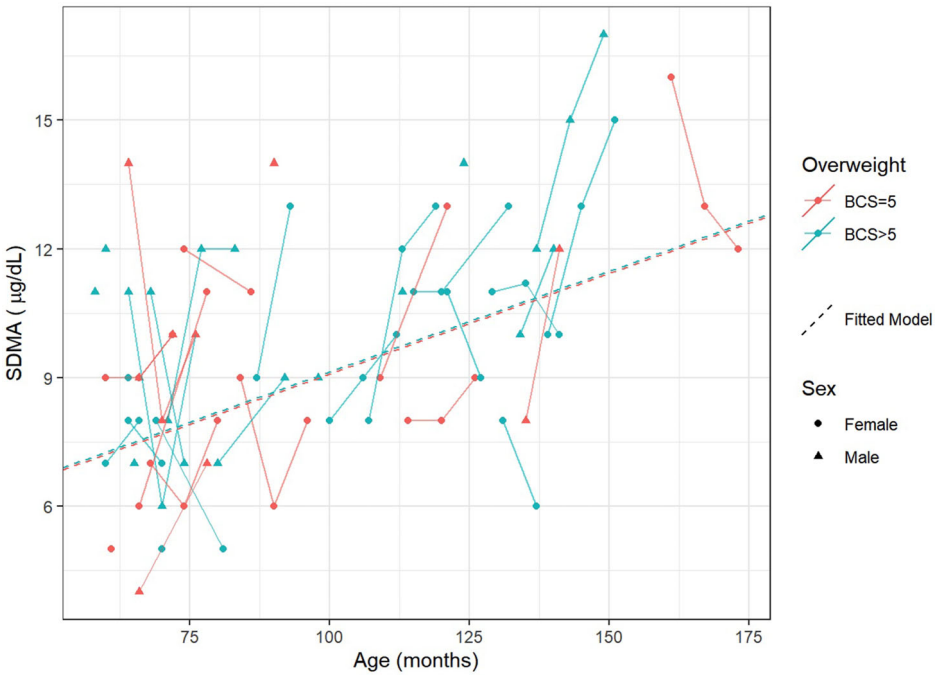

FIGURE 1 SDMA concentration according to sex and age in cats with BCS = 5 and cats with BCS > 5 after a median follow-up of 6 months. The triangles (male) and circles (female) linked with solid lines represent SDMA measurements performed in the same cat during their follow-up period. Broken lines represent the effect of age on SDMA according to whether the cats had a normal body condition score (red) or were overweight (green). The slope is significant ($p < 0.001$) but the distance between the lines is not ($p = 0.944$), reflecting the effect of age and lack of effect of overweight, respectively

system and glomerular hyperfiltration (Mende et al., 2019). The fatty kidney has been linked to the development of CKD and hypertension in people (Foster et al., 2011; Mende et al., 2019). Furthermore, perirenal or kidney tissue fat has also been detected in some animals with obesity. Obese rabbits have accumulation of sinus fat in their kidneys, as well as higher blood pressure, compared to controls (Dwyer et al., 1995; Dwyer et al., 2000). In addition, pigs fed a high-fat diet develop some of the characteristics of the human metabolic syndrome, and

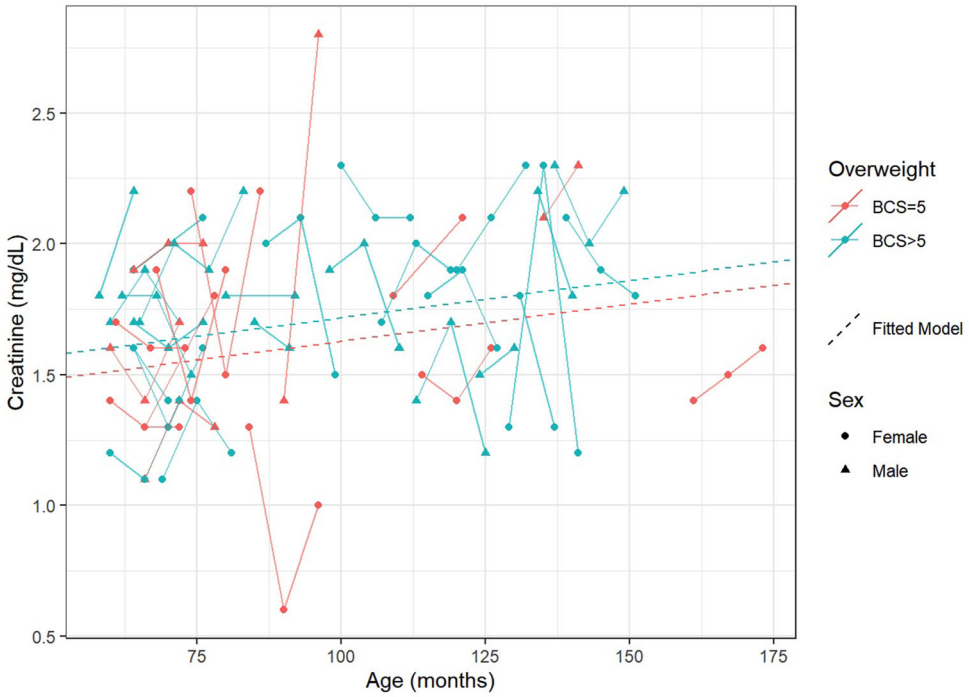

FIGURE 2 Creatinine concentration according to age and sex in cats with BCS = 5 and cats with BCS > 5 after a median follow-up of 6 months. The triangles (male) and circles (female) linked with solid lines represent creatinine measurements performed in the same cat during their follow-up period. Broken lines represent the effect of age on creatinine according to whether the cats had a normal body condition score (red) or were overweight (green). Neither the slope ($p = 0.061$) nor the distance between the lines ($p = 0.319$) is significant, reflecting the lack of effect of age and overweight, respectively.

structural kidney changes associated with kidney tissue fat deposits have been observed (Rodríguez-Rodríguez et al., 2020). Similarly, in dogs, obesity can lead to increased blood pressure, hyperinsulinaemia, activation of the renin-angiotensin system, glomerular hyperfiltration and structural kidney changes, such as increased mesangial matrix and thickening of the glomerular and tubular basement membranes (Henegar et al., 2001). To our knowledge, no histological studies have been specifically performed in obese cats.

In agreement with a previous study, our analyses did not show a significant effect of age on the progression of creatinine concentration in adult and mature healthy cats (Reynolds et al., 2010). In addition, the linear mixed model showed an effect of age on the progression of SDMA. The age range of the cats included in the present study was rather small, and therefore, results regarding the effect of age on SDMA should be interpreted carefully. However, it is reasonable to think that a physiological decrement of GFR associated to age might have occurred, as has been previously suggested (Hall et al., 2014b). Nonetheless, discrepancies exist about the correlation between GFR and age. One study reported differences between young (6–12 months) and aged adult cats (9–12 years) in GFR estimated with creatinine clearance, but not with iohexol clearance (van Hoek et al., 2007), whereas another study including cats of a wide age range (1–17 years) did not find a correlation between age and GFR by any of these methods (Heiene et al., 2009). On the other hand, this study suggested that among cats of the same age and same body condition score, those that are male might show a higher SDMA concentration. When a linear mixed effects model is fitted to predict SDMA as function of age, sex and visit, we arrive at the conclusion that there are no differences between visits ($p = 0.62$), but there is an effect of age ($p < 0.001$) and sex ($p = 0.007$). For every month of age SDMA increases by 0.048 units (95% CI: 0.026, 0.069). For the same age, male cats have an average SDMA concentration of 1.88 units greater than females (95% CI: 0.62, 3.15). More specifically, at the average age of 98.3 months, male cats have an SDMA concentration of 10.83 (95% CI: 9.85, 11.92), while female cats have a concentration 8.95 (95% CI: 8.08, 9.83). Larger studies may be needed to further evaluate this possible effect of sex on SDMA concentrations and whether this might affect the established thresholds to detect chronic renal disease in cats.

We acknowledge that this study has some limitations. Time of exposure to overweight may be crucial to observe changes in kidney function and may not have been long enough in this study, though we tried to minimise this effect by including cats that were at least 5 years old, knowing the incidence of obesity peaks in middle-aged (5–11 years) cats (German, 2006). On the other hand, the number of cats included is small, time of follow-up is relatively short and the amount of missing data might result in an underpowered study. Furthermore, the inclusion of cats older than 10 years will be necessary to obtain higher incidence of CKD.

In summary, in the short term, markers of renal function did not show an association with overweight in adult and mature cats. Further analysis with larger sample size and longer follow-up, or histological studies could be of interest. Furthermore, analysis through direct mea-

surements of glomerular filtration rate may be warranted for better evaluation of kidney function in overweight or obese cats.

AUTHOR CONTRIBUTIONS

Laura Pérez-López: conceptualisation, data acquisition, investigation, funding acquisition, methodology, resources, project administration, writing-original draft. Mauro Boronat: conceptualisation, investigation, methodology, supervision, writing-review and editing. Carlos Melián: funding acquisition, methodology, supervision, writing-review and editing. Ángelo Santana: formal analysis, resources, writing-review and editing. Yeray Brito-Casillas: investigation, methodology, resources, writing-review and editing. Ana M. Wägner: conceptualisation, investigation, funding acquisition, methodology, resources, project administration, supervision, writing-review and editing.

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

Data set and analyses are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the University's Animal Welfare Ethics Committee (Comité Ético de Bienestar Animal, CEBA-ULPGC), and the owners signed an informed content before the samples were obtained.

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PEER REVIEW

I would not like my name to appear with my report on Publons https://publons.com/publon/10.1002/vms3.1021.

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