

Original Article

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# Maternal mental health and infant emotional reactivity: a 20-year two-cohort study of preconception and perinatal exposures

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## Abstract

**Background.** Maternal mental health during pregnancy and postpartum predicts later emotional and behavioural problems in children. Even though most perinatal mental health problems begin before pregnancy, the consequences of preconception maternal mental health for children's early emotional development have not been prospectively studied.

**Methods.** We used data from two prospective Australian intergenerational cohorts, with 756 women assessed repeatedly for mental health problems before pregnancy between age 13 and 29 years, and during pregnancy and at 1 year postpartum for 1231 subsequent pregnancies. Offspring infant emotional reactivity, an early indicator of differential sensitivity denoting increased risk of emotional problems under adversity, was assessed at 1 year postpartum.

**Results.** Thirty-seven percent of infants born to mothers with persistent preconception mental health problems were categorised as high in emotional reactivity, compared to 23% born to mothers without preconception history (adjusted OR 2.1, 95% CI 1.4–3.1). Ante- and postnatal maternal depressive symptoms were similarly associated with infant emotional reactivity, but these perinatal associations reduced somewhat after adjustment for prior exposure. Causal mediation analysis further showed that 88% of the preconception risk was a direct effect, not mediated by perinatal exposure.

**Conclusions.** Maternal preconception mental health problems predict infant emotional reactivity, independently of maternal perinatal mental health; while associations between perinatal depressive symptoms and infant reactivity are partially explained by prior exposure. Findings suggest that processes shaping early vulnerability for later mental disorders arise well before conception. There is an emerging case for expanding developmental theories and trialling preventive interventions in the years before pregnancy.

## Introduction

Early life environments shape patterns of childhood growth with long-lasting effects on health and human potential (Barker, 1990; Gluckman *et al.*, 2009). Effects extend to later life mental health, with early exposure to maternal mental health problems predicting later childhood emotional and behavioural problems, many of which persist into adulthood (Swanson and Wadhwa, 2008; Pearson *et al.*, 2013; Stein *et al.*, 2014). According to theories of the developmental origins of health and disease, in utero and postpartum development are characterised by heightened adaptive plasticity, allowing maternal transmission of environmental information to offspring to confer a later developmental advantage (Gluckman and Hanson, 2004). Heightened antenatal exposure to maternal stress-related hormones and inflammatory processes (Oberlander *et al.*, 2008; Chan *et al.*, 2018), and altered

caregiving postnatally (Meaney and Szyf, 2005; Newland *et al.*, 2016), have both been implicated as risk processes.

However, links between maternal mental health and offspring development may have their origins in the years before pregnancy (Keenan *et al.*, 2018). According to evolutionary developmental and life course models, maternal biology and behaviour during pregnancy and postpartum reflect experience accumulated during the preconception years (Kuzawa and Quinn, 2009). For most women, perinatal mental health problems are preceded by similar problems before pregnancy, many beginning in adolescence (Patton *et al.*, 2015). The persistence of preconception mental health problems into pregnancy may therefore affect offspring through increased exposure to antenatal and postnatal risks. Alternatively, animal studies have raised a possibility of preconception maternal mental health affecting the periconceptional environment or gamete directly, with independent effects on offspring stress responses (Zaidan *et al.*, 2013). In this latter case, it is further possible that effects previously attributed to perinatal exposures are in fact confounded by exposures occurring before pregnancy (Keenan *et al.*, 2018).

One early phenotypic indicator of infant vulnerability to later mental disorder is heightened emotional reactivity, characterised by irritability, negative mood, and intensity of reactions (Rothbart and Bates, 2006). It has been seen as an indicator of differential susceptibility to context, reflecting a greater capacity to benefit from enriched environments and interventions but also a heightened vulnerability to stress (Belsky, 2005; Boyce and Ellis, 2005; Slagt *et al.*, 2016; Hartman and Belsky, 2018). Emotional reactivity predicts mental health problems in childhood with effects varying across contexts. Four-month-old infants classified by observers as highly reactive to stimuli were, for example, twice as likely to have anxious symptoms at age 7 years (Kagan *et al.*, 1999). Similarly, the parent-reported intensity of infant emotional reaction predicted a 1.5-fold increase in the odds of interviewer-assessed child psychiatric disorder at age 7 years (Sayal *et al.*, 2014). Maternal mental health problems also predict infant emotional reactivity, leading to a suggestion that this heightened early sensitivity to environmental context may be one step in the intergenerational transmission of mental health risks (Davis *et al.*, 2004; Huot *et al.*, 2004; Bruder-Costello *et al.*, 2007; Davis *et al.*, 2007; Rouse and Goodman, 2014).

Questions remain as to the timing of these maternal effects, with implications for our understanding of the mechanisms involved and the optimal timing of interventions. In this study, using data from two longstanding Australian prospective datasets we consider the relative contributions of preconception, antenatal, and postnatal maternal mental health problems to the development of heightened emotional reactivity in infants. We further examine the extent to which any preconception associations are mediated by maternal mental health during pregnancy and in offspring infancy, as well as the extent to which any associations between perinatal mental health and offspring infant emotional reactivity are explained by a history of prior problems.

## Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## Methods

### Sample

We used data from two prospective preconception cohorts located in Australia: The Victorian Intergenerational Health Cohort Study (VIHCS) and the Australian Temperament Project, Generation 3 (ATPG3). These cohorts both assessed women's mental health before, during and after pregnancy, and offspring infant emotional reactivity at 1 year postpartum (appendix p 1).

### VIHCS sample

The VIHCS is an ongoing prospective intergenerational study of preconception predictors of infant and child health, described elsewhere (Patton *et al.*, 2015). It arose from a cohort study commencing in 1992 in the state of Victoria, Australia (The VAHCS) (Patton *et al.*, 2014). Briefly, a close-to-representative sample of 1943 Victorian mid-secondary school students (1000 female) were selected via a two-stage cluster sampling design and assessed six-monthly during adolescence (VAHCS Waves 1–6: mean age 14.9–17.4 years), and three times in young adulthood (VAHCS Waves 7–9: 20.7, 24.1 and 29.1 years). VIHCS began in 2006 during the ninth wave of VAHCS. Between 2006 and 2013 [participant age 29–35 years, encompassing median maternal and paternal age for Australian births (Australian Bureau of Statistics, 2013)], VAHCS participants were screened six-monthly for pregnancies via SMS, email, and phone calls. Participants reporting a pregnancy or recently born infant were invited to participate in VIHCS, and asked to complete telephone interviews in trimester 3, 2 months' postpartum and 1 year postpartum for each infant born during VIHCS screening. Participants' parents or guardians provided informed written consent at recruitment into VAHCS, and participants provided informed verbal consent at every subsequent wave. Protocols were approved by the human research ethics committee at the Royal Children's Hospital, Melbourne.

### ATPG3 sample

The ATPG3 study is an ongoing prospective study of infants born to a 35-year, 15-wave, population-based cohort. The study has tracked the social and emotional health and development of the main cohort (Generation 2) since they were 4–8 months of age in 1983, along with their parents (Generation 1). The original sample ( $N = 2443$  G2 infants and their G1 parents) were recruited through maternal and child health centres in 20 urban and 47 rural local government areas in the state of Victoria, Australia. The sample paralleled population characteristics at the time (Prior *et al.*, 2000). Families were since invited to participate via mail survey every 1–2 years until 19–20 years and every 4 years thereafter. In 2012, the study commenced recruitment of the Generation 3 (G3) infant offspring born to G2 participants and their partners, with a similar design to VIHCS. Identification of pregnancies occurred via participant email or phone every 6 months between 2012 and 2018, representing the peak period of first births in Australia when participants were aged 29–36 years. Telephone or web interviews were conducted in trimester 3, 2 months postpartum and 1 year postpartum. Consent was provided by Generation 1 participants from Waves 1–7, and additionally by Generation 2 participants from Waves 8–15, using consent forms approved by the relevant ethics committees. Generation 2 then provided informed written consent again on

recruitment to the Generation 3 component of the study. Dependent on wave of data collection, study protocols were variously approved by human research ethics committees at the University of Melbourne, the Australian Institute of Family Studies and the Royal Children's Hospital, Melbourne.

### Measures

Preconception maternal mental health problems were assessed during VAHCS Waves 2–7 (participant ages 14–21 years) using the Revised Clinical Interview Schedule (CIS-R) (Lewis *et al.*, 1992), a structured psychiatric interview designed to assess symptoms of anxiety and depression in community samples. The CIS-R has been validated for use with adolescent populations (Patton *et al.*, 1999). At each wave the total score was dichotomised at  $\geq 12$  to identify mixed depression-anxiety symptoms at a level lower than major depressive or anxiety disorder, but which a general practitioner would view as clinically significant (Lewis *et al.*, 1992). At Waves 8 and 9 (participant ages 24 and 29), symptoms of psychological distress were assessed with the 12-item General Health Questionnaire (GHQ-12), a screening measure widely used to assess psychiatric illness in the general population. Total scores were dichotomised at  $\geq 3$ , a threshold that has been found to indicate psychological distress with sensitivity 76% and specificity 83% (Goldberg *et al.*, 1997; Donath, 2001), and corresponds to a CIS-R threshold of  $\geq 12$  (Lewis *et al.*, 1992).

Preconception maternal mental health problems in the ATP study were measured in adolescence and young adulthood using age-appropriate scales. Depressive symptoms were assessed in waves 10–12 (participant ages 13–18) using the 13-item Short Mood and Feelings Questionnaire (Turner *et al.*, 2014). At each wave the total score was dichotomised at  $\geq 11$  to identify moderate to severe depressive symptoms (Turner *et al.*, 2014). Anxiety symptoms were assessed using adapted versions of the Revised Behavior Problem Checklist Short Form in wave 10 (age 13–14) (Quay and Peterson, 1987; Letcher *et al.*, 2012) and the Revised Children's Manifest Anxiety Scale (Reynolds and Richmond, 1978; Letcher *et al.*, 2012) in waves 11–12 (ages 15–18). For each scale, respondents rated frequency of anxious feelings on a scale from 0 'never/rarely' to 1 'sometimes' to 2 'often/almost always', with mean scores  $>$  'sometimes' denoting moderate to severe symptoms. At each wave, a summary variable was derived denoting presence of depressive and/or anxious symptoms. At waves 13–15 (ages 19–28), symptoms of depression and anxiety were assessed using the 21-item Depression Anxiety and Stress Scale (DASS-21; Lovibond and Lovibond, 1995; Antony *et al.*, 1998). The DASS-21 comprises three 7-item subscales measuring depression, anxiety, and stress. It has good psychometric properties and can distinguish symptoms of clinical-level severity (Antony *et al.*, 1998). Participants rated their psychological distress and physiological symptoms on a scale from 0 'did not apply to me at all' to 3 'applied to me very much or most of the time'. The depression, anxiety, and stress subscale scores were dichotomised at their respective thresholds for moderate to severe symptoms ( $\geq 7$ ,  $\geq 6$ ,  $\geq 10$ ), and for each wave a summary variable was derived denoting the presence of symptoms on one or more subscales.

For each cohort, we constructed variables denoting the presence of any mental health problems at  $\geq 1$  adolescent wave (VAHCS Waves 2–6, ATP Waves 10–12), and  $\geq 1$  young adult wave (VAHCS Waves 7–9, ATP Waves 13–15). Based on these

dichotomous variables, we created a four-level variable denoting continuity of mental health problems ('none', 'adolescent only', 'young adult only', and 'both adolescent and young adult').

Antenatal and postnatal maternal depressive symptoms were assessed in both VIHCS and ATPG3 in trimester 3 and at 1 year postpartum for each pregnancy, using the Edinburgh Postnatal Depression Scale (EPDS) (Cox *et al.*, 1987). The EPDS is a 10-item rating scale designed to screen for postpartum depression, which has also been validated for antenatal use (Murray and Cox, 1990). The total score (range 0–30) at each wave was dichotomised at a threshold ( $\geq 10$ ) that is appropriate for use in community samples and when administered via telephone (Gibson *et al.*, 2009; de Figueiredo *et al.*, 2015). This cut-off has been found to indicate depressive disorder with sensitivity 76% and specificity 94% (Bergink *et al.*, 2011).

Infant offspring emotional reactivity was assessed in both VIHCS and ATPG3 via maternal report at 1 year postpartum using the Short Temperament Scale for Toddlers (STST), a 30-item survey designed to assess temperament in toddlers aged 1–3 years (Fullard *et al.*, 1984; Prior *et al.*, 1989). The reactivity subscale comprises eight items. High scores indicate a tendency to react negatively to unpleasant experiences (e.g. cries after a fall or bump), intensity of reaction [e.g. responds to frustration intensely (screams, yells)], and high activity levels [e.g. plays actively (bangs, throws, runs) with toys indoors]. Parents rate the frequency of each item along a Likert scale, from 1 (almost never) to 6 (almost always). We calculated standardised mean scores for each individual, such that mean effects can be interpreted in units of standard deviations. In the absence of an established threshold we defined heightened emotional reactivity as an unstandardised mean score of  $\geq 4$  ('usually does').

Covariates. Our conceptual causal model included factors that were potential confounders of the associations between maternal mental health at each phase and offspring infant emotional reactivity. These were selected based on prior evidence in the literature, and included socioeconomic circumstances, maternal substance use, and offspring birth order and outcomes. Each of these potential confounding factors is associated with maternal mental health, and may affect offspring socio-emotional development through alternative pathways including effects on fetal neurodevelopment, parenting behaviour, and/or broader environmental exposures. Binary variables were constructed as follows: *Family of origin and adolescent characteristics*: mother's parents' high school completion (neither parent *v.* at least one parent completed) and divorce/separation before or during mother's adolescence (ever *v.* never divorced/separated), mother's high school completion (never *v.* ever completed), mother's adolescent smoking (daily smoking at one or more adolescent wave *v.* no daily smoking), and mother's history of divorce or separation (ever *v.* never divorced/separated); *pregnancy characteristics*: mother's periconceptional smoking ( $\geq$  *v.*  $<$  daily smoking immediately prior to pregnancy recognition), household perinatal poverty ( $<$  *v.*  $\geq$  AUD \$ 40 000/annum), and mother's primiparity (first *v.* subsequent liveborn infant); and *birth characteristics*: infant low birth weight ( $<$  *v.*  $\geq$  2.5 kg), and premature birth ( $<$  *v.*  $\geq$  37 weeks).

### Statistical analysis

Given that the cohorts were drawn from similar populations and employed similar offspring sampling and assessment procedures, the primary analyses used an integrated dataset that combined

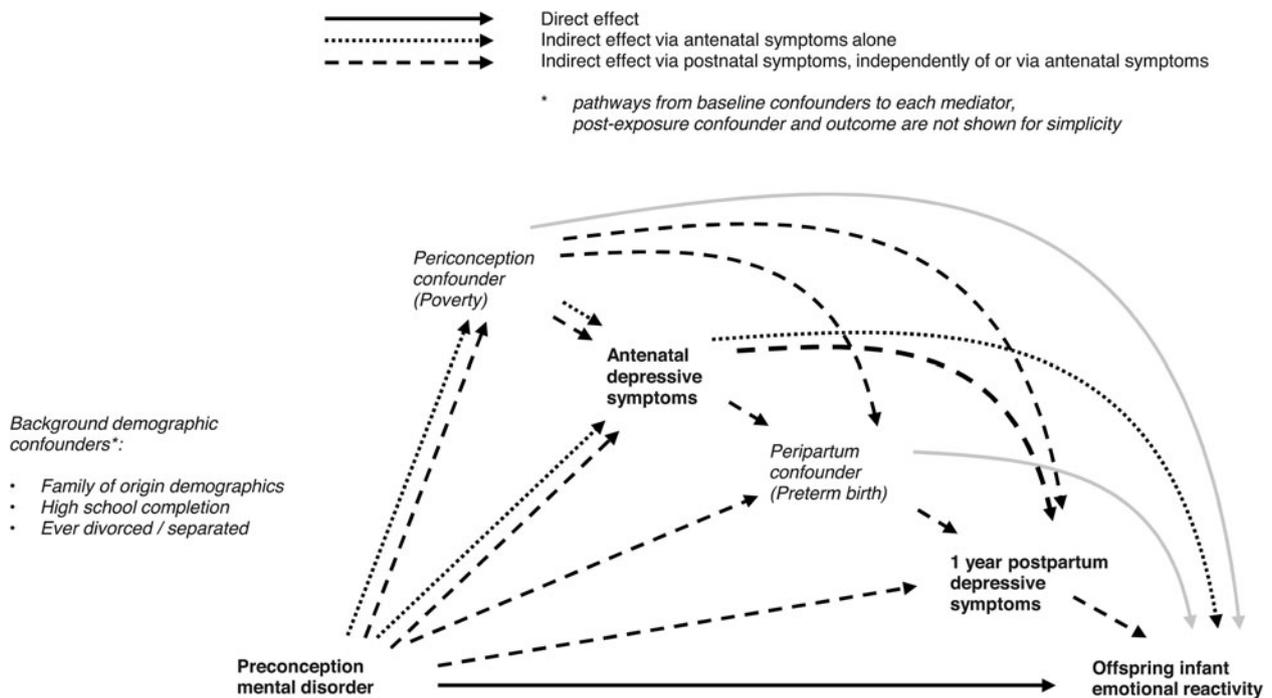


Fig. 1. Directed acyclic graph illustrating the causal pathways estimated in the two-mediator model.

participant-level data from each cohort in order to increase sample size and statistical precision (Curran and Hussong, 2009; Hofer and Piccinin, 2009; Hutchinson *et al.*, 2015). We used linear and logistic regression to estimate the association between maternal mental health problems at each time-point (preconception, antenatal, and postnatal) and offspring infant reactivity at 1 year postpartum. Each model was fitted within a generalised estimating equation (GEE) framework to account for correlation between outcomes due to within-family clustering, and adjusted for cohort and background covariates occurring prior to or at the time of exposure. The antenatal and postnatal models were then progressively adjusted further for prior mental health problems. In online Supplementary analyses we repeated these analyses for each cohort separately.

We then performed a causal mediation analysis to examine the extent to which associations between persistent preconception mental health problems and offspring infant reactivity were mediated by antenatal or postnatal maternal depressive symptoms. We used a potential outcomes framework, specifically an interventional effects approach, which is considered appropriate given correlated, sequential mediators, and exposure-induced confounding of mediator-outcome associations (Vansteelandt and Daniel, 2017; Moreno-Betancur and Carlin, 2018).

An illustrative example of the conceptual model, with two mediators and two post-exposure confounders, is shown in Fig. 1. The interventional *indirect effect* via a mediator is defined as the change in the mean standardised outcome score if, hypothetically, we could change the distribution of the mediator in the exposed group to that in the unexposed group, while holding the distribution of any descendent mediator(s) to that in the unexposed group. This amounts to removing changes in mean standardised outcome score that arise via the pathways from exposure via the mediator but not via its descendants. The

interventional *direct effect* is defined as the magnitude of the exposure-outcome effect that would remain if, hypothetically, we could change the joint distribution of all mediators in the exposed group to that in the unexposed group. The component effects sum to the total marginally-adjusted effect (as opposed to the conditionally-adjusted GEE effect estimate), allowing us to determine the percentage via each component.

The mediation model was adjusted for background demographic characteristics, post-exposure pregnancy and birth characteristics (perinatal poverty and preterm birth), and cohort. Because the post-exposure characteristics may be influenced by the exposure and in turn may influence the outcome, they were treated technically as mediators in the model. We estimated interventional effects as standardised mean differences using regression-standardisation methods based on Monte Carlo simulation (43, 44). Inferences were based on the non-parametric bootstrap.

All analyses included participants who responded at least once in each phase (adolescent, young adult, and perinatal). Among these, there were low levels of missing data on most variables (<10%). However, due to challenges detecting pregnancies, a greater proportion missed the antenatal interview (36%). Incomplete data were handled using multiple imputations by chained equations (White *et al.*, 2011). We imputed 35 complete datasets separately for each cohort, based on the proportion of participants with missing data (Bodner, 2008). Parameter estimates were obtained by pooling results across imputed datasets using Rubin's rules (Rubin, 1987). We performed online Supplementary analyses using available case data. To assess the potential for participation bias, we compared characteristics of participants in each cohort with those who were either not screened for pregnancies due to prior study withdrawal, or who were screened and eligible but did not participate. We used Stata 15 (StataCorp, 2015).

**Table 1.** Estimated preconception and perinatal sample characteristics of infants and mothers, in each cohort and combined

Preconception	VIHCS <i>N</i> = 609		ATPG3 <i>N</i> = 622		Combined <i>N</i> = 1231	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Family background						
Mother's parents divorced/separated	110	(18)	100	(16)	210	(17)
Mother's parents didn't complete high school	225	(37)	150	(24)	375	(30)
Mother's preconception characteristics						
Ever separated or divorced	90	(15)	82	(13)	172	(14)
Never completed high school	43	(7)	29	(5)	73	(6)
Any daily cigarette smoking in adolescence	122	(20)	99	(16)	221	(18)
Mother's mental health problems						
Any adolescent mental health problems	301	(49)	306	(49)	606	(49)
Any young adult mental health problems	224	(37)	228	(37)	452	(37)
Continuity of mental health problems						
None	242	(40)	243	(39)	485	(39)
Adolescent only	143	(23)	150	(24)	294	(24)
Young adult only	67	(11)	73	(12)	139	(11)
Both adolescent and young adult	157	(26)	156	(25)	313	(26)
Perinatal						
Mother's periconceptional characteristics						
Primiparous	282	(46)	281	(45)	563	(46)
Household perinatal poverty	41	(7)	33	(5)	74	(6)
Daily cigarette smoking	76	(12)	60	(10)	135	(11)
Mother's mental health problems						
Antenatal depressive symptoms (third trimester)	76	(12)	100	(16)	175	(14)
Post-natal depressive symptoms (1 year)	49	(8)	70	(11)	119	(10)
Infant characteristics						
Female sex	307	(50)	316	(52)	623	(51)
Pre-term birth (<37 weeks)	37	(6)	48	(8)	85	(7)
Low birthweight (<2.5 kg)	29	(5)	43	(7)	72	(6)
Infant emotional reactivity (mean, s.d.)	2.46	(0.65)	2.64	(0.57)	2.54	(0.62)

VIHCS, The Victorian Intergenerational Health Cohort Study; ATPG3, The Australian Temperament Project, Generation 3.

Frequency estimates were calculated from imputed percentage estimates and total number of infants.

The difference in mother's parents' secondary completion reflects between-cohort differences in the original study data capture, with VIHCS capturing non-completion of secondary school and ATPG3 capturing non-completion of post-secondary school qualifications. Other covariates were assessed consistently across the two cohorts.

## Results

The flow of participants through each study is presented in Appendix p 2. In total, 398 women participated in VIHCS with 609 infants and 395 in ATPG3 with 676 infants. Of these, 37 ATPG2 women did not participate in adolescence and were excluded from the analysis sample, leaving 358 ATPG2 women with 622 ATPG3 infants, and a combined analysis sample of 756 women with 1231 infants who participated at least once in each phase (adolescence, young adulthood, and perinatally). Comparisons of women screened *v.* not screened and participating *v.* eligible non-participants are presented in Appendix pp 3–4. Women who participated were broadly representative of those with live births during the screening on measured baseline characteristics in each study, but there were some differences between

those screened and not screened due to prior loss to follow-up. The ATP women screened were less likely to have parents born outside of Australia, but remained similar to the original ATP sample on the level of parental education. The VIHCS women screened were less likely to have engaged in frequent adolescent drinking, but there were no other notable differences on measured demographic, mental health or risky behaviours in adolescence at VIHCS study entry.

Table 1 summarises infants' and their mothers' characteristics, by cohort and combined. The majority of infants [61%; (95% CI 58–64)] had mothers who reported preconception mental health problems at least once in adolescence and/or young adulthood; of these, most were adolescent-onset. Post conception, 14% of

**Table 2.** Estimated adjusted associations of preconception and perinatal maternal mental health problems with infant emotional reactivity, in combined data ( $N = 1231$  infants of 756 women)

Maternal mental health problems	$n^1$	Offspring infant emotional reactivity							
		Logistic regression					Linear regression		
		$n^2$	%	OR	(95% CI)	$p$	$\beta$	(95% CI)	$p$
<b>Preconception<sup>a</sup></b>									
Adjusted for background characteristics									
No waves (reference)	485	109	23						
Adolescent only	294	78	27	1.3	(0.9, 2.0)	0.226	0.11	(-0.08, 0.30)	0.251
Young adult only	139	36	26	1.3	(0.7, 2.1)	0.414	0.15	(-0.09, 0.38)	0.217
Adolescent and young adult	313	115	37	2.1	(1.4, 3.1)	<0.001	0.38	(0.20, 0.57)	<0.001
<b>Antenatal<sup>b</sup></b>									
Adjusted for background characteristics									
Further adjusted for preconception mental health	175	73	42	2.2	(1.3, 3.8)	0.003	0.37	(0.17, 0.56)	<0.001
Further adjusted for preconception mental health	175	73	42	1.9	(1.1, 3.3)	0.021	0.27	(0.07, 0.48)	0.008
<b>Postnatal<sup>c</sup></b>									
Adjusted for background characteristics									
Further adjusted for preconception mental health	119	52	44	2.2	(1.4, 3.6)	0.001	0.31	(0.10, 0.53)	0.004
Further adjusted for preconception mental health	119	52	44	1.9	(1.2, 3.1)	0.009	0.23	(0.01, 0.45)	0.044
Further adjusted for antenatal mental health	119	52	44	1.7	(1.1, 2.9)	0.030	0.18	(-0.05, 0.41)	0.129

$n^1$  = number exposed;  $n^2$  = number with exposure and outcome. Frequency estimates were calculated from imputed percentage estimates and total number of infants. Heightened infant reactivity at 1 year of age defined as unstandardised STST reactivity mean score  $\geq 4$ . Linear regression estimates are presented as standardised mean score differences.

<sup>a</sup>Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, and mother's adolescent smoking.

<sup>b</sup>Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, mother's adolescent smoking, mother's history of separation and divorce, periconceptional smoking, perinatal poverty, and parity.

<sup>c</sup>Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, mother's adolescent smoking, mother's history of separation and divorce, periconceptional smoking, perinatal poverty, parity, infant preterm birth, and low birthweight.

women reported antenatal depressive symptoms and 10% reported postpartum depressive symptoms. Because 4% of women reported depressive symptoms at both timepoints, the overall rate of antenatal and/or postnatal depression was 20%. There were negligible differences between cohorts on most variables, consistent with expectations given the samples were drawn from similar populations, though rates of perinatal depressive symptoms were slightly higher in the ATPG3 than in VIHCS.

Table 2 shows estimated associations of preconception, antenatal and postnatal maternal mental health problems with offspring infant reactivity. The estimated proportion of infants with heightened reactivity was higher in infants of mothers with both adolescent and young adult mental health problems than in infants of those without [37% (31–44) *v.* 23% (19–27)]. After adjusting for background demographic characteristics and cohort, preconception maternal mental health problems that persisted across adolescence and young adulthood predicted a twofold increase in the odds of heightened infant reactivity [adjusted OR 2.1 (1.4–3.1)], compared with those with no preconception mental health problems. Similarly, in linear regression analyses, we found a mean difference in infant reactivity scores of 0.38 standard deviations between offspring of mothers with persistent preconception mental health problems and those with no preconception mental health problems. Maternal mental health problems antenatally and at 1 year postpartum were similarly associated with offspring infant reactivity, but the magnitude of these perinatal associations reduced somewhat after adjustment for prior exposure. Available case analyses of the combined cohorts yielded a similar pattern of results (Appendix p 5). In

online Supplementary analyses we repeated these analyses in each cohort (Appendix pp 6–7). Preconception, antenatal and postpartum effects were evident in both cohorts. Postpartum effects were somewhat weaker in VIHCS linear models than ATPG3 linear models, but consistent across cohorts in the logistic models. In fully adjusted models, cohort was not associated with infant reactivity.

Table 3 shows the results of the mediation analysis as depicted in Fig. 1, examining the extent to which associations between persistent preconception mental health problems and offspring infant reactivity are mediated by antenatal or postnatal exposure. The marginally-adjusted total effect of persistent maternal preconception mental disorder on offspring infant reactivity was 0.42 of a standard deviation (0.41–0.44). Of this, around 1% was mediated by poverty alone. A further 6% was mediated by antenatal depression and not depression at 1 year postpartum, and 7% was mediated by depression at 1 year postpartum. The percentage mediated by preterm birth and not postpartum depression was -2%, slightly reducing the overall mediated effect size via an opposite pathway. The remaining 88% of the total effect was a direct effect of persistent maternal preconception mental health problems on offspring infant reactivity; not mediated by perinatal poverty, preterm birth, or maternal depressive symptoms antenatally or at 1 year postpartum.

## Discussion

Mothers with persistent mental health problems before pregnancy had twice the odds of having an infant with high emotional

**Table 3.** Estimated direct and indirect pathways from persistent preconception maternal mental health problems to offspring infant emotional reactivity at 1 year of age, after adjusting for baseline and intermediate confounding, in combined data ( $N = 1231$  infants of 756 women)

	Mean difference	(95% CI)	Proportion attributable
Direct effect <sub>(interv)</sub>	0.37	(0.35, 0.39)	88
Indirect effect <sub>(interv)</sub>	0.05	(0.04, 0.06)	12
Indirect via perinatal poverty	0.01	(0.00, 0.01)	1
Indirect via antenatal depressive symptoms	0.02	(0.02, 0.03)	6
Indirect via preterm birth	-0.01	(-0.01, -0.01)	-2
Indirect via postnatal depressive symptoms	0.03	(0.03, 0.04)	7
Total causal effect <sub>(interv)</sub>	0.42	(0.41, 0.44)	100

Marginally adjusted linear regression estimates are presented as standardised mean score differences. Proportion attributable was calculated as a percentage of the total effect. Persistent preconception maternal mental health problems defined as the presence of mental health problems during both adolescence and young adulthood. Model adjusted for baseline confounders (cohort, mother's parents high school completion and divorce, mother's high school completion, and mother's history of separation/divorce). The postnatal estimate includes an effect via the mediator's interdependence [see Vansteelandt and Daniel (2017)] which was very small in this study.

reactivity. This effect was robust across two independent samples, and is similar in size to the effects found for antenatal and postnatal maternal depressive symptoms, in this and prior studies (Davis *et al.*, 2004; Huot *et al.*, 2004; Davis *et al.*, 2007). Despite strong continuities between maternal preconception and perinatal mental health, the effects of preconception maternal mental health problems on offspring infant reactivity were, for the most part, not mediated through greater offspring exposure to maternal depressive symptoms during pregnancy or postpartum. Furthermore, at least part of the associations between perinatal depression and infant emotional reactivity are accounted for by preconception exposure. Infants of mothers with preconception mental health problems may have greater emotional reactivity due to greater exposure during pregnancy and after birth but also through risk processes well before the recognition of the pregnancy.

Associations between both antenatal and postnatal maternal depressive symptoms and heightened infant reactivity are consistent with prior work. However, a finding of a similar-sized and largely direct effect of exposure to persisting maternal mental health problems prior to pregnancy is new. We cannot exclude confounding by genetic susceptibility (Luciano *et al.*, 2018), though 'children of twin' studies indicate that independent links between parent depressive symptoms and offspring internalising or externalising problems persist after accounting for genetic transmission (McAdams *et al.*, 2015). We have considered a range of baseline confounders related to family background, as well as those that might confound the relationship with mediators including perinatal household poverty and infant prematurity. It nevertheless remains possible that other unmeasured contextual factors have confounded the observed associations. These may include stressful life events, family violence or other childhood trauma, caregiver and peer relationship quality, or perceived social support (Stein *et al.*, 2014; Yehuda and Meaney, 2018).

### Potential mechanisms

We considered the possibility that preconception mental health problems might affect offspring infant reactivity through the persistence of maternal symptoms into the antenatal and postnatal periods (Meaney and Szyf, 2005). However, preconception exposure effects on infant reactivity were largely direct, with mediation through antenatal and postnatal processes relatively small.

Although it is possible that a failure to fully identify maternal antenatal and postnatal mental health problems has led to an underestimation of mediation effects, depressive symptoms are the commonest perinatal mental health problem and prevalence at each timepoint in our study was consistent with previous meta-analyses in high-income countries (Woody *et al.*, 2017).

It is also possible that chronic preconception mental health problems might have an enduring effect on maternal endocrine and immune-inflammatory physiology, affecting the fetal environment even when mothers report few perinatal depressive symptoms (Moog *et al.*, 2018). One recent study linked maternal abuse in childhood to increased placental hormone production during later pregnancies, providing preliminary evidence that maternal stress before conception may influence offspring neurodevelopment through changes to the *in utero* environment (Moog *et al.*, 2016). We assessed antenatal maternal depressive symptoms in the third trimester and may not have captured periconceptional exposure including during embryogenesis and implantation, both sensitive to environmental influence including maternal stress (Ord *et al.*, 2017). Brain regions integral to stress response regulation and susceptible to excess exposure to maternal hormones are identifiable by eight weeks gestation (Gunnar and Davis, 2013). Similarly, preconception mental health problems may also be linked to infant emotional reactivity through increased risk of other exposures during pregnancy and postpartum, including health-related behaviours such as maternal substance use or diet, or social factors such as perceived social support, maternal attachment style, partner relationship quality and conflict, or family violence (Howard *et al.*, 2014).

A final possibility is that persistent maternal mental health problems prior to pregnancy might directly affect the maternal germline with persisting effects on offspring stress response and reactivity (Chan *et al.*, 2018). The epigenetic profile of gamete DNA can be altered by parental exposure to stress (Klengel *et al.*, 2015) but until recently these alterations were thought to be completely erased during embryonic development. There is now evidence that some epigenetic marks persist after fertilisation (Klengel *et al.*, 2015). Animal data support the intergenerational transfer of stress-related behaviours through epigenetic modifications to the paternal germline (Klengel *et al.*, 2015). Though studies of maternal germline transmission are limited, evidence is emerging that stress reactivity traits may also be maternally transmitted by epigenetic modifications to methylation of gamete genes

associated with altered stress response (Mitchell *et al.*, 2016). Non-epigenetic gametic alterations, such as the accumulation of metabolites and proteins in oocyte cytoplasm, may also influence fetal development and offspring phenotype (Kovalchuk, 2012).

### **Developmental origins of mental health and disease: a role for preconception influences**

Heightened reactivity in response to ante- and postnatal stress may have predictive adaptive utility, altering stress physiology and brain structure to confer survival advantage in environments characterised by scarcity or threat (Gluckman *et al.*, 2009; Sheriff *et al.*, 2017). For example, evidence suggests that infants exposed to maternal depressive symptoms during only one perinatal timepoint (either pregnancy or postpartum) demonstrate lower mental development at 1 year postpartum compared to infants not exposed at either timepoint or exposed at both timepoints (Sandman *et al.*, 2011). The current study raises the question about whether predictive adaptive responses might arise prior to pregnancy, with longer-term maternal stress prior to conception providing a more stable source of environmental information (Kuzawa and Quinn, 2009). Yet such adaptations might come at a cost with reactive infants having greater susceptibility to childhood emotional and behavioural problems (Belsky, 2005; Boyce and Ellis, 2005; Bylsma *et al.*, 2008; Slagt *et al.*, 2016; Hartman and Belsky, 2018).

### **Strengths and limitations**

This study drew together data from two rare prospective intergenerational studies, with repeated assessment across adolescence and young adulthood, and during pregnancy and postpartum of the next generation, allowing us to examine the relative contribution of mental health problems at each phase. Combining data allowed us to achieve greater precision estimates via pooled analyses, and to examine the consistency of findings across intergenerational samples. The two studies maintained high retention rates, and 85% and 88% of women with live births during the VIHCS and ATPG3 recruitment phases respectively participated in the intergenerational studies. However, a number of limitations should be noted. First, despite consistency in most measures in VIHCS and ATPG3 (i.e. mediators, outcomes and most covariates), measurement of preconception mental health varied between studies. Nonetheless, the prevalence of preconception mental health problems and demographic characteristics were similar across cohorts; the overall pattern of results was similar in the pooled and within cohort analyses; and adjustment for cohort in the models did not alter effect estimates. Sample loss and related bias are further potential limitations. Aside from the loss of a small number of women with frequent adolescent drinking (VIHCS) or parents born outside Australia (ATPG3), those screened for and participating in each study remained broadly similar to the original and eligible study samples on measured characteristics at baseline. Even so, it is possible that the achieved sample differed on unmeasured confounders with some effect on associations found. There were low levels of missing data at most waves, in both cohorts; however, around one-third of antenatal interviews were missed due to difficulties in detecting eligible pregnancies. We addressed potential biases due to missing data using multiple imputation. We also only included infants born to women aged 29–36 years. This included the median maternal age at birth in Australia and maximised the number of included

births, but it remains possible that the risk profiles of older and younger mothers may differ from those in focus in this study.

Finally, infant emotional reactivity was assessed by maternal report and usefully draws on a mother's knowledge of her baby's usual behaviour across contexts, particularly relevant for the study of phenotypic traits such as emotional reactivity (Shiner and Caspi, 2003; Bates *et al.*, 2014). Maternally reported infant reactivity predicts later child social and emotional problems, with effect sizes similar to studies of independently assessed infant reactivity (Kagan *et al.*, 1999; Sayal *et al.*, 2013). However, maternal report of infant outcomes may be affected by a mother's mental state such that depressed mothers perceive their infant as more reactive (Najman *et al.*, 2001; Luoma *et al.*, 2004). We investigated this possibility by including maternal depressive symptoms at the time of the outcome in our mediation model. The association between preconception maternal mental health and offspring infant emotional reactivity was overwhelmingly independent of maternal depressive symptoms at the time of the outcome, suggesting a minimal role of maternal reporting bias due to concurrent depression. These findings align with previous research indicating that depression-related biases explain only a small proportion of variance in maternally reported child behavioural traits (Goodman *et al.*, 2011; Rothbart and Bates, 2006; Bagnier *et al.*, 2013).

### **Conclusion**

Maternal mental health problems remain one of the most significant early life risk factors for childhood emotional and behavioural problems. The current findings do not detract from the importance of antenatal and infancy phases as intervention points for both mothers and offspring, to improve mental health outcomes for infants higher in emotional reactivity (Belsky, 2005; Boyce and Ellis, 2005; Slagt *et al.*, 2016). Indeed, highly reactive children encountering few challenges may have a lower likelihood of externalising problems, and greater prosocial behaviours, school engagement and cognitive competence than low-reactive children (Obrovčić *et al.*, 2010; Slagt *et al.*, 2016). Yet the current study suggests that intervention in the perinatal period alone is unlikely to be sufficient to eliminate risks for the offspring of women with persistent mental health problems prior to pregnancy. It is perhaps one reason why the effects of existing postnatal interventions on maternal depression have been mixed (Poobalan *et al.*, 2007; Stein *et al.*, 2018). There is now a need to further explore whether the effects of maternal preconception mental health problems extend to higher rates of emotional and behavioural problems in later childhood, as well as understand the processes whereby preconception exposure leads to heightened infant reactivity. Even so, the current findings suggest that a reorientation of clinical services and public health responses to the years prior to pregnancy is warranted. Current approaches to preconception care, for example, have largely focused on contraception (Patton *et al.*, 2018) with little attention to maternal mental health. The growing calls for preconception health care around other aspects of health and health risk (Barker *et al.*, 2018) should also extend to mental health (Wilson *et al.*, 2018). It is likely that the benefits will extend beyond women themselves to their children's emotional development.

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