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The Smoking MUMS (Maternal Use of Medications and Safety) Study: protocol for a population-based cohort study using linked administrative data

Alys Havard,[1] Louisa R Jorm,[1,2] David Preen,[3] Michael Daube,[4] Anna Kemp,[3] Kristjana Einarsdóttir,[5] Deborah Randall,[1] Duong Thuy Tran[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Alys Havard;
a.havard@uws.edu.au

ABSTRACT

Introduction: Approximately 14% of Australian women smoke during pregnancy. Although the risk of adverse outcomes is reduced by smoking cessation, less than 35% of Australian women quit smoking spontaneously during pregnancy. Evidence for the efficacy of bupropion, varenicline or nicotine replacement therapy as smoking cessation aids in the non-pregnant population suggest that pharmacotherapy for smoking cessation is worth exploring in women of childbearing age. Currently, little is known about the utilisation, effectiveness and safety of pharmacotherapies for smoking cessation during pregnancy; neither the extent to which they are used prior to pregnancy nor whether their use has changed in response to related policy reforms. The Smoking MUMS (Maternal Use of Medications and Safety) Study will explore these issues using linked person-level data for a population-based cohort of Australian mothers.

Methods and analysis: The cohort will be assembled by linking administrative health records for all women who gave birth in New South Wales or Western Australia since 2003 and their children, including records relating to childbirth, use of pharmaceuticals, hospital admissions, emergency department presentations and deaths. These longitudinal linked data will be used to identify utilisation of smoking cessation pharmacotherapies during and between pregnancies and to explore the associated smoking cessation rates and maternal and child health outcomes. Subgroup and temporal analyses will identify potential differences between population groups including indigenous mothers and social security recipients and track changes associated with policy reforms that have made alternative smoking cessation pharmacotherapies available.

Ethics and dissemination: Ethical approval has been obtained for this study. To enhance the translation of the project's findings into policy and practice, policy and clinical stakeholders will be engaged through a reference group and a policy forum will be held. Outputs from the project will include scientific papers and summary reports designed for policy audiences.

ARTICLE SUMMARY

Strengths and limitations of this study

- In a context where experimental studies are not feasible, this population-based cohort study will enable exploration of longitudinal relationships while minimising the risk of selection bias.
- There are advantages and disadvantages associated with the use of administrative data; while biases associated with recall and socially desirable reporting are minimised, the identification of smoking and medication exposure is likely to be incomplete.

INTRODUCTION

Maternal smoking during pregnancy is a leading cause of adverse pregnancy outcomes, with increased risk of placental abruption, preterm delivery, low birth weight and perinatal mortality.[1–3] The harms of maternal smoking extend well beyond the perinatal period to increase the risk of adverse outcomes to the child in early life, including sudden infant death syndrome,[4] asthma,[5] lower respiratory illnesses and hospitalisation.[6] The prevalence of smoking during pregnancy is declining,[7] but it is still common, with data from 2010 indicating that 13.5% of pregnant Australian women smoked.[8] Although the risk of adverse outcomes can be significantly reduced by quitting,[2 9–10] only 4–34% of Australian women who smoke early in pregnancy stop later in their pregnancy.[11] Of further concern is the observation that the lowest cessation rates are among the heaviest smokers,[12 13] who are at the greatest risk of harm.[1 6] The risk of harm related to smoking in pregnancy is increased in some subpopulations of Australian women and their children. In particular, indigenous women and women of low socioeconomic

status (SES) are at least three-times more likely than other mothers to smoke during pregnancy, more likely to be heavy smokers and significantly less likely to quit smoking during their pregnancy.[14]

Strategies that effectively aid quitting smoking during pregnancy, especially among women at elevated risk, are urgently needed. Behavioural smoking cessation interventions in pregnant women produce modest outcomes, reducing the prevalence of smoking during pregnancy by only 6%.[10] Behavioural interventions achieve similarly low cessation in non-pregnant smokers, but when combined with pharmacotherapy, cessation rates increase 1.5-fold to 3-fold,[15] with the greatest relative benefit achieved in the heaviest smokers.[16] Although there has been some uptake of pharmacotherapies among pregnant smokers, it is unclear whether this is advisable, as the benefits and risks of using these medications during pregnancy have not been adequately assessed.

Smoking cessation pharmacotherapies

Three medications are licensed for use as smoking cessation aids in Australia: nicotine replacement therapy (NRT), bupropion and varenicline. NRT aims to reduce withdrawal symptoms by providing some of the nicotine that would otherwise be obtained from cigarettes, while limiting exposure to harmful substances in tobacco. It is available in the form of transdermal patches, inhalers, lozenges, sublingual tablets and gum. Bupropion is a non-nicotine drug and although its exact mechanism of action is unclear, it was observed to alleviate nicotine withdrawal symptoms while being used as an antidepressant.[17] Varenicline is a partial agonist of the nicotine receptor, stimulating the dopamine reward pathway to a lesser extent than nicotine, but preventing nicotine itself from binding.[17] Current guidance recommends against the provision of varenicline during pregnancy and suggests the use of bupropion or NRT only when the expected benefits outweigh the potential risks.[18]

Although access to NRT initially required a prescription in Australia, it has been available over the counter (OTC) since 1997. Since 1 January 2009, NRT patches have been subsidised through the Pharmaceutical Benefits Scheme (PBS) for indigenous patients and the subsidy was extended to all patients on 1 February 2011.[19] The cost of a full 12-week course of NRT if bought OTC is currently[i] $A165.95, while the subsidised costs are $A108.30 for general beneficiaries and $A17.70 for social security beneficiaries. Bupropion and varenicline are prescription only and they have been PBS listed for all eligible patients since 1 February 2001 and 1 January 2008, respectively. Subsidies are such that the maximum out-of-pocket cost for a full course of bupropion or varenicline is $A72.20 for general patients and $A11.80 for social security patients. Subsidised supply is restricted to individuals who have indicated they are ready to cease smoking and have entered or are entering a comprehensive support and counselling programme.[20] Bupropion is not PBS-subsidised as an antidepressant in Australia.

Use of smoking cessation pharmacotherapies during pregnancy

Smoking cessation pharmacotherapies are currently being used during pregnancy, despite the uncertainty surrounding their safety and efficacy. Population-based record linkage studies of pregnancies in Denmark between 1996 and 2002 and in Tayside, Scotland in 2007, found that 8%[21] and 16%[22] of smokers, respectively, used NRT during pregnancy. Among pregnant smokers enrolled in a randomised controlled trial (RCT) of telephone counselling for smoking cessation conducted in Massachusetts between 2001 and 2004, 3% reported using bupropion during their pregnancy and 7% used NRT.[23] Furthermore, surveys of obstetric providers in the USA and the UK have found 26–44% of obstetric providers prescribe these pharmacotherapies to patients who smoke.[24–26] As yet, there are no published data on the use of varenicline during pregnancy, however, given that it is the most effective of the three pharmacotherapies in the non-pregnant population,[27] some use during pregnancy is plausible. With the exception of estimates produced through the power calculations for this study, the extent to which these medications are used by Australian women during pregnancy is unknown. Although existing utilisation data are from Western countries with similar guidelines to Australia,[28] the out-of-pocket costs for prescription medicines in Australia are slightly higher than in Denmark, almost twice those in Scotland, but only a fraction of those in the USA.[29 30] Given that prescription medicine utilisation is highly sensitive to out-of-pocket costs,[31] utilisation rates in Australia are likely to differ from those documented internationally. Furthermore, the policy reforms in Australia over the last decade that has made alternative smoking cessation pharmacotherapies available and reduced their out-of-pocket costs, are likely to have resulted in increased utilisation.

Benefits and risks of smoking cessation pharmacotherapies during pregnancy

Although RCTs provide the best evidence regarding the benefits and risks of an intervention, RCTs of bupropion and varenicline in pregnancy are not ethically acceptable given their unknown safety during pregnancy. Consequently, robust observational studies offer the only feasible method for obtaining evidence regarding the effects of these agents in pregnancy. As yet, no such studies of varenicline has been reported, however, data relating to bupropion use in pregnancy exist, much of it in the context of treating depression.[32–34] Although the lack of a control group meant that no definitive

[i]At the time of writing, the purchasing power of $A1 was 0.74 British pounds (GB£) and US$0.66; http://stats.oecd.org/Index.aspx?DataSetCode=CPL

conclusions could be drawn from the bupropion registry set up by the manufacturer,[35] its findings raised concern about the possibility of an association between bupropion use in pregnancy and cardiovascular malformations. This prompted the conduct of controlled observational studies, which found no evidence of increased congenital abnormalities among women taking bupropion during pregnancy relative to those exposed to other antidepressants[34] and those not exposed to any teratogens.[33] An increased risk of spontaneous abortion[33] and infant left outflow heart defects[32] was observed for pregnant bupropion users relative to women not taking potentially teratogenic substances, but given that no comparisons were made with pregnant smokers, these findings provide little insight into the safety of bupropion relative to smoking during pregnancy. The only study to include a pregnant smoker comparison group was a very small (n = 44) matched controlled study which found a significantly higher cessation rate among women taking bupropion (45% vs 14%, p = 0.047).[36] This study did not report the safety of bupropion.

Although nicotine is toxic, when delivered through NRT it is not accompanied by the other toxins present in tobacco smoke. Theoretically, this implies that NRT is safer than smoking during pregnancy and some experts sanction its use during pregnancy on this basis.[37] There is currently insufficient evidence to support or refute this assumption, however, with recent meta-analyses[28] of findings from RCTs showing NRT to be associated with improvements in five of seven pregnancy and neonatal outcomes, but not to a statistically significant extent. Similarly, the pooled estimates of smoking cessation rates were such that the effectiveness of NRT in pregnancy remains unclear and the authors recommend that further RCTs be conducted. Public awareness of the uncertainty surrounding NRT use during pregnancy, however, is proving to be a barrier in obtaining RCT samples of sufficient size,[38] adding further weight to the utility of observational studies in this area. Data from observational studies reported thus far have shed some light on the question of NRT safety during pregnancy, with a population-based cohort study in Denmark finding no association between NRT and stillbirth,[21] but an increased risk of congenital malformations in pregnant NRT users relative to unmedicated non-smokers.[39] The impact of NRT on other pregnancy, neonatal and early childhood outcomes remains to be examined and further investigation of the effectiveness of NRT in pregnant smokers is required.

Use and effectiveness of smoking cessation pharmacotherapies prior to pregnancy

While the effectiveness and safety of smoking cessation pharmacotherapies during pregnancy are largely unknown, it seems prudent to encourage women who are unlikely to stop smoking spontaneously during pregnancy to complete this form of treatment prior to conception. Although this is not necessary for all female smokers of reproductive age, given that up to 35% are able to quit spontaneously when they become pregnant,[11] it appears appropriate for women who smoked throughout a previous pregnancy since two-thirds of these women smoke during subsequent pregnancies.[40] Despite this, the extent to which these therapies are being used prior to pregnancy by Australian women, particularly those at increased risk of harm, is currently unknown, as is the degree to which Federal government policy changes regarding access to these medications have had an impact on this population. Moreover, the suggestion that use of smoking cessation pharmacotherapies should be encouraged among women who persist with smoking throughout pregnancy is based on the assumption that these pharmacotherapies are as effective in these women as in the general population, which has not been confirmed. Indeed, the distinctive profile of women who continue to smoke throughout pregnancy, in terms of education, income and heaviness of smoking,[12–14] suggest that estimates of effectiveness from general population samples may not be applicable to pregnant women who smoke.

Using comprehensive linked person-level data, the Smoking MUMS (Maternal Use of Medications and Safety) Study will explore the utilisation and effectiveness of bupropion, varenicline and NRT prior to and during pregnancy, as well as health outcomes for mothers and babies when these medications are used during pregnancy. Our specific objectives are as follows:

1. To measure utilisation of publicly subsidised pharmacotherapies for smoking cessation during pregnancy and interpregnancy periods;
2. To measure the extent to which the use of smoking cessation pharmacotherapies during pregnancy and interpregnancy periods has changed with the introduction of national policies regarding subsidies for these medications;
3. To investigate potential differences between subpopulations in the utilisation of medications during pregnancy and the interpregnancy period and the impact of relevant policy changes on utilisation during these periods;
4. To measure smoking cessation rates associated with the use of smoking cessation pharmacotherapies during pregnancy and interpregnancy periods;
5. To investigate maternal and child health outcomes associated with the use of smoking cessation pharmacotherapies during pregnancy.

METHODS AND ANALYSIS

Study design and population

This is a population-based cohort study, comprising all women who gave birth in New South Wales (NSW) or Western Australia (WA) since 2003. Records from the NSW and WA statutory midwifery data collections will be

linked to PBS data and a range of state-based administrative health data collections.

Data sources

The cohort will be constructed from records in the NSW Perinatal Data Collection (PDC) and the WA Midwives Notification Scheme (MNS), which include records for all live births and stillbirths of at least 20 weeks gestation or at least 400 g birth weight in NSW and WA. Information on maternal characteristics, pregnancy complications and labour, delivery and neonatal outcomes are recorded by the attending midwife or doctor. Initially the cohort will include pregnancies relating to births in the period 1 January 2003 to 31 December 2010 (approximately 1 million births) and in later years of the project the cohort will be expanded to include more recent births. Pre-2003 midwifery records for cohort members will also be obtained as they provide relevant information regarding previous pregnancies. These data are available from 1994 in NSW and 1980 in WA.

The PBS data collection includes a record for every pharmaceutical product for which a subsidy is paid under this Australian Commonwealth government scheme. Records contain the item name, anatomical therapeutic chemical (ATC) code, date of prescribing, date of supply, the patient's postcode and their beneficiary status (social security or general). All records of supply of bupropion, varenicline and NRT to women in the cohort on or after 1 January 2003 will be obtained (ATC codes with the prefix N07BA). Although data regarding bupropion dispensing are available from 2001, personal identifiers for social security beneficiaries were recorded inconsistently in PBS data prior to 2003, rendering these early data partially unreliable for linkage studies.

The NSW Admitted Patients Data Collection (APDC) and the WA Hospital Morbidity Data Collection (HMDC) include a record for every public and private hospital separation in NSW and WA. All available records belonging to cohort members or their children will be obtained (from 1 July 2000 in NSW and 1980 in WA). The information reported includes patient demographics, diagnoses, procedures and external causes of injuries coded according to the Australian modification of the International Statistical Classification of Diseases and Related Problems, 10th revision (ICD-10-AM)[41] for all APDC records and HMDC records of separations on or after 1 July 1999. HMDC records relating to separations between 1 January 1979 and 31 December 1987 are coded according to the ninth revision (ICD-9), whereas HMDC records between 1 January 1988 and 30 June 1999 are coded according to the Clinical Modification of the ninth revision (ICD-9-CM).

The NSW Emergency Department Data Collection (EDDC) and the WA EDDC include a record for every presentation to all metropolitan and the majority of regional, emergency departments in NSW and WA. Recorded information includes patient demographics, provisional diagnoses and procedures. All available records for the cohort and their children will be obtained from 2005 in NSW and 2002 in WA.

The NSW Registry of Births, Deaths and Marriages (RBDM) Death Registrations and the WA RBDM Death Registrations include a record for each registered death in NSW and WA. Information in RBDM data is limited to date of death, with information on underlying causes of death and contributing causes of death obtained from the Australian Bureau of Statistics (ABS) Mortality Data. Records of all registered deaths among cohort members and their children will be obtained. RBDM records up to December 2012 are currently available for linkage, while ABS Mortality records beyond December 2007 are not yet available.

Data linkage

The Australian Institute of Health and Welfare will perform linkage of the PBS and midwifery records for our study. Other records relating to WA residents will be linked by the WA Data Linkage Branch, while records relating to NSW residents will be linked by the Centre for Health Record Linkage. Records are linked using probabilistic matching of name, date of birth, sex and address using the 'best practice protocol' for preserving individual privacy.[42] Quality assurance data show false positive and false negative rates of 0.3% and <0.1%, respectively, for NSW[43] and both are estimated to be 0.11% for WA.[44]

Measurement of smoking

The NSW PDC contains an item indicating whether a mother smoked during the pregnancy and another item indicating the number of cigarettes smoked per day during the second half of the pregnancy. For births since September 1997, the WA MNS also contains an item indicating whether a mother smoked during the pregnancy. For births since January 2010, the WA MNS contains items indicating the number of cigarettes smoked per day during the first 20 weeks of pregnancy and the number smoked per day after the first 20 weeks of pregnancy. In both the NSW APDC and the WA HMDC, smoking can be recorded by assigning diagnostic codes related to tobacco use (the ICD-10 AM code relevant to smoking during pregnancy is Z72.0, which indicates current use of tobacco during the admission and the previous 28 days).

Smoker pregnancies will be defined as pregnancies during which any smoking is reported in the midwifery record or a smoking diagnosis is present in the hospital admission record associated with the delivery.

Non-smoker pregnancies will be pregnancies during which smoking is not reported in the midwifery record and no smoking diagnosis is present in the hospital admission record associated with the delivery.

Previous smoker pregnancies will be pregnancies among women who had at least one record of a previous

pregnancy in the dataset (births from September 1997 in WA and from January 1994 in NSW), where *any smoking* during the immediately preceding pregnancy is recorded in the midwifery record or a smoking diagnosis is assigned in the hospital admission record associated with the delivery. Sensitivity analyses, using NSW data and post-2009 records from WA, will be performed to assess an alternative definition, based on *smoking during the second half* of the immediately preceding pregnancy.

These categories are not exclusive (previous smoker pregnancies will include smoker and non-smoker pregnancies) and will be used in various combinations to address specific study objectives.

Measurement of potential confounding factors

Maternal age, parity, gestational age, smoking quantity and year of delivery will be ascertained directly from the midwifery records.

Maternal medical conditions and adverse outcomes of previous pregnancies which may confound the relationship between the use of smoking cessation pharmacotherapies and maternal and child health outcomes, for example asthma, hypertension and diabetes, will be identified through prebirth emergency department and hospital admission records, through the supply of relevant medications as recorded in PBS data and through hospital admission records and midwifery records associated with previous births.

Other prescription medication use will be identified through PBS records.

SES will be ascertained from midwifery and hospital records and will include individual measures (private health insurance and concession card holders) and area-based measures (quintiles of the Socioeconomic Indexes for Areas, Index of Relative Socioeconomic Advantage mapped to statistical local area (SLA) of residence[45]).

Remoteness of residence will be classified according to the Accessibility Remoteness Indicator of Australia (ARIA)[46] applied to SLA of residence ascertained from midwifery and hospital records.

Indigenous status from hospital admission records will be used to supplement identification from midwifery records given that indigenous people are underenumerated in administrative datasets.

Analysis plan for each objective

Objective 1: To measure utilisation of smoking cessation pharmacotherapies during smoker pregnancies, the period of pregnancy will be estimated, with the first day of pregnancy equalling the baby's date of birth—gestational age (days) +14 days.[47] Instances where the date of supply of a bupropion, varenicline and NRT falls within the period of pregnancy will be identified. Utilisation during interpregnancy periods will be measured among women with a previous smoker pregnancy, by identifying instances where the date of supply of a smoking cessation medication coincides with the period between the current and previous pregnancy. Utilisation will also be explored in women with no smoking behaviour recorded in relation to their current or previous pregnancy, to provide information regarding utilisation in smokers who are not identified as such and women who take up or resume smoking postpregnancy. Utilisation counts and rates during each period (ie, pregnancy or interpregnancy) will be calculated separately for each smoking cessation pharmacotherapy and for all three medications together. Trends in utilisation rates for each period will be assessed using Poisson regression, adjusting for the potential confounders listed above.

Objective 2: Separate interrupted time-series analyses will be used to identify policy-related changes in the utilisation of subsidised smoking cessation pharmacotherapies during pregnancy and interpregnancy periods. The study period will be divided into segments according to the date on which each subsidy was introduced. The magnitude and statistical significance of changes in utilisation level or trend associated with the subsidy changes will be measured using Poisson regression models or Autoregressive Integrated Moving Average models.

Objective 3: To identify potential differentials in the utilisation of medications during pregnancy and the interpregnancy periods, calculations performed in relation to objective 1 will be stratified by indigenous status and SES. Comparisons will be made using χ^2 tests and multivariate logistic regression to control for the other modifying factors outlined above. To identify potential differences in the impact of relevant policy changes on utilisation, indigenous status and SES will be included as covariates in the models constructed for objective 2.

Objective 4: Cessation of smoking during pregnancy will be measured among smoker pregnancies by identifying women who reported not smoking during the second half of their pregnancy (possible only for NSW and post-2009 births in WA). Cessation of smoking during interpregnancy periods will be measured among previous smoker pregnancies (NSW and WA) using the mother's recorded smoking status in the current pregnancy. Separate medication-specific cessation rates will be calculated according to whether a smoking cessation medication was prescribed during the first half of the pregnancy or during the interpregnancy period, as appropriate. Comparisons of cessation rates between women who were and were not prescribed a smoking cessation pharmacotherapy during each period of interest will be conducted with χ^2 tests and logistic regression controlling for potential confounders. Analyses regarding the interpregnancy period will be adjusted for the duration of this period.

Objective 5: Maternal health outcomes will be ascertained from the midwifery, hospital admissions, emergency department and death data. Hospitalisations for seizure-related and mental health conditions during pregnancy will be examined, as these have been reported as potential adverse effects of bupropion and

varenicline, respectively.[48] Readmission within 6 weeks postpartum and all-cause admissions will be examined to identify potential adverse outcomes that have not been reported previously. Neonatal outcomes will include low birth weight (for gestational age), preterm birth (<37 weeks) and perinatal mortality. To identify potential adverse outcomes that have not been reported previously, the infant and child health outcomes initially explored will be all-cause hospital admissions, emergency department presentations and deaths, followed by analyses of specific causes should patterns emerge. Smoker pregnancies will be categorised according to whether a pharmacotherapy was supplied during the pregnancy. Comparisons will be made between: (1) smoker pregnancies during which a pharmacotherapy was used, (2) smoker pregnancies in which a pharmacotherapy was not used and (3) non-smoker pregnancies. For NSW records and post-2009 WA records, the pregnancies during which pharmacotherapy was used will be further subdivided according to whether smoking stopped or continued throughout the second half of the pregnancy. Comparisons will comprise logistic regression models for binary outcomes and negative binomial regression modelling for count variables, adjusting for potential confounders.

In all analyses, we will use techniques such as Generalised Estimating Equations or multilevel modelling to adjust for the clustering of births within the same women and confounding factors.

Statistical power

Data from national reports[49 50] indicate that there were approximately 135 000 smoker pregnancies in NSW and WA in 2003–2010 and extrapolation from preliminary analyses of WA MNS records linked to PBS records suggest approximately 273 women in NSW and WA were prescribed bupropion during pregnancy. This sample will be sufficient to estimate a utilisation rate of 2/1000 pregnancies with a 95% CI of 1.8 to 2.0. Among NSW women, the minimum detectable rate ratio (RR) for comparing smoking cessation in bupropion users versus unmedicated smokers is 2.5 (assuming an unmedicated cessation rate of 4%). The minimum detectable RRs for low birth weight, preterm birth and perinatal mortality, in NSW and WA women, are 1.8, 1.8 and 4.0, respectively (assuming respective prevalences of 7.3%, 8.2% and 1.1% in unmedicated smokers[3]). Given the absence of data on NRT use in pregnant indigenous women, monthly prescription rates for the general indigenous population (from the Medicare Australia website[51]) were projected and applied, resulting in an estimated 181 prescriptions of NRT among pregnant indigenous women in 2009–2012. This will allow a utilisation rate of 17/1000 pregnancies to be estimated with a 95% CI of 14 to 19. In this sample, the minimum detectable RRs for the above-mentioned outcomes will be 2.8, 2.0, 2.0 and 5.1 for NRT users versus unmedicated smokers. All minimal detectable RR calculations assumed 80% power, 5% significance, two-sided tests and an intraclass correlation for clustering of births within women of 0.46.[52] With respect to varenicline during pregnancy, our project is exploring completely new territory and consequently data on which to base power calculations are not available.

Preliminary analyses of internally linked midwives records in NSW suggest that, in NSW and WA, there will be approximately 67 000 previous smoker pregnancies in 2003–2010, 40 000in 2008–2012 and 4500 among indigenous women in 2009–2012. Application of general population prescription rates to estimate interpregnancy utilisation results in approximately 1600 bupropion prescriptions, giving a rate of 24/1000 (95% CI 23 to 25), 6800 varenicline prescriptions, giving a rate of 167/1000 (95% CI 163 to 170), but only 75 NRT prescriptions for indigenous women, giving a rate of 17/1000 (95% CI 13 to 21). The minimum detectable RRs for smoking cessation in the interpregnancy period will be lower than the during-pregnancy estimates for bupropion, but higher for NRT among indigenous women.

Ethics and dissemination

To enhance the translation of the project's findings into policy and practice, a reference group will be convened, comprising policy stakeholders and organisations involved in indigenous and non-indigenous antenatal care. During the final stages of the project, we will also hold a policy forum to promote academic, professional and public debate on policy and practice issues arising from the project. Outputs from the project will include scientific papers, summary reports in formats designed for policy audiences and presentations given at conferences, collaborator meetings and reference group meetings.

DISCUSSION

The Smoking MUMS Study will provide evidence regarding current policy-relevant and practice-relevant issues. The findings regarding the effectiveness and safety of smoking cessation pharmacotherapies during pregnancy have the potential to inform guidelines relating to the prescription of these agents during pregnancy, as well as to guide policy decisions regarding the extent to which their use should be encouraged and supported, particularly for indigenous and other high-risk mothers. Our investigation of how changing subsidies for these medications has driven changes in their use is important both in terms of evaluating current policies and in shaping future policy initiatives that aim to influence the uptake of smoking cessation pharmacotherapies, in pregnancy and more generally.

An additional benefit of this project is that once the linkage keys for the study population are established, there is potential to use this infrastructure (pending appropriate ethics approval) to examine the utilisation and safety of other medications during pregnancy,

simply by obtaining linked PBS records relating to additional medications. Indeed, we plan to conduct a programme of research based on this resource, known as the MUMS Study. This study has the potential to contribute greatly to knowledge of the safety of medications during pregnancy, which is currently lacking for many licensed pharmaceuticals as pregnant women are commonly excluded from participating in clinical trials.

Limitations

Although the use of population-based data collections for research presents various advantages, including large sample sizes and therefore greater statistical power to detect rare outcomes, the avoidance of biases associated with recall or social desirability and the prevention of selection bias associated with the collection of individual patient consent and voluntary participation, there are also limitations.

The first of these relates to the incomplete ascertainment of medication exposure in the PBS data. OTC sales of NRT do not result in PBS records and will therefore not be captured in our study. Similarly, use of subsidised smoking cessation pharmacotherapies may also be underascertained among indigenous women in remote areas because subsidised supply of medications to indigenous people in these areas does not always result in an individual patient-level PBS record. Special arrangements exist for the supply of pharmaceutical benefits to clients of eligible remote area Aboriginal Health Services, whereby prescription medications are provided free of charge without the need for a prescription.[53] In addition to leading to conservative utilisation rates, this underascertainment means the unmedicated smoker pregnancy group will potentially include some pregnancies in which NRT, bupropion or varenicline was in fact used. This would result in a bias of the risk estimates towards the null, that is, the potential benefits and harms of smoking cessation pharmacotherapy use will be underestimated.

The second major limitation arises from the reliance on midwifery and hospital admission data to identify smokers. It has been shown that smokers are underenumerated in these data collections, although the rate of false identification of smokers is less than 1%.[54 55] This underdetection of smokers will bias comparisons with non-smokers towards the null, but it is not expected to influence comparisons between medicated and unmedicated smokers.

Author affiliations
[1]Centre for Health Research, University of Western Sydney, Penrith, New South Wales, Australia
[2]The Sax Institute, Haymarket, New South Wales, Australia
[3]Centre for Health Services Research, University of Western Australia, Crawley, Western Australia, Australia
[4]Public Health Advocacy Institute of WA, Curtin University, Perth, Western Australia, Australia
[5]Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Subiaco, Perth, Western Australia, Australia

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Contributors AH had overall responsibility for the conception of this study and drafting this manuscript. All authors contributed to the design of the study and the drafting of this manuscript and all authors approved the final version of this manuscript.

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Competing interests None.

Ethics approval Australian Department of Health and Ageing Departmental Ethics Committee, the Australian Institute of Health and Welfare Ethics Committee, the NSW Population and Health Services Research Ethics Committee, the Aboriginal Health and Medical Research Council of NSW Ethics Committee, the Department of Health WA Human Research Ethics Committee, the WA Aboriginal Health Ethics Committee and the University of Western Sydney Human Research Ethics Committee.

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