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Title: Cigarette smoking, proteinuria, and renal function in middle-aged Japanese men from an occupational population

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Abstract: Objectives: To clarify the renal effects of cigarette smoking in a middle-aged occupational population because the effects have previously been demonstrated mainly in community populations that included many elderly people who are thought to be vulnerable to such effects. **Methods:** In 990 middle-aged men recruited from a chemical plant, proteinuria was measured by a dipstick method and the glomerular filtration rate was estimated (eGFR) using a formula proposed by the Japanese Society of Nephrology. **Results:** Proteinuria was found in 4.6% of the current smokers and 1.5% of the never-smokers. It was found in 4.8% of the subjects having a Brinkman Index (BI) of 400-599 and 6.3% of those having a BI of 600 or above. The odds ratio for proteinuria in them was 2.94 (CI: 1.01-8.55) and 3.61 (CI: 1.29-10.1), respectively, adjusting for possible confounders. The mean eGFR was higher in smokers than in nonsmokers throughout middle age up to 64 years. Normal but high eGFR was found in 6.7% of the current heavy smokers and subnormal eGFR in 5.7% of the largest cumulative cigarette consumers in contrast to 3.0% or less of the never-smokers. Proteinuria was found in 13.3% of the subjects showing subnormal eGFR, specifically in 16.7% of the smokers and 8.3% of the nonsmokers. **Conclusions:** Smoking causes proteinuria in working middle-aged men. Smokers tend to have a high eGFR, but those with subnormal eGFR showed proteinuria most frequently. Whether the high eGFR in smokers will eventually decrease and cause proteinuria remains an important focus for further studies.

Response to Reviewers: see attachment.