Commentary: Mendelian randomization study of tobacco smoking and cardiovascular risk factors: hazards of tobacco smoking greatly outweigh any benefits

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Tobacco smoking is a major cause of adult mortality worldwide.1 On average about 50% of young men and 10% of young women are current smokers. Whereas tobacco smoking accounted for about 5 million deaths in 2010, this could double and result in 10 million deaths in a few decades from now, when the current smokers reach middle and old age.1 Prospective studies in the UK, USA, Japan and India have examined the effects on mortality in populations of men and of women who began to smoke in early adult life and persisted. These publications demonstrated that, in middle age, mortality among cigarette smokers was two to three times the mortality among otherwise similar persons who had never smoked, leading to a reduction in life span by an average of about 10 years.2–5 Recent research among UK women also demonstrated that two-thirds of all deaths of smokers in their 50s, 60s and 70s were caused by smoking.6 Although the hazards of smoking until the age of 40 years and then stopping are substantial, the hazards of continuing are 10 times greater.6 Women who stop smoking before age 40 years (and preferably well before age 40 years) avoid more than 90% of the excess mortality caused by continuing smoking; stopping before age 30 years avoids more than 97% of it.6

The report by Asvold and colleagues examined the associations of smoking with cardiovascular risk factors in a cross-sectional analysis of the Hunt study, a population-based study of 56,625 adults living in Norway that was surveyed in 1995–97.7 Asvold and colleagues reported that smoking was a major public health problem in Norway, with 31% current smokers, 25% former smokers and 44% never smokers in this population.7 The study demonstrated that tobacco smoking greater than five cigarettes per day was associated with adverse levels of almost all cardiovascular risk factors, including body mass index (BMI), blood pressure, heart rate, non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol and glucose. However, light smoking (less than five cigarettes/day) was associated with a lower BMI and lower blood pressure but higher heart rate and estimated glomerular filtration rate.

To address the causal relevance of the discrepant associations of light vs average or heavy smoking, the authors adopted a Mendelian randomization (MR) approach to study the associations of rs1051730 (a predictor of smoking quantity) with levels of cardiovascular risk factors. The MR approach adopted an instrumental variables analysis using this genetic instrument to assess causality.8–11 The fundamental principles of MR involve use of genetic variants that can either alter the level of, or imitate the biological effects of, a potentially modifiable environmental exposure affecting disease risk, which is then related to disease risk to the extent predicted by their influence on the exposure to the risk factor.8 MR studies have become increasingly popular for assessing the causal role of a risk factor and reducing the effects of confounding and reverse causality that limit classical observational studies. However, MR studies have not been widely used to assess the role of environmental exposures on other risk factors. The report by Asvold and colleagues examined the utility of this approach when assessing causal associations of tobacco smoking with cardiovascular risk factors.7
The authors used a single nucleotide polymorphism (rs1051730) in the nicotinic acetylcholine receptor gene cluster (CHRNA5-CHNRA3-CHRNB4) on chromosome 15 to assess whether each additional copy of the T allele was associated with the quantity of cigarettes smoked. They then estimated the impact of each additional copy of the T allele on cardiovascular risk factors (including measures of adiposity, blood pressure, heart rate, blood lipids and blood glucose) in 56,625 participants of whom 17,528 were current smokers. Carriers of the rs1051730 T alleles were more likely to be current smokers than former or never smokers. Surprisingly, rs1051730 T alleles were associated with lower levels of adiposity [body mass index (BMI) and waist and hip circumferences] and these associations varied by smoking status. Current smokers had per T allele associations of 0.24 kg/m\(^2\) [95% confidence interval (CI): 0.15–0.33] lower BMI; 0.46 cm (95% CI: 0.23–0.68) lower waist circumference; and 0.43 cm (95% CI: 0.26–0.61) lower hip circumference. The associations per T allele for BMI and waist and hip circumference were weaker or absent in former smokers and modestly higher in never smokers.

Although the paper by Asvold et al. demonstrated some positive effects of smoking on BMI, these effects would be outweighed by the adverse effects of smoking on cardiovascular disease.\(^7\) For example, the Prospective Studies Collaboration meta-analysis of prospective studies, which assessed the associations of BMI with cause-specific mortality,\(^12\) demonstrated that a 0.24-kg/m\(^2\) lower BMI was associated with only a 1.6% lower risk of death from ischaemic heart disease for men and women combined [i.e. hazard ratio of 0.98 (95% CI: 0.98–0.99)].\(^12\) However, the Million Women study reported hazard ratios of death from ischaemic heart disease in smokers compared with never smokers of 4.49 (95% CI: 4.19–4.77).\(^6\) Moreover, any beneficial effects of light smoking on body mass index were offset by adverse effects of heavy smoking that were directly proportional to the amount of cigarettes smoked. Hence, claims of any beneficial effects of smoking on body weight are overwhelming outweighed by adverse effects of smoking on disease incidence and premature death, which are even greater for women than for men.\(^13\)

References