Obesity does not modify the effect of continuous positive airway pressure on insulin resistance in adults with obstructive sleep apnoea

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To the Editor:

Obstructive sleep apnoea (OSA) and obesity are independent risk factors for the development of insulin resistance [1]. Studies on the impact of continuous positive airway pressure (CPAP) treatment on insulin resistance [2] have shown the CPAP significantly improved insulin resistance based on the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values in patients with type 2 diabetes and OSA. However, the effect of obesity on the insulin resistance response to CPAP treatment of adults with OSA is unknown. The goal of this study was to compare the changes in HOMA-IR following 4 months adherence to CPAP treatment in obese and non-obese adults with OSA. We postulated that HOMA-IR would improve with the reversal of OSA pathophysiology caused by adherence to CPAP treatment, and that the benefits of CPAP would differ in obese and non-obese individuals.

We analysed data from the Penn Iceland Sleep Apnea (PISA) (www.clinicaltrials.gov identifier number NCT03176732) cohort, and examined HOMA-IR at baseline and 4 months in obese and non-obese participants adherent to CPAP, and who did not self-report having diabetes and were not prescribed insulin or any oral hypoglycaemic agent. PISA was an observational study in adults with OSA adherent to CPAP; details of this study have been previously reported [3, 4].

Participants performed an overnight polysomnogram at baseline. Fasting blood draws and HOMA-IR measurements were performed at baseline and following 4 months CPAP treatment. HOMA-IR was calculated using the formula [5]:

$$\text{HOMA-IR} = \frac{\text{fasting blood glucose} \times \text{fasting plasma insulin}}{22.5}$$

Participants who had an average daily positive airway pressure (PAP) use $\geqslant 4\ \text{h}\cdot\text{day}^{-1}$ over $\geqslant 90$ days follow-up were included in this study. Body mass index (BMI) was used to classify participants as obese (BMI $>30\ \text{kg}\cdot\text{m}^{-2}$) or non-obese (BMI $\leqslant 30\ \text{kg}\cdot\text{m}^{-2}$).

Wilcoxon rank-sum and Fisher's exact tests were used to compare continuous and categorical variables, respectively, at baseline. HOMA-IR levels were natural logarithm transformed in all analyses. ln(HOMA-IR) at baseline and changes from baseline within and between BMI groups following CPAP treatment were evaluated. All analyses were restricted to participants with nonmissing values at both baseline and follow-up. Comparisons of changes from baseline in ln(HOMA-IR) and estimates of within-subject changes were evaluated in the context of a generalised linear model with subject-specific change scores as the outcome. Models were adjusted for baseline ln(HOMA-IR), baseline age, BMI, race, sex, site, 24-h mean arterial pressure and current smoking status. Results are presented as the ratio of follow-up to baseline values (*i.e.* the proportional change from baseline) for within-group changes and the ratio of change scores for between group comparisons. Statistical significance was based on $p<0.05$. SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6 (www.r-project.org) were used for all analyses.

Shareable abstract (@ERSpublications)
This study found no evidence that obesity significantly modifies the effect of 4 months of CPAP treatment on HOMA-IR. Longer duration of CPAP treatment may be needed in order to reduce insulin resistance and determine whether obesity modifies the effect. https://bit.ly/3CtX7jZ

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We evaluated 107 adults (84% males) with newly diagnosed OSA. Mean±SD BMI was 31.1±4.0 kg·m^{-2} and apnoea–hypopnea index (AHI) was 37.2±15.8 events per h. The mean±SD PAP adherence was 5.72 ±0.98 h CPAP usage per night overall, and 5.63±1.05 h in the obese and 5.85±0.87 h in the non-obese groups (p=0.152). Significant differences in baseline ln(HOMA-IR) were found between obese and non-obese participants (p=0.003), with higher ln(HOMA-IR) levels observed among the obese (4.43±0.61) compared to the non-obese (4.09±0.51). BMI was positively correlated with ln(HOMA-IR) (ρ=0.322, p=0.0007), whereas there was no significant association between AHI and ln(HOMA-IR) (ρ=0.027, p=0.783) among our sample of persons with OSA.

We found no statistically significant evidence that obesity modifies the effect of 4 months CPAP treatment on ln(HOMA-IR). Among obese participants, ln(HOMA-IR) showed a nonsignificant 8% increase from baseline to follow-up (1.08, 95% CI 0.98–1.18) compared to no meaningful change among the non-obese (0.98, 95% 0.86–1.11). Relatedly, the change in ln(HOMA-IR) among obese participants was 10% greater than in non-obese participants (1.10, 95% CI 0.94–1.30; p=0.25) but not statistically significant (figure 1).

We report on the impact of CPAP treatment on HOMA-IR in obese and non-obese adults with OSA following 4 months CPAP adherence. Obese participants with OSA demonstrated significantly higher HOMA-IR at baseline, which is consistent with literature showing increased HOMA-IR with increasing obesity [6]. The non-obese HOMA-IR levels were slightly lower compared to obese participants and this has previously been shown in the literature in the general population [7, 8]. The lack of correlation between baseline AHI and HOMA-IR is consistent with a prior study also showing no correlation with these parameters [9]. There were no differences in the response to 4 months CPAP treatment between obese and non-obese participants. Our results of no significant effect of CPAP on HOMA-IR are consistent with a prior small study showing no effect of 3 months CPAP in 42 men with type 2 diabetes and OSA who were randomised to receive therapeutic or placebo CPAP [10]. In contrast, a recent meta-analysis showed that CPAP may significantly improve HOMA-IR in individuals with type 2 diabetes and OSA [2], although they did not directly examine whether the effect of CPAP on HOMA-IR depends on obesity.

The strengths of our study include objective monitoring of hours of CPAP used, exclusion of self-reported diabetics and individuals on insulin or oral hypoglycaemic agents, and comprehensive measures of HOMA-IR at baseline and follow-up. The limitations of our study include the relatively small overall sample size and, in particular, a limited number of women. As our objective was to examine the

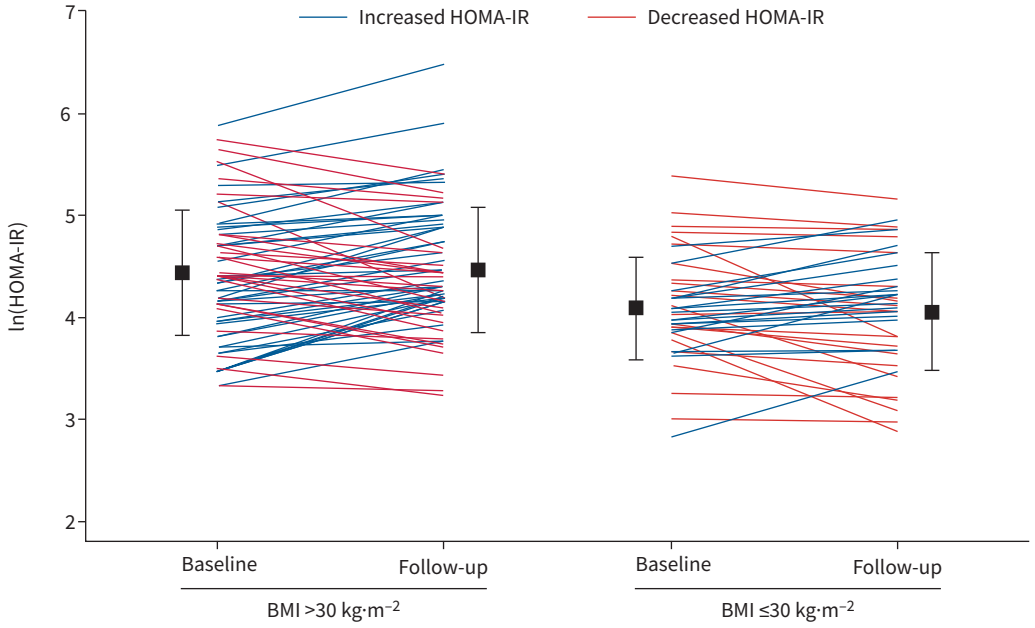

FIGURE 1 Natural logarithm transformed Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values in obese and non-obese participants before and after continuous positive airway pressure. Squares represent the mean and error bars, the standard deviation. BMI: body mass index.

differences in response to adequate CPAP therapy in obese and non-obese participants following CPAP treatment, we did not include those who did not adhere to therapy. Inclusion of these patients in future studies would be important to understand the specific benefits of adherence *versus* nonadherence to CPAP.

In conclusion, obese participants with OSA demonstrated higher HOMA-IR at baseline, although there were no differences in the response to 4 months CPAP treatment between obese and non-obese participants. We found no evidence that obesity significantly modifies the effect of 4 months CPAP treatment on HOMA-IR. Longer duration of CPAP treatment may be needed to reduce insulin resistance and determine whether obesity modifies the effect.

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Conflict of Interest: All authors have nothing to disclose.

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