



Cohort Profile Update

Cohort Profile Update: The Mater-University of Queensland Study of Pregnancy (MUSP)

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Abstract

The Mater-University of Queensland Study of Pregnancy (MUSP) and its outcomes began in 1981 with data collected on 7223 pregnant woman-child pairs (6753 mothers, of whom 520 had 2 study children, less 50 who had multiple births). These women, and their children, were initially followed for up to 21 years. Since then there have been additional follow-ups of the mothers (27 years) and their children (30 years). There has also been a substantial increase in the breadth of topics addressed, with the collection of biological samples, the administration of structured clinical assessments of mental health and cognitive capacity, and markers of physical health such as lung function and blood pressure. MUSP was originally developed as a birth cohort study. It has become a longitudinal study of growth, development and ageing with an emphasis on the generational transmission of a wide range of factors impacting on adult health outcomes. We welcome interest in our study; for study background and publications visit [www.socialscience.uq.edu.au/musp] or contact [j.najman@uq.edu.au].

Key Messages

- Long running cohorts have substantial changes in aims, focus and direction, so broadly based measures covering a wide range of topic areas are suggested at the time of study initiation.
- Having parent-child paired data provides additional opportunities for testing hypotheses and research ideas. Sibling data and other parent data also can enhance a studies' capacity to test hypotheses.
- Long term follow-ups often involve substantial attrition. We find that the negative consequences of attrition on estimates of association may have been overstated.

What is the rationale for the new focus?

Birth cohort studies may have a natural beginning but they have no obvious end. MUSP began as a cohort study of some 8556 consecutive, pregnant women recruited at the first antenatal visit. Since the previously reported 21-year follow-up of mothers and their offspring,¹ there have been additional follow-ups of the mothers (27 years) and the children (30 years). Investigators have commenced a study of the children of the children (third generation).

Although the advantages of having a 'linked' (mother-offspring) birth cohort remain, the study now comprises two cohorts: one of women over their reproductive life course and beyond, and also a cohort of their offspring, many of whom now have their own children.

Many of the research topics, which are currently of interest and which involve the use of data collected over a 30-year period, could not have been anticipated when the MUSP commenced. There have been changes in research interest which are partly a consequence of emerging public health research priorities in the broader population, (for example, increasing concern with obesity and illicit drug use), changes in the availability of validated measures (developments using the Composite International Diagnostic Interview) and changes in the research team, its priorities and skills. Birth cohort studies constitute a repository of data to which researchers can turn when new research questions arise.^{2,3} Collecting data on a wide range of indicators continues to be a core feature of MUSP.

What will be the new areas of research?

Follow-ups of mothers for up to 21 years were in tandem with child follow-ups. Beginning in 2008, MUSP investigators commenced the first follow-up of mothers as an independent cohort. Some 3561 of the mothers provided data, and comprised 52.7% of the sample of mothers originally recruited. With mothers now in middle age and with many of their children having left home, the focus in this follow-up was on the menopausal transition, the quality of domestic relationships and experiences of intimate partner violence, as well as mental and physical health.

For the 30-year follow-up of the offspring, the focus was on the possibility of detecting gene-environment interactions as these account for variations in mental and physical health, work and home life.

Record linkage added

As the mothers (G1) and their offspring (G2) age, record linkage projects are of increased interest. At about the time of the 14-year follow-up, a paediatrician⁴ undertook a

'manual' linkage of reports to the government agency of child abuse and/or neglect. Some 11% of the MUSP offspring sample was identified as suspected cases, and 7% of the offspring cohort was confirmed as cases of abuse and/or neglect. This record of child maltreatment has recently been linked to the 21-year follow-up. MUSP investigators now routinely seek permission from mothers and offspring to link data to a variety of databases, including hospital and health records, and other government agency data such as police and social welfare. There is a current project aiming to link MUSP data to death certification records.

Next stage—children of the children

With the offspring in the study now over 30 years of age, many have their own children. Based on data collected at the 30-year follow-up, there are now 3000–4000 children of the children (G3), across an age range of 0–18 years. MUSP is now in the process of assessing physical and mental health and developmental outcomes for the third generation.

Who is in the cohort?

Figure 1 provides details of follow-up and attrition. At the mothers' 27-year follow-up, some 52.7% of respondents remained in the sample. The loss to follow-up of the offspring is of greater concern at the 30-year phase. We attribute this loss to two factors: first, the collection of 'fasting' blood samples (early morning collections) and, second, many parents being at a busy phase of life. Many parents were employed and had childcare commitments.

The age distribution of the mother and offspring cohorts are presented in Table 1. Perhaps the most obvious change, from mothers to their offspring, has been the reduction in the percentage who are married. At recruitment in 1981–83, some 74.2% of women described themselves as married and 10.9% as single. Among their offspring, some 44.0% are married and 49.9% report they have not ever married. About one in three mothers (33.2%) describe themselves as ex-smokers, but fewer of the children have ever taken up smoking.

There is an assumption that loss to follow-up poses a threat to the validity of findings. In MUSP a good deal of social, demographic and medical history data were collected at recruitment, so a great deal is known about those subsequently lost to follow-up. Those disproportionately lost to follow-up are young, economically disadvantaged, of separated/divorced marital status and with higher rates of anxiety, depression and alcohol, tobacco and illicit substance use behaviours. Consequently, it is routine to undertake some forms of adjustment (e.g. inverse probability

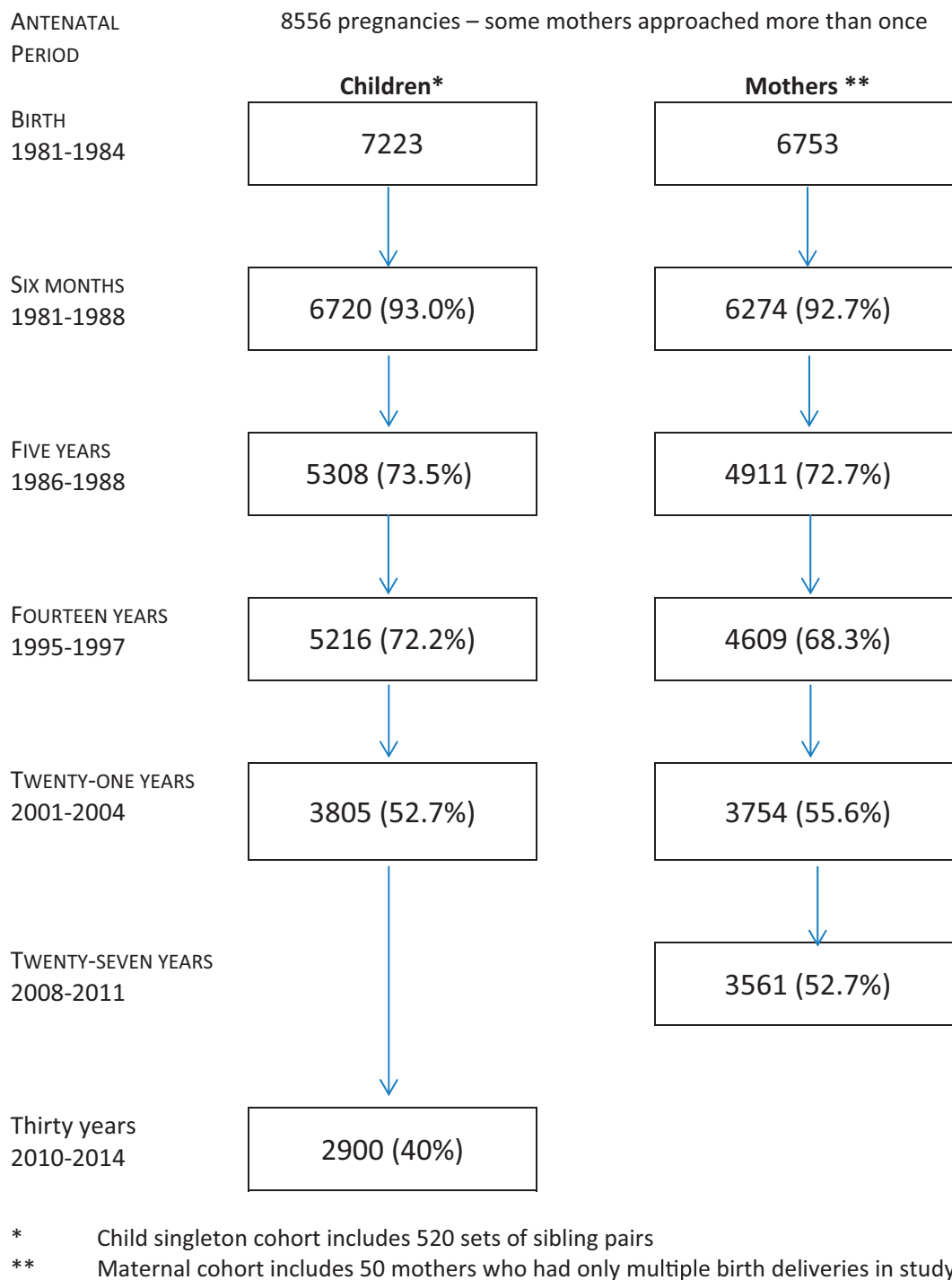


Figure 1. Flowchart: number (%) retained in study at each phase (age) of data collection. Child singleton cohort includes 520 sets of sibling pairs. Maternal cohort includes 50 mothers who had only multiple birth deliveries during the study.

weighting, multiple imputation) to ‘correct’ for bias associated with differential loss to follow-up. After publication of many papers which include these corrections, and repeatedly finding that after adjustment for loss to follow-up the results remain unaffected, MUSP investigators are questioning many of the taken-for-granted assumptions about the consequences of loss to follow-up. Bias in

follow-up may, in theory, impact on findings, but in practice this may rarely be a problem. The extent to which biased loss to follow-up affects an association has been discussed in some papers.^{1,5}

In a new strategy to assess the possible impact of bias, we take a known association at the time of recruitment and then ‘strip’ those subsequently lost to follow-up.

Table 1. Sociodemographic characteristics of cohort samples at most recent data collection

	Mother 27-yr F/U (<i>n</i> = 3501) %	Offspring 30-r F/U (<i>n</i> = 2541) %
Age (years)		
27–33		100.0
40–49	28.7	
50–59	60.6	
60–73	10.7	
Gender		
Male	–	42.6
Female	100.0	57.4
Marital status		
Married	65.8	44.0
Separated/widowed	9.9	3.6
Divorced	20.9	2.5
Not ever married	3.5	49.9
Smoking status		
Current	22.3	21.3
Ex-smoker	33.2	23.4
Never	43.0	51.4
Only a few times	1.5	3.9

F/U, follow-up.

We compare the ‘known’ finding with the estimates of association after removing those subsequently lost to follow-up. We are consistently finding the observed associations robust to even highly biased attrition and large levels of loss to follow-up.

What has been measured?

Measurements are in three categories. First, each additional phase of data collection includes measures which have previously been used. This is to enable estimates of change over time [e.g. the Delusions-Symptoms-States-Inventory (DSSI) to assess maternal anxiety and depression]. Second, some measures are intended to assess experiences and events since the previous phase of data collection (e.g. life events occurring between follow-ups are routinely assessed). Finally, there are new measures administered which are appropriate to the life-course stage and research focus of the specific phase of the study (e.g. for the 27-year follow-up, a detailed menopausal symptom inventory; for the offspring, a detailed measure of four dimensions of intimate partner violence).

MUSP investigators have now extended the collection of biological samples to include blood, urine, saliva and buccal swabs from the offspring (G2 at 30 years of age). Initially, these biological samples are being screened for

markers of cardiovascular risk and metabolic syndrome. Genotyping is currently under way. The study now includes a number of measurements of physical health (e.g. blood pressure, respiratory function and body fat composition via bioimpedance). MUSP investigators administered the World Health Organization Composite International Diagnostic Interview (WHO-CIDI) at the 27-year follow-up of mothers and 30-year follow-up of offspring. A subsample of participants (*n* = 1108), who reported psychotic symptoms in adolescence, are being interviewed by clinicians to assess the validity of the CIDI diagnosis and document mental health outcomes and psychological functioning. There is now a focus on the specific episodes of mental illness and their duration, severity and impact over the life course, extending—it is anticipated—to G3 (children of the children). Data have also been collected on a wide variety of measures of cognition. The modified mini mental state examination (3MS) was administered to mothers at the 27-year follow-up.

The most recent follow-ups have also involved larger and more detailed measurements of many constructs. For example, there has been the administration of a food frequency questionnaire. The inclusion of more detailed measures has increased the respondent burden, with a consequent increase in cost and a reduction in the response rate.

Methodological issues

Since data collection commenced in 1981, the computer software supporting data collection has demonstrated marked advances. Participant tracking software now deals much more effectively and systematically with updating contact details. Another important change has involved the analysis of data. Initial papers largely involved linking data from earlier phases to outcomes at a subsequent phase. The statistical methods involved were relatively routine and did not require highly specialized statistical skills. As data collection continues, MUSP investigators find they have to deal with the problem of multiple repeated measures, highly correlated variables, and questions of reverse causality. Increasingly there is a need to use complex data analysis strategies with non-dependent covariance structures. These include multi-level (hierarchical) models, models with generalised estimating equations (GEE), trajectory analyses with explanatory covariates, structural equation modelling and random effects models which involve a variety of probability distributions.

What has it found? Key findings and publications

With data collected over a 30-year period, and over 160 research papers published since the previous cohort profile,

Table 2. Illicit substance use: history of cohort samples at most recent data collection (CID1)

		Mother 27-yr F/U (n = 3495)	Offspring 30-yr F/U	
			Female (n = 1450)	Male (n = 1072)
Ever used marijuana	Yes	32.1%	63.2%	71.3%
Ever used cocaine	Yes	1.1%	17.2%	26.9%
Ever used club drugs	Yes	0.9%	29.4%	38.7%
Ever used hallucinogens	Yes	4.6%	14.6%	27.1%
Ever used opioids	Yes	1.0%	3.2%	4.2%
Ever used inhalants/solvents	Yes	0.6%	3.9%	7.1%

F/U, follow-up.

papers vary widely in their content [www.socialscience.uq.edu.au/musp]. It is, for example, possible to assess generational changes in important health-related behaviours (Table 2). Pregnant women (G1), when they were recruited, were between the ages of 13.2 and 46.9 years (mean 25.0 years), with 75% of women (IQR) aged 21.1–28.3 years in the 1981–83 recruitment period. The generational increase in illicit drug use (mothers to daughters) is substantial (note that the mean age of first drug use is around 20 years of age). By the 27-year follow-up, some 32.1% of mothers report ever having used cannabis. Their daughters report twice this level of ever cannabis use. For cocaine and club drugs, the increase in levels of use is even more substantial. It is clear that there has been a substantial generational increase in the lifetime ever use of a wide range of illicit drugs.

Publications can be seen to fit into a matrix comprising types of papers, namely: (i) those assessing exposures at one point in time and their putative consequences on the other; (ii) those assessing repeated exposures at a number of points in time and their consequences; and (iii) those which examine exposures and outcomes at a number of time points, and which explicitly address the causal sequence that best characterizes the observed association. Table 3 provides a partial list of the topic areas.

What are the main strengths and weaknesses?

The strengths of MUSP include the degree of clinician input from the first planning of the study, the subsequent high level of recruitment to the study, the continuing involvement of some of the same investigators since the study commenced and the commitment to a broadly based study which covers a diverse range of topics.

Two investigators (J.M.N. and G.M.W.) have effectively been involved in the study since it commenced. Two others (M.O., W.B.) had joined the study by the 5-year follow-up. Four others have played a prominent role in obtaining recent grant funding (A.C., R.A., A.M., J.S.). A number of other investigators have been working with MUSP for some 10 years and longer. In recent years there has been an increase in the number of investigators and PhD students who participate in the study.

Clinician participation in MUSP was a feature of its initiation, although the range of clinical interests and the specialties involved have changed. Initially, the study involved the obstetricians responsible for the care of the pregnant women. As a consequence some 200 items of obstetric relevance (including the current and prior obstetric history of the women) were extracted from the medical records and added to the database. As the offspring matured, the obstetricians reduced their involvement and paediatricians and child and adolescent psychiatrists became involved. This involvement has now been supplemented by an endocrinologist and an obstetric physician, as well as physicians, psychiatrists, pathologists and geneticists. Involvement in MUSP tends to mean attending many meetings associated with planning a follow-up, contributing to the measures that are used and providing support during the data collection.

Some characteristics of MUSP are both a strength and a weakness. MUSP is unusual insofar as it has never sought (or been offered) any secure or dedicated funding. Each phase of data collection is dependent upon competitive funding from government-supported (e.g. the National Health and Medical Research Council) agencies, with success rates that generally average around 20–25%. The requirement that MUSP compete for funding has the consequence that data collection is planned well before it ever begins. However, a negative consequence of this pattern of funding is that the duration of time between phases of data collection can vary depending upon the outcomes of the applications. Unfortunately, follow-ups tend to be widely spaced out and the gaps between phases of data collection may be variable and substantial.

Perhaps the most obvious weakness of MUSP is that few data were obtained on the father, at the time of recruitment. Fathers in G1 are likely to have contributed to the health and development of G2 in a variety of ways, but this is a topic MUSP is largely unable to address. Despite some weaknesses, MUSP's longitudinal methodology spanning over 30 years has contributed to our understanding of health in a wide range of areas. The recent collection of biological samples, along with the future data collection proposed for the third generation, will shift MUSP from a focus on individual life-course

Table 3. Selected findings by type of research paper

Findings	Early exposures, later outcomes	Multiple exposure, later outcomes	Multiple exposures and outcomes → causal sequences
Mental illness / substance use	There is a weak but statistically significant inverse association between the birthweight of the child and adult symptoms of depression, supporting a fetal origin of depression hypothesis ⁶	Children who exhibit symptoms of mental illness at age 5 and 14 years are disproportionately likely to have psychotic symptoms and non-affective psychotic disorder at 21 years of age ⁷	Maternal marital quality declines and maternal depression levels increase following the birth of a baby. In a causal analysis, depression predicts subsequent poor marital quality ⁷
Obesity/BMI/CVD	Maternal smoking during pregnancy predicts offspring obesity even after a wide range of potential confounders are considered ⁸	Hypertensive disorders of pregnancy predict a diagnosis of diabetes mellitus 21 years after the pregnancy, after adjustment for a wide range of potential confounders ⁹	
Social determinants of health	Children who experience poverty at any developmental stage have reduced cognitive (IQ) scores when they reach adolescence. These effects appear to be cumulative ¹⁰	Female adolescents with mothers who smoked during pregnancy and after the child was born have an increased rate of symptoms of asthma in adolescence ¹¹	There is an association between physical activity and IQ but the evidence does not support the claim that it is causal ¹²
Methodological issues	When describing the mental health of their children, mothers who are emotionally impaired attribute more symptoms of mental illness to their children than do the children themselves. ¹⁸ The extent to which it is possible to 'screen' adolescents for future (young adult) mental health problems is assessed using a number of measures. Generally, adolescent screening provides only a weak prediction of subsequent clinical diagnoses ¹³	Taking advantage of the fact that, at the 27-year follow-up, many daughters are the same age as were their mothers at initial recruitment, this study examines female changes in levels/frequency (quantity) of alcohol consumption. Daughters are found to consume substantially higher levels of alcohol than did their mothers at the same age ¹⁴	The observed association between cannabis use and psychosis could be attributed to uncontrolled confounding. This paper used sibling pair analyses to test the impact of cannabis use on subsequent psychotic symptoms, with sibling pair data used to adjust for other environmental factors. It finds a positive association between cannabis use and symptoms of psychosis ¹⁵

BMI, body mass index; CVD, cardiovascular disease.

trajectories to a focus on trans-generational patterns of health and illness. Birth cohort studies are resource- and labour-intensive. They are likely to be most useful if they are large in scale, few in number and inclusive of many diverse interests.

Can I get the data? Where can I find more?

Collaborations with other researchers are generally welcomed; these collaborations may take any number of forms including the preparation of research papers on specific topics, development of grant applications to support a data collection, and extended visits by colleagues with complementary interests. These collaborations generally involve working with one or more of the MUSP investigators. Details of each follow-up (see guidelines for follow-up) and data collections are found at [www.socialscience.uq.edu.au/musp].

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