

REPLY

The importance of testosterone clinical trials

Matthew Spitzer, Grace Huang, Shehzad Basaria, Thomas G. Travison and Shalender Bhasin

We much appreciate the thoughtful comments of Dr Schooling and Dr Cowling (*Nat. Rev. Endocrinol.* 9, doi:10.1038/nrendo.2013.73-c1)¹ on our Review (Risks and benefits of testosterone therapy in older men. *Nat. Rev. Endocrinol.* 9, doi:10.1038/nrendo.2013.73).²

We agree that meta-analyses can provide useful information in assessing the risk of adverse events, particularly that of uncommon adverse events. Previous meta-analyses have been limited by the heterogeneity of study populations and clinical trial protocols, variations in testosterone regimens and on-treatment testosterone levels, relatively small sample sizes, and poor ascertainment of adverse events in clinical trials. The updated meta-analysis by Xu *et al.*³ includes several trials that were not included in prior analyses and thus provides a more precise estimate of the rate of cardiovascular events than previous meta-analyses.^{4,5} Nevertheless, large, prospective, randomized controlled trials are important for the evaluation of testosterone's efficacy in improving patient-important outcomes as well as for determining the risks of testosterone therapy and ascertaining whether some subsets of

men (for example, frail elderly men with high burden of comorbid conditions) are at increased risk of adverse events.

Schooling and Cowling suggest that large prospective randomized trials to establish the effects of testosterone on cardiovascular health should be of an agent that reduces testosterone. This proposal has considerable merit, but we do not think that statins are the right drugs for this purpose, as they exert only a modest effect on testosterone levels and are well-known to reduce LDL-cholesterol levels, which has an independent effect on cardiovascular events. As indicated by the authors, statins lower serum testosterone levels by 0.66 nmol/l in men.⁶ Of note, men with prostate cancer undergoing androgen deprivation therapy exhibit profound suppression of testosterone levels and an increased risk of diabetes mellitus and cardiovascular disease. Hence, low as well as high testosterone levels might be associated with an increased cardiovascular risk.

The Research Program in Men's Health: Ageing and Metabolism, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA (M. Spitzer, G. Huang, S. Basaria, T. G. Travison, S. Bhasin).

Correspondence to: S. Bhasin
sbhasin@partners.org

Competing interests

The authors declare no competing interests.

1. Schooling, C. M. & Cowling, B. J. Testosterone therapy and cardiovascular events. *Nat. Rev. Endocrinol.* <http://dx.doi.org/10.1038/nrendo.2013.73-c1>.
2. Spitzer, M., Huang, G., Basaria, S., Travison, T. G. & Bhasin, S. Risks and benefits of testosterone therapy in older men. *Nat. Rev. Endocrinol.* <http://dx.doi.org/10.1038/nrendo.2013.73>.
3. Xu, L., Freeman, G., Cowling, B. J. & Schooling, C. M. Testosterone and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med.* **11**, 108 (2013).
4. Haddad, R. M. *et al.* Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin. Proc.* **82**, 29–39 (2007).
5. Calof, O. M. *et al.* Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J. Gerontol. A. Biol. Sci. Med. Sci.* **60**, 1451–1457 (2005).
6. Schooling, C. M., Au Yeung, S. L., Freeman, G. & Cowling, B. J. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. *BMC Med.* **11**, 57 (2013).