obesity [4]. Because both obesity and sleep apnoea cause systemic inflammation [5, 6], the association of the inflammatory markers and insulin sensitivity with FMD should be further examined.

Fourthly, the menopause and menstrual cycle significantly affect sleep apnoea and endothelial function [7, 8]. The menopausal transition is significantly associated with an increased likelihood of having sleep-disordered breathing, independent of known confounding factors [7]. FMD increases in menstrual phase, when serum oestradiol level is low and the value is comparable to that in male subjects [8]. Because endothelium-dependent vasodilatation varies during the menstrual cycle, the timing of FMD measurements of female subjects is critical for the precise assessment of allopinol effects.

The incidence of cardiovascular disease is lower in premenopausal females compared with males in the same age group; following menopause, the risk of mortality from cardiovascular disease increases in females [9]. FMD-induced vasodilatation is lower in females aged 55 yrs than those aged 35 yrs [10]. The lower FMD in females aged 55 yrs, compared with those aged 35 yrs, could be due to postmenopausal hormonal changes.

It has been suggested that endothelial function assessment using hyperaemia-induced FMD is adequately reproducible in healthy middle-aged males and females [2]. However, there are many confounding factors including age, sex, obesity, smoking, elevated blood lipids, high blood pressure and systemic inflammation. Thus, FMD measurement may not be an appropriate method for the assessment of the endothelial function in female obese patients with sleep apnoea.

Further study using a large sample size should be carefully assessed by age, obesity and sex differences. The improvement of endothelial function by allopurinol effects on the vascular function in patients with sleep apnoea will then be adequately realised.

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From the authors:

We thank S. Teramoto and colleagues for their comments on our recent article [1]. We agree that changes in flow-mediated vasodilation (FMD) are influenced by a variety of intrinsic and extrinsic factors such as endogenous, environmental and familial factors [2], of which age, sex and body mass index (BMI) are the classic examples. Indeed, analysis by sex of our data showed that male participants had larger arterial diameters and smaller FMD at baseline compared with female subjects ($6.1 \pm 2.6\%$ in males and $8.0 \pm 1.7\%$ in females). However, in contrast to the remarks of S. Teramoto and colleagues, the median FMD improvement after allopurinol treatment was larger in women (4.3%; 95% confidence interval (CI) 1.0–7.6%) than in their male counterparts (3.4%; 95% CI 1.5–5.4%); although not to a statistically significant degree. Correlation analyses also revealed no significant relationship between changes in FMD (before and after treatment) and either age ($r=0.2$; $p=0.5$) or BMI ($r=0.06$; $p=0.85$). We acknowledge that the power of the study is too small to detect any significant difference and we alluded to this limitation in the manuscript. As pointed out by S. Teramoto and colleagues, FMD is influenced by circulating levels of oestrogen and progesterone, and by the phase of the subject's menstrual cycle [3]. This variability would have been significant had our female participants been of a child-bearing age; however, only one of the four female subjects fell into that category. Finally, we concur with S. Teramoto and colleagues that a larger sample size would be needed to confirm our findings. Now that our randomised clinical trial has shown potential efficacy, we hope it stimulates further long-term research studies to determine the role and side-effects of allopurinol in the treatment of obstructive sleep apnoea-related endothelial dysfunction.

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ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke

To the Editors:

In a recent issue of the *European Respiratory Journal*, VAN DE GARDE *et al.* [1] demonstrated that the use of angiotensin-converting enzyme (ACE) inhibitors is not associated with a decreased risk of hospitalisation for community-acquired pneumonia (CAP) in a general, essentially white population. Their conclusion that the beneficial effect of ACE inhibitors on pneumonia risk is not observed in a general white population is in contrast with previous findings in Asian populations [1]. This was an excellent good study examining the association of ACE inhibitor treatment of cardiovascular disease with a risk reduction of CAP using a large sample size. The results are acceptable and not surprising; however, the discussion and conclusion are misleading.

As shown in table 1, there are controversies regarding the ACE inhibitor effects on the risk reduction of pneumonia even in Asian countries; furthermore, the study samples are very different among the studies. In a prospective study by SEKIZAWA *et al.* [2], ACE inhibitor use reduced pneumonia incidence for 2 yrs. They did not examine the general population; subjects were hypertensive elderly patients with a history of stroke or lacuna infarction, and a mean age 10 yrs older than that of the study by VAN DE GARDE *et al.* [1]. However, the study by ARAI *et al.* [3] examined the association of ACE inhibitors and the risk reduction of pneumonia in the general hypertensive elderly without stroke in Japan [3]. Surprisingly, they had an 8.3–8.9% incidence of pneumonia over 3 yrs, an incidence twenty times higher than the previous data [6, 7]. It is hard to believe that ~3% of hypertensive elderly outpatients without major complications suffered from pneumonia. We have previously presented data showing no association of ACE inhibitor use with pneumonia risk in elderly hypertensive subjects without stroke history [4]. Since ACE inhibitors, through the inactivation substance P, improve upper airway reflexes such as swallowing and cough, resulting in the reduction of aspiration pneumonia in elderly patients, they may not reduce the CAP in those patients without deglutition problems. Current evidence indicates that ACE inhibitors play a significant role in the prevention of aspiration pneumonia in the elderly, but not in common CAP in healthy adults. This was confirmed by the sub-analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). OHKUBO *et al.* [5] re-analysed the PROGRESS data concerning the incidence of pneumonia. ACE inhibitor-active treatment significantly reduced the risk of pneumonia among participants of Asian ethnicity (mean (95% confidence interval) 47% (14–67%), p=0.01), with no significant effect among non-Asian participants (5% (-27–29%), p=0.7; p for homogeneity=0.04). These findings add to the body of

TABLE 1 The association of angiotensin-converting enzyme (ACE) inhibitor use and the rate of pneumonia in different trials

	VAN DE GARDE [1]	SEKIZAWA [2]	ARAI [3]	TERAMOTO [4]	OHKUBO [5]	OHKUBO [5]
Race	Caucasian	Asian	Asian	Asian	Asian	Caucasian
Age yrs	67	76–77	75.3–76.5	>65	64	64
Subjects n	4925	440	576	358	2352	3753
Observation period yrs	6	2	3	3	3.9	3.9
History of stroke	No	Yes	No	No	Yes	Yes
Pneumonia incidence %						
Without ACE inhibitors		9	2.77–2.97	0.25	1.04	1.3
With ACE inhibitors		3.5	1.1	0.56	0.56	1.24
Pneumonia prevention by ACE inhibitors	No	Yes	Yes	No	Yes	No