many of the characteristics of the study by KOCH *et al.* [2], the issue of subject randomisation will be critical to improve our confidence on the limits of normality for key CPET variables.

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**Statement of Interest:** None declared.

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DOI: 10.1183/09031936.00030809

*From the authors:*

Based on results of their important studies and assumptions concerning the Study of Health in Pomerania (SHIP) database, J.A. Neder questions the relevance of our report on reference values for cardiopulmonary exercise testing (CPET) [1]. The establishment of close-to-reality reference values for the clinical interpretation of CPET is indeed an important issue since a consensus has not yet been reached on the definition of normalcy. Therefore, we consider our study to be an additional contribution to present an ''ideal'' set of normative values for CPET. In this context, the major strength of the current study first lies in the use of data from a large population-based sample of adults. Secondly, the consideration of echocardiographical and lung functional data besides comprehensive information on past and current medical history, as well as the performance of all kinds of clinical examination methods contributes exceedingly to the establishment of a disease-free reference sample.

J.A. Neder mainly criticises the issue of voluntary participation and the aspect of too little consideration of physical activity in the current study sample on CPET. At this point, we would like to put emphasis on the fact that the SHIP study sample itself, including the participants in CPET, was randomly selected from the general population *via* registration offices [2]. Within a democratically ruled country, eventual participation in the study is dependent on voluntary participation. Therefore, one can argue that every epidemiological survey, to some extent, is biased, as stated in the published article; a selection bias towards younger and healthier individuals was evident. However, by means of adjusting for age and applying stringent exclusion criteria towards healthy participants, this should only marginally affect the normative limits for CPET.

J.A. Neder impeaches the applicability of the present reference values in the specific sub-population of sedentary elderly subjects since the described predicted values for peak oxygen uptake ($V'O_2$) were systematically higher than those previously described. Besides a selection bias towards younger and slimmer volunteers our data may be biased by analysing CPET results of physically more active participants aged $\geqslant$50 yrs ($<$2 h·week$^{-1}$ *versus* $\geqslant$2 h·week$^{-1}$; $p<0.01$). Within the group of participants in CPET (n=534 *versus* n=1,174) no significant difference in the levels of physical activity was found ($p=0.241$). So far, we agree with J.A. Neder. However, in our view the effect of excluding participants with coexisting and as yet unknown diseases has been shown to have an even more important impact in this subpopulation. Due to results derived within the examination process, 74% of the subjects aged $>$50 yrs had to be excluded. This clearly shows the importance of a wide spectrum of examination methods beside patients self report to detect and consequently exclude coexisting pathologies. NEDER *et al.* [3] tried hard to establish a disease free study sample, but alike comparable studies to some extent all cardiorespiratory disorders might not have been detected in advance. Furthermore, the majority of studies concerning reference values might be criticised for not being population based and, thus, of limited comparability to our study design. Besides less accurately assessed exclusion criteria, another major shortcoming of other previous studies seems to be the inclusion of individuals who smoke even though an impact of cigarette smoking on exercise capacity assessed by peak $V'O_2$ and $V'O_2$ at anaerobic threshold has been shown [4, 5].

One can easily argue that every existing study on reference values for CPET shows limitations. Nevertheless, every piece of work on this issue seems to contribute to close-to-reality normative values. It is incontrovertible that the present findings are the first considering such an amount of different medical examination methods for the establishment of a healthy study sample across a wide age range. However, everybody working on reference values for CPET should be encouraged to do so, since, and at this point we completely agree with J.A. Neder, the ''ideal'' set of reference values for CPET might still to be generated.

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**Statement of Interest:** None declared.

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DOI: 10.1183/09031936.00048109

# Sex differences in COPD

*To the Editors:*

I read with interest the elegant study by DE TORRES *et al.* [1] indicating that female patients with chronic obstructive pulmonary disease (COPD) have better survival than male patients. As eloquently discussed by the authors, despite previous conflicting data, several other recent studies support the survival advantage of females with this disease [1]. However, the underlying mechanisms for this survival advantage remain unknown. DE TORRES *et al.* [1] speculate that the increased mortality in males may be due to a higher prevalence of cardiovascular disease and/or lung cancer in this population. I propose an additional potential mechanism to explain the sex differences in COPD mortality.

Interestingly, females have been demonstrated to exhibit less severe hypoxic pulmonary hypertension (PH) than males (reviewed in [2]). Multiple studies have documented that females have a lower incidence of high-altitude pulmonary oedema (characterised by marked hypoxic vasoconstriction) [2, 3]. These mostly observational studies have been followed by mechanistic animal experiments demonstrating that females exhibit less severe hypoxic pulmonary vasoconstriction and hypoxic PH than males [4, 5]. Only recently have some of the molecular mechanisms been identified that may potentially contribute to the observed sex differences in acute and chronic hypoxic PH [6–8]. Based on the results demonstrated by DE TORRES *et al.* [1], it is feasible that the increased survival observed in females is, at least in part, due to less severe hypoxic PH in this patient population. Of particular interest is the finding that all-cause mortality was increased in males in all four BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) quartiles, while respiratory mortality was increased in males only in the highest BODE quartile, indicating that the males in this quartile may potentially have had more severe hypoxic PH than their female counterparts.

Right ventricular (RV) function is an important prognostic indicator in patients with PH [9]. Even subtle changes in indices RV function have been demonstrated to significantly impact on survival [9]. Interestingly, a recent study demonstrated that female patients with pulmonary arterial hypertension have a higher RV ejection fraction than males (controlled for left ventricular function and haemodynamics) [10]. This finding is in concordance with multiple reports indicating that females tolerate various forms of left ventricular injury better than males (reviewed in [2, 11]). Since severe COPD negatively affects RV function, it is therefore conceivable that RV function in female COPD patients may be better preserved than in males.

The study by DE TORRES *et al.* [1] adds to the growing evidence that female sex is associated with a better prognosis in several conditions associated with vascular dysfunction, hypoxia and inflammation, such as myocardial ischaemia, sepsis, severe trauma, acute lung injury and hypoxic PH [2]. While human studies yielded more conflicting results than laboratory investigations, most human studies did not control for the potentially confounding effects of menstrual cycle, menopause, hormone replacement therapy or changes in sex-hormone binding proteins. In addition, extra ovarian production of sex hormones in the adipose tissue of males and females, or prolonged effects of previous hormone replacement therapy in post-menopausal females may play clinically relevant roles. These observations underline the need for rigorously controlled clinical studies investigating the role of sex differences in COPD and other pulmonary diseases.

Understanding the mechanisms of sex differences in COPD may allow for the development of targeted nonhormonal therapies for both sexes. For now, it appears that, at least among patients with COPD and hypoxic pulmonary hypertension, it is better to be female.

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