Accurate measurement of tobacco smoke exposure and smoking behaviour matters

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Competing interests: The author has no competing interests to declare.

Key words: smoking, nicotine, cotinine, pregnancy, biomarkers, total nicotine equivalents

Concise statement: In pregnancy, 'total nicotine equivalents' (TNE) and 'total' cotinine (TC) concentrations reflect nicotine (tobacco smoke) exposure more accurately than the widely-used biomarker, 'free' cotinine. Although the number of cigarettes smoked daily (CPD) is similarly a poor proxy for such exposures, this measure can still be useful in population surveys.

Commentary: Taghavi and colleagues compare three measures of smoking: self-reported smoking data, urinary concentrations of the nicotine biomarker cotinine and urinary concentrations of 'total nicotine equivalents' (TNE), a more comprehensive measure of both nicotine and its metabolites. They then use this comparison to assess the utility of each for measuring nicotine exposure in pregnant women. [1] The TNE measure was used as a 'gold standard' against which other measures were judged because it reflects up to 88% of nicotine intake [2] and is not influenced by pregnancyinduced acceleration in the metabolism of nicotine and cotinine.[3] Using the TNE measure, nicotine exposure was similar in early and late pregnancy (approximately 13 and 30 weeks) but much higher by around 25 weeks postpartum [1], presumably because women who had stopped smoking in pregnancy re-started smoking afterwards. Most nicotine is metabolised to cotinine [4], so unsurprisingly, free cotinine levels showed a similar pattern; however, due to the faster metabolism of cotinine in pregnancy[5, 6], these levels were less strongly correlated with TNE during gestation. Consequently, free cotinine measurements would have under-estimated nicotine exposures by 55% in early and 65% in late pregnancy. In contrast, total cotinine (free cotinine and cotinine glucuronide combined) was more strongly correlated with TNE and this correlation remained consistent during and after pregnancy and also in women with faster and slower nicotine metabolisms, suggesting that total cotinine levels reflect nicotine exposures as accurately as TNE levels do.

For women who smoke in pregnancy and who don't use nicotine replacement therapy or ecigarettes, all nicotine exposure comes from tobacco smoke and any measure which accurately predicts nicotine intake also predicts heaviness of smoking and of tobacco smoke toxin exposure. Accordingly, Taghavi et al.'s findings have implications for how such exposures might be validated in observational, cohort studies investigating fetal, infant and maternal harms from smoking in pregnancy. Free cotinine (FC), a frequently-used biomarker, under-estimates nicotine exposure. TNE and total cotinine (TC) are the most accurate exposure biomarkers and future studies using either would minimise 'noise' incurred during exposure measurement, maximising the chances of detecting valid associations between exposure in pregnancy and outcomes. Hitherto unidentified dose-response relationships between smoking in pregnancy and adverse outcomes might become apparent and better quantification of known risks from smoking in pregnancy may be possible. For

example, using free cotinine, a biomarker which Taghavi et al show reflects nicotine less closely than others, it has recently been shown that there is no 'safe' level of second hand smoking as children with the very lowest detectable urinary free cotinine levels had poorer asthma outcomes than those with no measurable urinary free cotinine.[7] More sensitive quantification of tobacco smoke exposure in pregnancy using biomarkers such as TNE and total cotinine could lead to other, novel insights, potentially with substantial public health implications.

Due to discrepancies between numbers of cigarettes smoked daily (CPD) and TNE, Taghavi et al rightly question the use of CPD to measure nicotine exposure. [1] In a smoking cessation trial such as theirs [8], one might expect women who don't quit to report a lower CPD when asked later in pregnancy. The authors cite other reports of reduced CPD in late pregnancy and suggest there is bias against women admitting how heavily they smoke operating in those studies too. However, in those survey studies such bias is probably less important as there is no expectation, apart from the usual societal expectations, that participants should stop smoking during pregnancy, whereas cessation trials generally recruit women who are committed to stopping smoking. Hence trial participants may perceive greater pressure on to report changes in smoking behaviour at follow up. Behavioural surveys are generally cross-sectional [9] and, as some participants are inevitably lost to follow up, respondents at baseline and follow up may not be the same women; bias arising from such attrition could be more influential. To my knowledge, there is only one survey of pregnant women's smoking behaviour which has reported longitudinal CPD data at different times in pregnancy and which adjusts these for loss to follow up. [10] This showed very similar CPD levels in early and late pregnancy and also in the postpartum period.[10] Another longitudinal study reported movement between different categories of smoking heaviness as pregnancy progressed but similarly, didn't reveal a trend towards lighter smoking in later pregnancy either.[11] Perhaps the problem is less with the CPD measure itself and more a function of the design and analysis of studies using it? CPD may not be a great exposure measure but it is cheap and easily-administered and very likely remains a valid measure of smoking behaviour in pregnancy provided the biases inherent in collecting self-report data on this socially-undesirable habit are understood.

Acknowledgment: Tim Coleman is a National Institute for Health Research Senior Investigator.

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