The Victorian Intergenerational Health Cohort Study (VIHCS): Study design of a preconception cohort from parent adolescence to offspring childhood

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Synopsis

Study question

The Victorian Intergenerational Health Cohort Study (VIHCS) was designed to examine the contributions of parental mental health problems, substance use, and socioeconomic characteristics before pregnancy to child emotional, physical, social, and cognitive development.

What's already known

Parental exposures during pregnancy and postpartum predict offspring health and development throughout the life course. Emerging evidence suggests that many of these parental processes, including poor mental health, substance use, and socioeconomic characteristics, originate before conception.

What this study adds

VIHCS combines nine waves of prospectively obtained parental preconception data from adolescence to young adulthood, with three waves of parental and child perinatal data for 1030 subsequently born infants. These data allow examination of the extent to which parental risk processes before pregnancy predict offspring early development, and potential preconception, ante- and post-natal intervention targets.

Abstract

Background: There is increasing evidence that parental determinants of offspring early life development begin well before pregnancy.

Objectives: We established the Victorian Intergenerational Health Cohort Study (VIHCS) to examine the contributions of parental mental health, substance use and socioeconomic characteristics before pregnancy to child emotional, physical, social, and cognitive development.

Population: Men and women were recruited from the Victorian Adolescent Health Cohort (VAHCS), an existing cohort study beginning in 1992 that assessed a representative sample of 1943 secondary school students in Victoria, Australia, repeatedly from adolescence (Wave 1, mean age 14 years) to adulthood (Wave 10, mean age 35 years).

Methods: VAHCS participants with children born between 2006 and 2013 were recruited to VIHCS, and invited to participate during trimester three, at 2 months postpartum, and one year postpartum. Parental mental health, substance use and socioeconomic characteristics were assessed repeatedly throughout; infant characteristics were assessed postnatally and in infancy. Data will be supplemented by linkage to routine datasets. A further follow-up is underway as children reach eight years of age.

Preliminary results: Of the 1307 infants born to VAHCS participants between 2006 and 2013, 1030 were recruited to VIHCS. At VIHCS study entry, 18% of recruited parents had

preconception common mental disorder in adolescence and young adulthood, 18% smoked daily in adolescence and young adulthood, and 6% had not completed high school. Half of VIHCS infants were female (48%), 4% were from multiple births, and 7% were preterm (<37 weeks gestation).

Conclusions: VIHCS is a prospective cohort of 1030 children with up to nine waves of preconception parental data, and three waves of perinatal parental and infant data. These will allow examination of continuities of parental health and health risks from the decades before pregnancy to offspring childhood, and the contributions of exposures before pregnancy to offspring outcomes in childhood.

Background

Early life growth and development predict trajectories of health across the life-course. For this reason, maternal and child exposures in pregnancy and the first year of life have received much attention in research and policy.^{1,2} Perinatal exposures, including parental mental health, substance use and socioeconomic disadvantage, predict a range of adverse health and developmental outcomes across childhood and into adulthood.³⁻⁶ Yet increasingly we are coming to understand that determinants of early life growth and development can be identified before pregnancy.^{7,8} Poor maternal nutrition prior to pregnancy predicts an increased risk of pregnancy complications and poor birth outcomes.⁹ Other parental determinants of offspring mental health, health risks and disadvantage may also begin in the years before pregnancy.^{10,11} These include parental mental disorder and substance use, which become prominent following reproductive maturity at puberty,¹²⁻¹⁴ are the leading cause globally of disability in children and youth,¹⁵ and commonly persist into young adulthood and the subsequent transition to parenthood.^{13,14,16} Parental socioeconomic determinants of offspring growth and development are also typically established well before pregnancy,^{17,18} with the transition from adolescence to young adulthood marking a pivotal shift from family to individual educational, financial and other trajectories of socioeconomic attainment and role transitions.^{14,19,20}

The links between parental preconception exposures and early life offspring development have raised a question about whether preventive intervention should encompass the years before conception.^{21,22} There are a range of possible mechanisms whereby preconception parental characteristics may affect offspring early life and growth, including the persistence

of parental health risks and socioeconomic characteristics into pregnancy and the postpartum period,²³ and direct preconception effects on parental reproductive biology or the gamete that may affect future offspring development.²⁴ Prospectively quantifying the contribution of exposures across a longer timeframe before, during and after pregnancy is an important step toward determining the potential benefits of interventions with parents at each phase. However, prospective human studies able to map parental determinants of offspring early life development across the preconception years from parental adolescence through to childhood of their offspring are rare.

We designed The Victorian Intergenerational Health Cohort Study (VIHCS) to examine the prospective associations of preconception adolescent and young adult mental health, substance use and socioeconomic characteristics with offspring emotional, physical, social, and cognitive development from birth to childhood. Specifically, the study aims to:

1. Describe trajectories of parental mental health, substance use and socioeconomic characteristics from the adolescence of parents to the childhood of offspring.
2. Prospectively quantify associations between parental preconception exposures and next generation outcomes from birth to childhood.
3. Elucidate pathways by which parental exposures before pregnancy may affect next generation outcomes in infancy and childhood, and estimate the potential reduction in adverse outcomes from action on the mediating factors identified.

Methods

Cohort selection

The current study arose from a cohort study that commenced in 1992, the Victorian Adolescent Health Cohort Study (VAHCS; described elsewhere and briefly in Figure 1),¹⁶ with a stratified random sample of 1943 mid-secondary school students from Victoria, Australia, assessed 10 times from adolescence (Wave 1: mean age 14.9 years) to adulthood (Wave 10: mean age 35.1 years). The VAHCS was initially designed to examine the natural history and consequences of common adolescent mental disorders and health risks. Broadly, publications arising from VAHCS have encompassed the domains of common mental disorders, eating disorders, obesity, self-harm, substance use and dependence, and personality disorder. The study has found that the majority (60%) of adolescents with a common mental disorder reported a further episode in young adulthood, and duration rather than severity of adolescent disorder was the strongest predictor of young adult disorder.¹⁶ Conversely, most self-harming behaviour did not persist into adulthood,²⁵ and most adverse adult outcomes of self-harm could be explained by concurrent adolescent mental disorder and substance use.²⁶ Adolescent binge drinking and loss of control over drinking, as opposed to frequency of alcohol use, predicted young adult alcohol use disorders.²⁷ Adverse consequences of cannabis use were most pronounced in heavy early adolescent users; these included persisting mental health problems, lower educational attainment, and progression to using other substances.²⁸ Adolescent mental disorder, antisocial behaviour and frequent cannabis use were also associated with adverse socio-economic outcomes, including lower likelihood of transitioning from education to

employment.²⁹ A list of further VAHCS publications can be found at

<https://www.mcrci.edu.au/research/projects/2000-stories>.

Insert Figure 1 here.

We began VIHCS in 2006 during the ninth wave of VAHCS follow-up (Wave 9: mean age 29.0 years) when 13 VAHCS participants had died, 163 had withdrawn, and 96 were lost to follow-up (Figure 2). Between 2006 and 2013, the remaining 1671 active VAHCS participants were screened for pregnancies and live births. This window spans the peak reproductive years, encompassing the median age of mothers (30.7 years) and fathers (33.0 years) for births in Australia.³⁰ During screening, VAHCS participants were contacted every six months and asked if they or their partner were pregnant or had a child born in the past year. Initially, participants were mailed a reply-paid card to report pregnancies, but from 2008 participants were contacted via email, with text message, telephone or postal follow-up. Participants reporting a pregnancy or recently born child were sent an invitation letter and information statement, and contacted via telephone to discuss the study and obtain verbal consent. VAHCS participants were invited to participate for every infant born during VIHCS screening, and thus many participated with more than one infant. Protocols for both VAHCS and VIHCS were approved by the human research ethics committee at the Royal Children's Hospital, Melbourne.

Insert Figure 2 here.

The cohort remained open during the first three VIHCS waves (third trimester of pregnancy, two months postpartum and one year postpartum), such that eligible VAHCS participants and their children could join at the wave two or wave three assessment even if they had not participated in the earlier wave/s. This was done because the challenges in maintaining six-monthly contact with all VAHCS participants meant that we did not detect all eligible pregnancies in time for wave one and/or two. This strategy allowed us to maximize the number of births included in the VIHCS cohort for future follow-up.

Procedures

The defining feature of VIHCS is the prospective collection of parental data across adolescence and young adulthood, and again in pregnancy, and offspring infancy and childhood. The main preconception risk factors and perinatal and childhood outcomes of interest are outlined in Table 1. The study aims to capture mental health, health risks and socioeconomic characteristics at each phase from adolescence before pregnancy through to offspring childhood. We therefore aim to use consistent measures at each wave; where necessary, developmentally appropriate adaptations are used. Validated measures are used when possible.

Insert Table 1 here.

Preconception adolescent and young adult data on the VAHCS cohort parent were collected as part of the VAHCS study, via self-administered laptop questionnaires in adolescence with telephone follow-up of absent students (VAHCS waves 1-6, mean age 14.9 to 17.4 years),

and computer-assisted telephone interviews (CATI) in young adulthood (VAHCS waves 7-9, mean ages 20.7, 24.1 and 29.1 years, respectively). At every wave, participants reported on a range of exposures including frequency and quantity of alcohol, tobacco and cannabis use, common mental disorder, self-harm, antisocial behaviour, sexual activity and health, height and weight, educational attainment, and other socio-economic characteristics, providing rich data on change and continuity of exposures over time. Other factors assessed at developmentally appropriate windows include personality and personality disorder, eating behaviours and disorders, family and life stressors, parent-adolescent relationships, childhood sexual abuse, parent and peer substance use, and substance use disorders. DNA samples (buccal swabs) were also collected (age 24 years).

Three perinatal waves of VIHCS data collection are also complete: in the third trimester of pregnancy (Wave 1), two months postpartum (Wave 2), and one year postpartum (Wave 3). Perinatal data were obtained via CATI, with written versions offered to participants on request (<2% at each wave). Both mothers and fathers responded at VIHCS wave one, providing opportunity to retrospectively collect background demographic data on the parent who was not an existing VAHCS participant. At waves two and three, mothers provided data regardless of whether they or their partner was the original VAHCS participant. Paternal antenatal mental health, drug and alcohol use were assessed via paternal report at VIHCS wave one. All other perinatal data were obtained via maternal report, given that over 95% of primary carers in Australia are mothers.³¹ These include repeated assessment of maternal mental health and substance use, maternal-fetal/infant bonding, maternal social support, socio-economic characteristics and partner relationship

quality, and infant feeding, sleeping and eating. At the VIHCS wave three interview, mothers also reported on infant temperament, behaviour, language and cognition.

A multi-informant, multi-modal follow-up is underway as the children reach eight years of age (VIHCS Wave 4, 2014-2021), incorporating parent, teacher and child surveys, and direct assessments of parent-child bonding, child growth and cognition. Saliva samples are collected. Other domains are assessed via multi-informant surveys. Children complete an interviewer-assisted iPad survey on mental health, somatic symptoms and body image, parent, peer, parent and sibling relationships, sleep, activity, and quality of life. Teachers report on child emotional and behavioural problems, and academic performance, via online survey. Mothers and fathers complete more extensive computer-assisted telephone interviews on their own mental health, substance use, partner relationships, socio-economic characteristics and hardship, and on child emotional and behavioural problems, temperament, physical health and activity, and relationships.

The study is also undertaking linkage to routine datasets. Data on labour and birth will be supplemented through Victorian Perinatal Data Collection record linkage, currently underway. Linkage to the National Assessment Program – Literacy and Numeracy, and School Entry Health Questionnaire, are being sought, and will provide nationally standardised data on reading, writing, language and numeracy in mid to late primary school as well as data on physical health, language and literacy, emotional and behavioural problems, family and stressors at child age 5-6 years.

Statistical analysis

The broad strategy for each aim is outlined here; specific methods will vary according to the requirements of individual research questions.

Aim 1. Describe trajectories of parental mental health, substance use and social characteristics from the adolescence of parents to the mid-childhood of offspring. We will examine individual trajectories and population-level risks across time using parent-specific random-effects and multi-state models, respectively.

Aim 2. Prospectively quantify associations between parental preconception exposures and next generation outcomes from pregnancy to mid-childhood. We will use a causal inference framework for analysis design in Aims 2 and 3 given the primary focus on informing potential intervention targets. We will use traditional multivariable regression or, where appropriate, methods of standardisation and propensity scores developed specifically in the field of causal inference, to estimate adjusted population-average causal effects.

Aim 3. Identify mediating paths between parental exposures before pregnancy and next generation outcomes in infancy and childhood, and estimate the potential reduction in adverse outcomes from action on each mediating factor. We will implement causal mediation analyses based on the potential outcomes framework, to decompose the total effects of preconception exposures on next generation outcomes into their effects via different perinatal pathways. An example of this framework, following the interventional effects methodology,^{32,33} is illustrated in Figure 3. The estimates of indirect effect via each

perinatal factor, expressed as a percentage of the total causal effect, allow us to quantify the roles of the different mediators on next generation outcomes. When expressed as a mean or risk difference, these estimates quantify the potential reduction in adverse next generation outcomes that might be achieved through preventive action to bring each mediating factor to a level of those without the preconception exposure.

We will account for within-family correlation structures using multilevel models where cluster-specific effects or variance decomposition are of substantive interest or where additional levels of clustering must be considered (e.g., repeated measures across waves), or generalised estimating equations otherwise.

Insert Figure 3 here.

Results

Recruitment and response rates

Flow of participants from VAHCS to VIHCS is shown in Figure 2. In total, 797 VAHCS participants reported 1307 eligible offspring during screening. eTable A shows the annual number of offspring births reported by VAHCS participants during screening, as well as the expected birth rates for the total VAHCS sample (1943 participants) and the sample of 1671 active participants when VIHCS screening commenced.³⁰ Overall, the reported number of live births (1307) was close to the number expected based on Australian birth rates by maternal or paternal age for the sample (1375). During the first years of screening (2006-2008), VAHCS participants reported fewer births than expected. However, for the latter part of screening (2009-2013) the reported number of births exceeded the expected number. This may reflect the change in identifying pregnancies from postal to email and telephone phone contact from 2008, or slightly delayed parenthood due to higher rates of postgraduate educational attainment in Victoria compared with other Australian states.³⁴

Insert Figure 2 here.

665 VAHCS participants consented to participate in VIHCS for 1030 offspring born during the screening period. Many parents consented with more than one child born during the recruitment phase: 280 parents consented with 2 children, 38 parents consented with 3 children and 3 parents consented with 4 children. Reasons for non-participation were:

declined participation (excluding 86 children), or retrospective reporting of eligible offspring after the window for VIHCS participation (excluding 191 children).

Sample characteristics

Table 2 presents baseline adolescent and family of origin characteristics of VAHCS participants who were screened, identified as eligible, and participated in VIHCS. Sixty per cent of VAHCS parents who participated in VIHCS participants were female, compared to 51% of the original VAHCS sample; this was due primarily to a greater number of births reported by female than male VAHCS participants during VIHCS screening. Aside from a small difference in rates of exposure to parental divorce or separation during VAHCS participants' adolescence, due primarily to a lower rate amongst participants with births during screening compared to those without, there was no other evidence of differences in sample characteristics between groups. A similar pattern of results was observed when the sample was stratified by sex of VAHCS participant (eTable B).

Insert Table 2 here.

At the time of VIHCS study entry, 18% of recruited parents had preconception common mental disorder in adolescence and young adulthood, 18% smoked daily in adolescence and young adulthood, and 6% had not completed high school. Characteristics of the recruited VIHCS offspring sample are shown in Table 3. Half (48%) of 1030 infants were female, half were a firstborn child (47%), and 42 (4%) of infants were part of a multiple birth. Mothers were primiparous for 479 infants (47% of participating offspring). Recruited VIHCS offspring

were similar to all births in the Victorian population on most measured characteristics, though fewer VIHCS offspring were categorised as born low birthweight (5% vs. 7%).³⁵

Insert Table 3 here.

Perinatal assessment response rates

Participation increased over the perinatal phase (Figure 2), from 806 infants assessed in pregnancy to 975 at one year postpartum. eTable C shows the number of completed VAHCS preconception and VIHCS perinatal waves by participant. With the exception of the antenatal assessment, participation was high at most VAHCS and VIHCS waves. Of the sample of 1030 recruited VIHCS offspring, 712 have data in all eight preconception VAHCS waves and 728 have data in all three perinatal VIHCS waves. Overall, 532 have data in all eleven waves across the preconception and perinatal periods; a further 227 have data in ten of the eleven waves, and a further 145 have data in nine of the eleven waves. Only eleven participants had fewer than six waves of participation and none had fewer than three.

Childhood follow-up

We have maintained a high level of participant engagement. Participant engagement strategies include regular contact through newsletter mailouts and a study Facebook page, as well as invitations to participate in study media activities and the development of data collection protocols. Thirty-one of the 1030 children recruited to VIHCS were lost to follow-up after participating at least once in the perinatal phase, leaving 999 available for the

current follow-up in childhood (Figure 2). 628 of these children had reached eight years of age by January 2019; of these, 515 (82%) had participated in the childhood follow-up to as of April 2019. The remaining assessments will be completed as more children reach eight years of age in 2019-2021.

Comment

Strengths of the study

Key strengths of VIHCS include the two-generation, longitudinal design with prospective assessment of preconception exposures over 15 years from adolescence to young adulthood, as well as assessment during subsequent pregnancies, postnatally, and in offspring infancy and childhood. We have begun to implement new statistical methods for causal mediation analysis to decompose the total effects of preconception risk factors on child outcomes into their component effects through antenatal, postpartum and early childhood pathways, as illustrated in Figure 3.^{32,33,36} The combination of prospectively collected data and the adopted causal inference framework allows us to estimate the potential benefit of intervening on each mediating factor, and identify preconception characteristics of those who may benefit most from intervention. We used standardised validated measures for most constructs across all assessment phases. Data were prospectively collected across parent socio-economic and family characteristics, as well as parent and offspring mental health and health risks, allowing consideration of a broad range of individual and contextual influences on parent and offspring health in childhood. Both male and female VAHCS participants were recruited to VIHCS, providing opportunity to investigate continuities in risk processes for both men and women from the preconception period to offspring childhood, preconception prediction of both maternal and paternal parenting and parent-child bonding, and effects of maternal and paternal exposure on offspring health outcomes.

Limitations of the data

Recruitment of offspring occurred between 2006 and 2013, and children born to VAHCS participants before or after this period are not included in the sample. The study was designed to maximise recruitment within a discrete timeframe over the years of peak fertility for Australian males and females. For that reason, extrapolation of the findings to offspring from older or younger parents is difficult. Substantial efforts were made to retain participants in the study and facilitate assessment completion at each wave, but the long study lifespan and repeated assessments led to some attrition and non-response. Rates of non-participation in the VIHCS sample were generally low, ranging from 2% to 14% per wave for the preconception and postnatal waves, but were 33% at the antenatal interview (VIHCS Wave 1) due to the logistical challenges of detecting all pregnancies prior to birth. We use multiple imputation to address potential biases due to missing data, with additional sensitivity analyses to assess potential departures from missing at random assumptions.³⁷ Reliance on maternal report of infant development at the early postpartum waves introduces the possibilities of misclassification; linkage to routine datasets spanning birth to childhood and the multi-informant and observational assessment at eight years of age will complement these data. Parental consent to link with other datasets such as parental criminal records or child protection notifications has not been sought. There is a seven-year gap between VIHCS wave three (1 year postpartum) and VIHCS wave four (8 years of age), an important developmental window. This window reduced respondent burden, given that many parents participated in VIHCS with more than one child and were asked to complete up to three perinatal assessments per child. To address the contribution of early childhood child mental and physical health, family and demographic characteristics, we are seeking

consent for data linkage to children's records from the Victorian School Entrant Health Questionnaire at child age 5 years.

Conclusions

The VIHCS study welcomes collaboration with researchers interested in using the data. For reasons of participant confidentiality and consent, the study ethics protocol precludes data access via public repository. Interested researchers are asked to complete a short proposal template. Approval is dependent on the topic and alignment with papers in progress, and is granted subject to formal agreement on standard terms and obligations around data usage. Further information is available from the principal investigator, Prof. George Patton (george.patton@rch.org.au). Examples of current research directions include the investigation of perinatal and infant outcomes for parents with a preconception history of common mental disorder,³⁸⁻⁴⁰ parental bonding problems,⁴¹ personality disorder,⁴² and self-harm.⁴³

Acknowledgements

The authors would like to thank the families who have participated in the Victorian Adolescent Health Cohort Study and the Victorian Intergenerational Health Cohort Study, and the study research team involved in the collection and management of VIHCS data (Maxine Gross, Rebecca Powers, Caitlin Macmillan, Rianna Chapman, Meaghan Maguire, Anna Snell, Caroline Murphy, Sophie Barker, Charlotte Hudson, Diana Crocker, Deborah Wagner, Joshua Muller, Anna Gorman, Sarah Egan, Emily Horwill, and Jane Watson).

Funding

This work was supported by the National Health and Medical Research Council [APP1008273, APP1063091, APP437015, APP1019887 to G.P., and APP 491205 and APP1103976 to S.B.]; Australian Rotary Health; Colonial Foundation; Perpetual Trustees; Financial Markets Foundation for Children (Australia); Royal Children's Hospital Foundation; Murdoch Children's Research Institute; Australian Postgraduate Award to E.S.; and the Australian Research Council [DP1311459 to C.O., DP110101036 to S.B.]. Research at the Murdoch Children's Research Institute is supported by the Victorian Government's Operational Infrastructure Program.

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Table 1. Key domains assessed by wave of The Victorian Adolescent Health Cohort (VAHCS) and The Victorian Intergenerational Health Cohort (VIHCS)

Study	VAHCS ^a									VIHCS			
Developmental phase	Adolescent						Young adult			Preg	Infant	Child	
Wave	1	2	3	4	5	6	7	8	9	1	2	3	4
Assessment modes
Parent													
Mental disorder and adjustment													
Depression and anxiety	✓ ⁴⁴	✓ ⁴⁴	✓ ⁴⁴	✓ ⁴⁴	✓ ⁴⁴	✓ ⁴⁴	✓ ⁴⁴	✓ ⁴⁵	✓ ⁴⁵⁻⁴⁷	✓ ^{45,48b}	✓ ⁴⁸	✓ ⁴⁸	✓ ⁴⁵
Personality and personality disorder			✓ ⁴⁹			✓ ⁴⁹	✓ ⁴⁹	✓ ^{50,51}					
Self-harm			✓ ⁵²	✓ ⁵²	✓ ⁵²	✓ ⁵²	✓ ⁵²	✓ ⁵²	✓ ⁵²				
Self-esteem	✓ ⁵³	✓ ⁵³	✓ ⁵³	✓ ⁵³									
Physical health and health risks													
Alcohol use / dependence	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ^{46,54}	✓ ^{46,54}	✓ ^{46,54}	✓		✓	✓
Tobacco use / dependence	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ^{54,55}	✓ ^{54,55}	✓ ^{54,55}	✓		✓	✓
Cannabis, other illicit drug use / dependence	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ⁵⁴	✓ ^{46,54}	✓ ^{46,54}	✓ ^{46,54}	✓		✓	✓
Parent, partner, peer substance use	✓	✓	✓	✓	✓	✓				✓			
Antisocial behaviour			✓ ⁵⁶	✓ ⁵⁶	✓ ⁵⁶	✓ ⁵⁶			✓ ⁵⁶				
Sexual activity and health				✓	✓	✓	✓	✓	✓				
Dieting, disordered eating	✓ ⁵⁷⁻⁵⁹	✓ ⁵⁷⁻⁵⁹	✓ ⁵⁷⁻⁵⁹	✓ ⁵⁷⁻⁵⁹	✓ ⁵⁷⁻⁵⁹	✓ ⁵⁷⁻⁵⁹	✓ ⁵⁷⁻⁵⁹		✓ ⁵⁷⁻⁵⁹				
Physical activity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Height and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Physical health, medications, supplements										✓			
Socioeconomic characteristics and context													

Study	VAHCS ^a									VIHCS			
Developmental phase	Adolescent					Young adult				Preg	Infant	Child	
Wave	1	2	3	4	5	6	7	8	9	1	2	3	4
Parent of VAHCS participant's divorce, death, education level	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Geographic/neighbourhood disadvantage						✓ ⁶⁰		✓ ⁶⁰		✓ ⁶⁰	✓ ⁶⁰	✓ ⁶⁰	✓ ⁶⁰
Employment					✓	✓	✓	✓	✓ ⁶¹	✓			✓
Education	✓	✓	✓	✓	✓	✓	✓ ⁶²	✓ ⁶²	✓ ⁶²				
Income and financial security									✓	✓		✓	✓ ⁶³
Household composition										✓		✓	✓
Relationships and cohabitation							✓	✓	✓	✓ ⁶⁴		✓	✓ ⁶⁴
Pregnancy and parenthood							✓	✓	✓	✓			
Social role satisfaction								✓ ⁶⁵	✓ ⁶⁵	✓			
Life stressors	✓ ⁶⁶	✓ ⁶⁶	✓ ⁶⁶	✓ ⁶⁶	✓ ⁶⁶	✓ ⁶⁶				✓ ⁶⁷			
Childhood sexual abuse								✓ ⁶⁸					
Social support					✓ ⁶⁹					✓ ⁷⁰		✓ ⁷⁰	
<i>Parent-child relationships</i>													
Maternal-fetal attachment										✓ ⁷¹			
Parent-child bonding											✓ ⁷²	✓ ⁷²	✓ ^{73,74}
Parenting practices												✓ ⁷⁵	✓ ⁷⁵
<i>Child</i>													
Emotional development													
Depression and anxiety													✓ ⁷⁶⁻⁷⁹
ADHD and CD													✓ ⁷⁷
Wellbeing													✓ ⁸⁰
Body image													✓
Somatic symptoms													✓
Temperament												✓ ^{81,82}	✓ ⁸³

Study	VAHCS ^a									VIHCS			
Developmental phase	Adolescent			Young adult						Preg	Infant		Child
Wave	1	2	3	4	5	6	7	8	9	1	2	3	4
Physical health and health risks													
Birth outcomes											✓ ⁸⁴	✓	✓
Sleeping patterns											✓	✓ ^{85,86}	✓ ⁸⁷
Feeding patterns												✓	
Diet and physical activity												✓	✓
Physical health problems											✓	✓	✓ ^{88,89}
Pubertal onset													✓ ⁹⁰
Height, weight, waist, blood pressure													✓
Cognitive development													
Language and cognitive development												✓ ⁹¹	✓ ⁹²
Numeracy and literacy													✓ ⁹³
Social development													
Peer, sibling, teacher relations													✓ ^{74,77}

^a Partners of original VAHCS participants also completed select items relating to their preconception history retrospectively, at the point of VIHCS study entry; these included family of origin parental death, family of origin parental divorce/separation, family of origin parental education, own education, own substance use, and own pregnancy history / previously born children. ^b At VIHCS Wave 1, expectant mothers completed the Edinburgh Postnatal Depression Scale and expectant fathers completed the General Health Questionnaire. Attributions: Laptop by Jonathan Gibson; measuring by pictohaven; Phone by Marek Polakovic; person by Knut M. Synstad; link by Oliver Kittler; DNA by Vectors Market; all from the Noun Project.

Table 2. Characteristics of (a) all Victorian Adolescent Health Cohort Study (VAHCS) participants, (b) those screened for Victorian Intergenerational Health Cohort study (VIHCS) eligibility, (c) those eligible for VIHCS and (d) those participating in VIHCS.

Baseline characteristics at VAHCS study entry	All VAHCS participants ^a (N = 1943)		Screened for VIHCS ^b (N=1671)		Eligible for VIHCS ^c (N = 797)		VIHCS participants ^d (N = 665)	
	mean	(SD, N ^e)	mean	(SD, N ^e)	mean	(SD, N ^e)	mean	(SD, N ^e)
Participant age (years)	15.5	(0.5, 1943)	15.5	(0.5, 1671)	15.5	(0.4, 797)	15.5	(0.4, 665)
	%	(n / N ^e)	%	(n / N ^e)	%	(n / N ^e)	%	(n / N ^e)
Background/demographic factors								
Participant sex (female)	51%	(1000 / 1943)	53%	(885 / 1671)	58%	(465 / 797)	60%	398 / 665
Participant's parents divorced/separated	23%	(438 / 1941)	22%	(368 / 1671)	19%	(153 / 797)	19%	128 / 665
Neither parent completed high school	33%	(617 / 1843)	33%	(534 / 1633)	35%	(273 / 782)	34%	224 / 657
Adolescent health risks								
Common mental disorder (CIS-R ≥ 12) ^f	26%	(510 / 1943)	26%	(437 / 1671)	24%	(191 / 797)	24%	158 / 665
Regular cigarette smoking ($\geq$ daily)	12%	(241 / 1943)	11%	(189 / 1671)	10%	(78 / 797)	9%	63 / 665
Regular cannabis use ($\geq$ weekly)	4%	(81 / 1912)	4%	(63 / 1653)	3%	(24 / 790)	3%	22 / 659
Frequent drinking (> 3 times per week)	4%	(79 / 1943)	4%	(59 / 1671)	3%	(27 / 797)	3%	23 / 665

^a 1943 participants originally recruited to VAHCS in adolescence

^b 1671 participants still active in VAHCS at VIHCS commencement, and screened for VIHCS eligibility

^c 797 VAHCS participants identified as eligible to participate in VIHCS because they reported one or more children born during VIHCS screening

^d 665 VAHCS participants who participated in VIHCS with one or more children

^e N: number with data; n: number with exposure. N varies between measures based on the number responding to each measure at study entry. Because the VAHCS cohort remained open across the first five adolescent waves, we also estimated sample characteristics of each group adjusted for wave of entry. The pattern of results was similar, so we present here unadjusted results in the observed data.

^f Lewis, G., Pelosi, A. J., Araya, R. & Dunn, G. (1992). Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological Medicine* 22, 465-86.

Table 3. Characteristics of 1030 recruited offspring to 665 VAHCS^a cohort participants

	n / N ^b	%	(95% CI)
Sex			
Female	496 / 1030	48	(45, 51)
Parity			
1	479 / 1030	47	(43, 50)
2	396 / 1030	38	(36, 41)
>=3	155 / 1030	15	(13, 17)
Multiple birth status			
Multiple birth	42 / 1030	4	(3, 5)
Birth outcomes			
Born preterm (< 37 weeks)	63 / 957	7	(6, 9)
Low birthweight (< 2.5kg)	46 / 950	5	(4, 6)

^a VAHCS = The Victorian Adolescent Health Cohort.

^b N represents the number with data on each measure, and so varies according to the number responding to each measure.

Figure 1. Sampling and ascertainment of the Victorian Adolescent Health Cohort, 1992-2014

The Victorian Adolescent Health Cohort Study (VAHCS) is a ten-wave cohort study of young people's health, which commenced in August 1992. Using a two-stage sampling procedure, a representative sample of mid-secondary school students (mean age 14.9 years) from Victoria, Australia was selected. First, 45 urban and rural schools were randomly selected from a stratified frame of government, independent and Catholic schools, with probability of selection proportional to the number of students in each sector. Secondly, one class from each participating school was randomly selected at the ninth year level to participate in Wave 1; a second randomly selected class from each school joined at Wave 2. One school withdrew after Wave 1, a loss of 13 students. School retention rates to year nine in Victoria at the time of sampling were 98%. Participants were assessed at six-monthly intervals during their teens (Waves 1-6, mean age 14.9-17.4 years). The baseline VAHCS sample comprised 1943 students who participated at least once during waves 1-6, 96% of the intended sample of 2032. Of these, 1761 participated at least once in young adulthood (age 20 years (wave 7), 24 years (wave 8), 29 years (wave 9) and 35 years (wave 10). Informed written consent was obtained from participants' parents/guardians at recruitment. For subsequent waves, informed verbal consent was obtained.

phase	Adolescent						Young adult			Adult
survey	wave 1	wave 2	wave 3	wave 4	wave 5	wave 6	wave 7	wave 8	wave 9	wave10
year	1992	1993	1993	1994	1994	1995	1998	2001/03	2006/08	2012/14
mean age (female)	14.9 yr	15.4 yr	15.9 yr	16.3 yr	16.8 yr	17.4 yr	20.6 yr	24.0 yr	29.0 yr	35.1 yr
sample n (female)	466	907	888	875	854	848	866	824	806	789
mean age (male)	15.0 yr	15.5 yr	15.9 yr	16.4 yr	16.8 yr	17.4 yr	20.7 yr	24.2 yr	29.2 yr	35.0 yr
sample n (male)	432	820	809	753	721	682	735	696	695	654
mean age (TOTAL)	14.9 yr	15.5 yr	15.9 yr	16.4 yr	16.8 yr	17.4 yr	20.7 yr	24.1 yr	29.1 yr	35.1 yr
sample n (TOTAL)	898	1727	1697	1628	1575	1530	1601	1520	1501	1443

2 entry points

Total intended sample = 1037(w1) + 995 (w2) = 2032

96% (1943) of sample participated at least once in waves 1-6

Recruitment to
VIHCS (Victorian
Intergenerational
Health Cohort)

Figure 2. Sampling of the Victorian Intergenerational Health Cohort Study (VIHCS), from 2006-2014

VAHCS = The Victorian Adolescent Health Cohort; VIHCS = The Victorian Intergenerational Health Cohort

* Eligibility for study entry at VIHCS wave 1 defined as a viable pregnancy in trimester three during VIHCS screening (1 September 2006 to 30 June 2013); eligibility at VIHCS wave 2/3 defined as a live birth during VIHCS screening.

† Of the 212 VAHCS participants who didn't participate for one or more eligible VIHCS children, 132 were completely excluded and the remaining 80 were recruited to participate in the study with at least one other child.

‡ The cohort remained open during Waves 1-3, so that parents could enter the study at Wave 2 or 3 if they had missed earlier wave/s. Many parents participated with more than one child born during the VIHCS recruitment phase.

Figure 3. Directed acyclic graph illustrating the estimated direct and indirect pathways from persistent preconception maternal mental health problems to offspring infant emotional reactivity, adjusting for baseline and intermediate confounding.

* pathways from baseline confounders to each mediator, post-exposure confounder and outcome are not shown for simplicity

We used an interventional effects approach to estimate direct and indirect pathways, given correlated sequential mediators, and exposure-induced confounding of mediator-outcome associations. The interventional indirect effect via each mediator is defined as the change in mean standardised outcome score if, hypothetically, we changed the distribution of the mediator in the exposed to that in the unexposed, while holding the distribution of descendent mediator(s) to that in the unexposed. The interventional direct effect is defined as the magnitude of the exposure-outcome effect that would remain if we changed the joint distribution of all mediators in the exposed to that in the unexposed (Moreno-Betancur and Carlin, 2018, Vansteelandt and Daniel, 2017). Figure adapted from Spry, E., et. al., 'Maternal mental health and infant emotional reactivity: a 20-year two-cohort study of preconception and perinatal exposures', Psychological Medicine, pp 1-11, Cambridge University Press, 2019, <https://doi.org/10.1017/S0033291719000709>

eTable A. Comparison of number of births per year reported by VAHCS (The Victorian Adolescent Health Cohort) participants with projected Australian population birth rates during the VIHCS recruitment phase (September 2006 - June 2013)¹

1. FEMALE VAHCS PARTICIPANTS

¹ 396 offspring born to female cohort participants before offspring study recruitment began.

² Total sample: 1000 (number of females who participated at least once in the VAHCS adolescent phase).

³ Active sample: 885 (number of females active in the VAHCS study at commencement of the VIHCS recruitment phase).

⁴ Recruitment occurred from September 2006 to June 2013; expected birth rates estimates for 2006 and 2013 are therefore proportional.

2. MALE VAHCS PARTICIPANTS

¹ 210 offspring born to male cohort participants before offspring study recruitment began.

² Total sample: 943 (number of males who participated at least once in the VAHCS adolescent phase).

³ Active sample: 786 (number of males active in the VAHCS study at commencement of the VIHCS recruitment phase).

⁴ Recruitment occurred from September 2006 to June 2013; expected birth rates estimates for 2006 and 2013 are therefore proportional.

eTable B. Characteristics of (a) all Victorian Adolescent Health Cohort Study (VAHCS) participants, (b) those screened for the Victorian Intergenerational Health Cohort study (VIHCS) eligibility, (c) those eligible for VIHCS and (d) those participating in VIHCS, by sex of VAHCS cohort participant.

A1. Characteristics of VAHCS female participants

Baseline characteristics at VAHCS study entry	All VAHCS women ^a (N = 1000)		Screened for VIHCS ^b (N=885)		Eligible for VIHCS ^c (N = 465)		VIHCS participants ^d (N = 398)	
	mean	(SD, N)	mean	(SD, N)	mean	(SD, N)	mean	(SD, N)
Participant age (years)	15.5	(0.5, 1000)	15.5	(0.4, 885)	15.5	(0.4, 465)	15.5	(0.4, 398)
	%	(n / N)	%	(n / N)	%	(n / N)	%	(n / N)
Background/demographic factors								
Participant's parents divorced or separated (by wave 6)	22%	(221 / 999)	22%	(195 / 885)	19%	(89 / 465)	20%	(79 / 398)
Neither parent completed high school	38%	(364 / 966)	38%	(329 / 870)	40%	(183 / 458)	39%	(152 / 393)
Adolescent health risks								
Any common mental disorder (CIS-R $\geq$ 12) ^e	34%	(342 / 1000)	34%	(305 / 885)	31%	(146 / 465)	30%	(121 / 398)
Any regular cigarette smoking ($\geq$ daily)	12%	(120 / 1000)	12%	(102 / 885)	11%	(51 / 465)	10%	(39 / 398)
Any regular cannabis use ($\geq$ weekly)	3%	(28 / 987)	3%	(22 / 876)	2%	(8 / 461)	2%	(7 / 394)
Frequent drinking ($>$ 3 times per week)	3%	(27 / 1000)	2%	(20 / 885)	2%	(8 / 465)	2%	(7 / 398)

N: number with data; n: number with exposure. N varies between measures based on the number responding to each measure at study entry. Because the VAHCS cohort remained open across the first five adolescent waves, we also estimated sample characteristics of each group adjusted for wave of entry. The pattern of results was similar, so we present here unadjusted results in the observed data.

a. 1000 women originally recruited to VAHCS in adolescence

b. 885 women still active in VAHCS at VIHCS commencement, and screened for VIHCS eligibility

c. 465 VAHCS women identified as eligible to participate in VIHCS because they reported one or more children born during VIHCS screening

d. 398 VAHCS women who participated in VIHCS with one or more children

e. Lewis, G., Pelosi, A. J., Araya, R. & Dunn, G. (1992). Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychological Medicine 22, 465-86.

A2. Characteristics of VAHCS male participants

Baseline characteristics at VAHCS study entry	All VAHCS men ^a (N = 943)		Screened for VIHCS ^b (N=786)		Eligible for VIHCS ^c (N = 332)		VIHCS participants ^d (N = 267)	
	mean	(SD, N)	mean	(SD, N)	mean	(SD, N)	mean	(SD, N)
Participant age (years)	15.5	(0.6, 943)	15.5	(0.5, 786)	15.5	(0.4, 332)	15.5	(0.4, 267)
	%	(n / N)	%	(n / N)	%	(n / N)	%	(n / N)
Background/demographic factors								
Participant's parents divorced or separated (by wave 6)	23%	(217 / 942)	22%	(173 / 786)	19%	(64 / 332)	18%	(49 / 267)
Neither parent completed high school	29%	(253 / 877)	27%	(205 / 763)	28%	(90 / 324)	27%	(72 / 264)
Adolescent health risks								
Any common mental disorder (CIS-R $\geq$ 12) ^e	18%	(168 / 943)	17%	(132 / 786)	14%	(45 / 332)	14%	(37 / 267)
Any regular cigarette smoking ($\geq$ daily)	13%	(121 / 943)	11%	(87 / 786)	8%	(27 / 332)	9%	(24 / 267)
Any regular cannabis use ($\geq$ weekly)	6%	(53 / 925)	5%	(41 / 777)	5%	(16 / 329)	6%	(15 / 265)
Frequent drinking ($>$ 3 times per week)	6%	(52 / 943)	5%	(39 / 786)	6%	(19 / 332)	6%	(16 / 267)

N: number with data; n: number with exposure. N varies between measures based on the number responding to each measure at study entry. Because the VAHCS cohort remained open across the first five adolescent waves, we also estimated sample characteristics of each group adjusted for wave of entry. The pattern of results was similar, so we present here unadjusted results in the observed data.

a. 943 men originally recruited to VAHCS in adolescence

b. 786 men still active in VAHCS at VIHCS commencement, and screened for VIHCS eligibility

c. 332 VAHCS men identified as eligible to participate in VIHCS because they reported one or more children born during VIHCS screening

d. 267 VAHCS men who participated in VIHCS with one or more children

e. Lewis, G., Pelosi, A. J., Araya, R. & Dunn, G. (1992). Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychological Medicine 22, 465-86.

eTable C. VAHCS and VIHCS assessment response across multiple waves

Number of VAHCS preconception waves completed ^a	Number of VIHCS perinatal waves completed		
	1 wave	2 waves	3 waves
	n	n	n
1 wave	0	0	0
2 waves	2	0	3
3 waves	3	3	5
4 waves	8	6	22
5 waves	6	9	18
6 waves	9	14	37
7 waves	28	34	111
8 waves	74	106	532

^a: 8 VAHCS waves (wave 1/2, 3, 4, 5, 6, 7, 8, 9).

VAHCS = The Victorian Adolescent Health Cohort.

VIHCS = The Victorian Intergenerational Health Cohort.