King's Research Portal

DOI:

[10.1017/S0033291719000709](https://doi.org/10.1017/S0033291719000709)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Spry, E., Moreno-Betancur, M., Becker, D., Romaniuk, H., Carlin, J. B., Molyneaux, E. F. L., Howard, L. M., Ryan, J., Letcher, P., McIntosh, J., Macdonald, J. A., J. Greenwood, C., Thomson, K. C., McAnally, H., Hancox, R., Hutchinson, D. M., Youssef, G. J., Olsson, C. A., & Patton, G. C. (2019). Maternal mental health and infant emotional reactivity: a 20-year two-cohort study of preconception and perinatal exposures. *Psychological Medicine*. <https://doi.org/10.1017/S0033291719000709>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

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

Accepted manuscript: This version has been accepted for publication in *Psychological Medicine* and will appear in a revised form, subsequent to editorial input, at <https://www.cambridge.org/core/journals/psychological-medicine>.

Cite as: Spry, E., Moreno-Betancur, M., Becker, D., Romaniuk, H., Carlin, J., Molyneaux, E., Howard, L.M., Ryan, J., Letcher, P., McIntosh, J., Macdonald, J.A., Greenwood, C.J., Thomson, K.C., McAnally, H., Hancox, R., Hutchinson, D.M., Youssef, G.J., Olsson, C.A., & Patton, G.C. (in press). Maternal mental health and infant emotional reactivity: a 20-year two-cohort study of preconception and perinatal exposures. *Psychological Medicine*.

Elizabeth Spry BA(Hons)^{1,2}, Margarita Moreno-Betancur PhD^{3,4}, Denise Becker MBIstats², Helena Romaniuk PhD^{3,5}, Prof John B. Carlin PhD^{3,4,8}, Emma Molyneaux PhD⁶, Prof Louise M. Howard MRCPsych⁶, Joanne Ryan PhD⁷, Primrose Letcher PhD⁸, Prof Jennifer McIntosh PhD¹, Jacqui A. Macdonald PhD^{1,2,8}, Christopher J. Greenwood BPsych(Hons)^{1,2}, Kimberley C. Thomson PhD^{1,8}, Helena McAnally PhD⁹, Prof Robert Hancox MD⁹, Delyse M. Hutchinson PhD^{1,2,8,10}, George J. Youssef PhD^{1,2}, Prof Craig A. Olsson PhD^{*1,2,8}, Prof George C. Patton MD^{*2,8}

* Joint senior authors

^{1.} Deakin University Geelong, Centre for Social and Early Emotional Development, School of Psychology, Faculty of Health; Geelong, AUSTRALIA

^{2.} Murdoch Children's Research Institute, Centre for Adolescent Health; Melbourne, AUSTRALIA

^{3.} Murdoch Children's Research Institute, Clinical Epidemiology & Biostatistics Unit; Melbourne, AUSTRALIA

^{4.} The University of Melbourne, Melbourne School of Population and Global Health; Melbourne, AUSTRALIA

^{5.} Deakin University Burwood, Biostatistics Unit, Faculty of Health; Melbourne, AUSTRALIA

^{6.} Section of Women's Mental Health, Health Service and Population Research Department; Institute of Psychiatry, Psychology & Neuroscience; King's College London, UK & South London and Maudsley NHS Foundation Trust, UK

^{7.} Monash University, School of Public Health and Preventive Medicine, Melbourne, AUSTRALIA

^{8.} The University of Melbourne, Department of Paediatrics, Victoria, AUSTRALIA

^{9.} Department of Preventive and Social Medicine, University of Otago, Dunedin, NEW ZEALAND

^{10.} National Drug and Alcohol Research Centre, Faculty of Medicine, University of New South Wales, AUSTRALIA

Corresponding author: Elizabeth Spry (elizabeth.spry@mcri.edu.au)

36 **Abstract**

37

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

42

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

48

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

56

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

63

64 Introduction

65

66 Early life environments shape patterns of childhood growth with long-lasting effects on health and
67 human potential (Barker, 1990, Gluckman *et al.*, 2009). Effects extend to later life mental health,
68 with early exposure to maternal mental health problems predicting later childhood emotional and
69 behavioural problems, many of which persist into adulthood (Pearson *et al.*, 2013, Stein *et al.*,
70 2014, Swanson and Wadhwa, 2008). According to theories of the developmental origins of health
71 and disease (DoHAD), in utero and postpartum development are characterised by heightened
72 adaptive plasticity, allowing maternal transmission of environmental information to offspring to
73 confer later developmental advantage (Gluckman and Hanson, 2004). Heightened antenatal
74 exposure to maternal stress-related hormones and inflammatory processes (Chan *et al.*, 2017,
75 Oberlander *et al.*, 2008), and altered caregiving postnatally (Meaney and Szyf, 2005, Newland *et*
76 *al.*, 2016), have both been implicated as risk processes.

77

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

90

91 One early phenotypic indicator of infant vulnerability to later mental disorder is heightened
92 emotional reactivity, characterised by irritability, negative mood, and intensity of reactions
93 (Rothbart and Bates, 2006). It has been seen as an indicator of differential susceptibility to context,
94 reflecting a greater capacity to benefit from enriched environments and interventions but also a
95 heightened vulnerability to stress (Belsky, 2005, Boyce and Ellis, 2005, Hartman and Belsky, 2018,
96 Slagt *et al.*, 2016). Emotional reactivity predicts mental health problems in childhood with effects
97 varying across contexts. Four-month old infants classified by observers as highly reactive to stimuli

98 were, for example, twice as likely to have anxious symptoms at age seven years (Kagan *et al.*,
99 1999). Similarly, parent-reported intensity of infant emotional reaction predicted a 1.5-fold
100 increase in the odds of interviewer-assessed child psychiatric disorder at age seven years (Sayal *et*
101 *al.*, 2014). Maternal mental health problems also predict infant emotional reactivity, leading to a
102 suggestion that this heightened early sensitivity to environmental context may be one step in the
103 intergenerational transmission of mental health risks (Bruder-Costello *et al.*, 2007, Davis *et al.*,
104 2007, Davis *et al.*, 2004, Huot *et al.*, 2004, Rouse and Goodman, 2014).

105

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

114

115 **Ethical standards**

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

119

120 **Methods**

121

122 **Sample**

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

127

128 **VIHCS sample**

129 The Victorian Intergenerational Health Cohort Study (VIHCS) is an ongoing prospective
130 intergenerational study of preconception predictors of infant and child health, described
131 elsewhere (Patton *et al.*, 2015). It arose from a cohort study commencing in 1992 in the state of
132 Victoria, Australia (The Victorian Adolescent Health Cohort Study; VAHCS) (Patton *et al.*, 2014).
133 Briefly, a close-to-representative sample of 1943 Victorian mid-secondary school students (1000
134 female) were selected via a two-stage cluster sampling design and assessed six-monthly during
135 adolescence (VAHCS Waves 1-6: mean age 14·9-17·4 years), and three times in young adulthood
136 (VAHCS Waves 7-9: 20·7, 24·1 and 29·1 years). VIHCS began in 2006 during the ninth wave of
137 VAHCS. Between 2006 and 2013 (participant age 29-35 years, encompassing median maternal and
138 paternal age for Australian births (Australian Bureau of Statistics, 2013), VAHCS participants were
139 screened six-monthly for pregnancies via SMS, email, and phone calls. Participants reporting a
140 pregnancy or recently born infant were invited to participate in VIHCS, and asked to complete
141 telephone interviews in trimester three, two months' postpartum and one year postpartum for
142 each infant born during VIHCS screening. Participants' parents or guardians provided informed
143 written consent at recruitment into VAHCS, and participants provided informed verbal consent at
144 every subsequent wave. Protocols were approved by the human research ethics committee at the
145 Royal Children's Hospital, Melbourne.

146

147 **ATPG3 sample**

148 The Australian Temperament Project Generation 3 (ATPG3) study is an ongoing prospective study
149 of infants born to a 35-year, 15-wave, population-based cohort. The study has tracked the social
150 and emotional health and development of the main cohort (Generation 2) since they were 4-8
151 months of age in 1983, along with their parents (Generation 1). The original sample (N=2443 G2
152 infants and their G1 parents) were recruited through maternal and child health centres in 20 urban
153 and 47 rural local government areas in the state of Victoria, Australia. The sample paralleled

154 population characteristics at the time (Prior *et al.*, 2000). Families were since invited to participate
155 via mail survey every 1-2 years until 19-20 years and every 4 years thereafter. In 2012, the study
156 commenced recruitment of the Generation 3 (G3) infant offspring born to G2 participants and their
157 partners, with a similar design to VIHCS. Identification of pregnancies occurred via participant
158 email or phone every six months between 2012 and 2018, representing the peak period of first
159 births in Australia when participants were aged 29-36 years. Telephone or web interviews were
160 conducted in trimester three, two months postpartum and one year postpartum. Consent was
161 provided by Generation 1 participants from Waves 1-7, and additionally by Generation 2
162 participants from Waves 8-15, using consent forms approved by the relevant ethics committees.
163 Generation 2 then provided informed written consent again on recruitment to the Generation 3
164 component of the study. Dependent on wave of data collection, study protocols were variously
165 approved by human research ethics committees at the University of Melbourne, the Australian
166 Institute of Family Studies and the Royal Children's Hospital, Melbourne.

167

168 **Measures**

169

170 **Preconception maternal mental health problems** were assessed during VAHCS Waves 2-7
171 (participant ages 14-21 years) using the Revised Clinical Interview Schedule (CIS-R) (Lewis *et al.*,
172 1992), a structured psychiatric interview designed to assess symptoms of anxiety and depression in
173 community samples. The CIS-R has been validated for use with adolescent populations (Patton *et*
174 *al.*, 1999). At each wave the total score was dichotomised at ≥ 12 to identify mixed depression-
175 anxiety symptoms at a level lower than major depressive or anxiety disorder, but which a general
176 practitioner would view as clinically significant (Lewis *et al.*, 1992). At Waves 8 and 9 (participant
177 ages 24 and 29), symptoms of psychological distress were assessed with the 12-item General
178 Health Questionnaire (GHQ-12), a screening measure widely used to assess psychiatric illness in
179 the general population. Total scores were dichotomised at ≥ 3 , a threshold that has been found to
180 indicate psychological distress with sensitivity 76% and specificity 83% (Donath, 2001, Goldberg *et*
181 *al.*, 1997), and corresponds to a CIS-R threshold of ≥ 12 (Lewis *et al.*, 1992).

182

183 Preconception maternal mental health problems in the ATP study were measured in adolescence
184 and young adulthood using age-appropriate scales. Depressive symptoms were assessed in waves
185 10-12 (participant ages 13 to 18) using the 13-item Short Mood and Feelings Questionnaire (Turner
186 *et al.*, 2014). At each wave the total score was dichotomised at ≥ 11 to identify moderate to severe
187 depressive symptoms (Turner *et al.*, 2014). Anxiety symptoms were assessed using adapted
188 versions of the Revised Behavior Problem Checklist Short Form in wave 10 (age 13-14) (Letcher *et*

189 *al.*, 2012, Quay and Peterson, 1987) and the Revised Children's Manifest Anxiety Scale (Letcher *et*
190 *al.*, 2012, Reynolds and Richmond, 1978) in waves 11-12 (ages 15-18). For each scale, respondents
191 rated frequency of anxious feelings on a scale from 0 'never/rarely' to 1 'sometimes' to 2
192 'often/almost always', with mean scores > 'sometimes' denoting moderate to severe symptoms. At
193 each wave, a summary variable was derived denoting presence of depressive and/or anxious
194 symptoms. At waves 13-15 (ages 19-28), symptoms of depression and anxiety were assessed using
195 the 21-item Depression Anxiety and Stress Scale (DASS-21; Antony *et al.*, 1998, Lovibond and
196 Lovibond, 1995). The DASS-21 comprises three 7-item subscales measuring depression, anxiety,
197 and stress. It has good psychometric properties and can distinguish symptoms of clinical-level
198 severity (Antony *et al.*, 1998). Participants rated their psychological distress and physiological
199 symptoms on a scale from 0 'did not apply to me at all' to 3 'applied to me very much or most of
200 the time'. The depression, anxiety, and stress subscale scores were dichotomised at their
201 respective thresholds for moderate to severe symptoms (≥ 7 , ≥ 6 , ≥ 10), and for each wave a
202 summary variable was derived denoting presence of symptoms on one or more subscales.

203

204 For each cohort, we constructed variables denoting presence of any mental health problems at ≥ 1
205 adolescent wave (VAHCS Waves 2-6, ATP Waves 10-12), and ≥ 1 young adult wave (VAHCS Waves
206 7-9, ATP Waves 13-15). Based on these dichotomous variables, we created a four-level variable
207 denoting continuity of mental health problems ('none', 'adolescent only', 'young adult only', and
208 'both adolescent and young adult').

209

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

218

219 **Infant offspring emotional reactivity** was assessed in both VIHCS and ATPG3 via maternal report at
220 one year postpartum using the Short Temperament Scale for Toddlers (STST), a 30-item survey
221 designed to assess temperament in toddlers aged 1-3 years (Fullard *et al.*, 1984, Prior *et al.*, 1989).
222 The reactivity subscale comprises eight items. High scores indicate a tendency to react negatively
223 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 ≥ 4 ("usually does").

230

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 are 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 birthweight ($<$ v. $\geq$ 2.5kg), and premature birth ($<$ v. $\geq$ 37 weeks).

248

249 **Statistical analysis**

250

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 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 one 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 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 (Moreno-Betancur and Carlin, 2018, Vansteelandt and Daniel, 2017).

An illustrative example of the conceptual model, with two mediators and two post-exposure confounders, is shown in Figure 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.

Insert Figure 1 about here

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 imputation by chained

294 equations (White *et al.*, 2011). We imputed 35 complete datasets separately for each cohort,
295 based on the proportion of participants with missing data (Bodner, 2008). Parameter estimates
296 were obtained by pooling results across imputed datasets using Rubin's rules (Rubin, 1987). We
297 performed supplementary analyses using available case data. To assess potential for participation
298 bias, we compared characteristics of participants in each cohort with those who were either not
299 screened for pregnancies due to prior study withdrawal, or who were screened and eligible but did
300 not participate. We used Stata 15 (StataCorp, 2015).

301 Results

302

303 The flow of participants through each study is presented in appendix p 2. In total, 398 women
304 participated in VIHCS with 609 infants and 395 in ATPG3 with 676 infants. Of these, 37 ATPG2
305 women did not participate in adolescence and were excluded from the analysis sample, leaving
306 358 ATPG2 women with 622 ATPG3 infants, and a combined analysis sample of 756 women with
307 1231 infants who participated at least once in each phase (adolescence, young adulthood, and
308 perinatally). Comparisons of women screened versus not screened and participating versus eligible
309 non-participants are presented in appendix pp 3-4. Women who participated were broadly
310 representative of those with live births during screening on measured baseline characteristics in
311 each study, but there were some differences between those screened and not screened due to
312 prior loss to follow-up. The ATP women screened were less likely to have parents born outside of
313 Australia, but remained similar to the original ATP sample on the level of parental education. The
314 VAHCS women screened were less likely to have engaged in frequent adolescent drinking, but
315 there were no other notable differences on measured demographic, mental health or risky
316 behaviours in adolescence at VAHCS study entry.

317

318 Table 1 summarises infants' and their mothers' characteristics, by cohort and combined. The
319 majority of infants (61%; [95% CI 58-64]) had mothers who reported preconception mental health
320 problems at least once in adolescence and/or young adulthood; of these, most were adolescent-
321 onset. Post conception, 14% of women reported antenatal depressive symptoms and 10%
322 reported postpartum depressive symptoms. Because 4% of women reported depressive symptoms
323 at both timepoints, the overall rate of antenatal and/or postnatal depression was 20%. There were
324 negligible differences between cohorts on most variables, consistent with expectations given the
325 samples were drawn from similar populations, though rates of perinatal depressive symptoms
326 were slightly higher in the ATPG3 than in VIHCS.

327

328 *Insert Table 1 about here*

329

330 Table 2 shows estimated associations of preconception, antenatal and postnatal maternal mental
331 health problems with offspring infant reactivity. The estimated proportion of infants with
332 heightened reactivity was higher in infants of mothers with both adolescent and young adult
333 mental health problems than in infants of those without (37% [31- 44] vs. 23% [19-27]). After
334 adjusting for background demographic characteristics and cohort, preconception maternal mental

335 health problems that persisted across adolescence and young adulthood predicted a twofold
336 increase in the odds of heightened infant reactivity (adjusted OR 2.1 [1.4-3.1]), compared with
337 those with no preconception mental health problems. Similarly, in linear regression analyses, we
338 found a mean difference in infant reactivity scores of 0.38 standard deviations between offspring
339 of mothers with persistent preconception mental health problems and those with no
340 preconception mental health problems. Maternal mental health problems antenatally and at one
341 year postpartum were similarly associated with offspring infant reactivity, but the magnitude of
342 these perinatal associations reduced somewhat after adjustment for prior exposure. Available case
343 analyses of the combined cohorts yielded a similar pattern of results (appendix p 5). In
344 supplementary analyses we repeated these analyses in each cohort (appendix pp 6-7).
345 Preconception, antenatal and postpartum effects were evident in both cohorts. Postpartum effects
346 were somewhat weaker in VIHCS linear models than ATPG3 linear models, but consistent across
347 cohorts in the logistic models. In fully adjusted models, cohort was not associated with infant
348 reactivity.

349

350 *Insert Table 2 about here*

351

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

363

364 *Insert Table 3 about here*

365

366 **Discussion**

367

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

380

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

393

394 **Potential mechanisms**

395

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

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

404

405 It is also possible that chronic preconception mental health problems might have an enduring
406 effect on maternal endocrine and immune-inflammatory physiology, affecting the fetal
407 environment even when mothers report few perinatal depressive symptoms (Moog *et al.*, 2018).
408 One recent study linked maternal abuse in childhood to increased placental hormone production
409 during later pregnancies, providing preliminary evidence that maternal stress before conception
410 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
411 not have captured periconceptional exposure including during embryogenesis and implantation,
412 both sensitive to environmental influence including maternal stress (Ord *et al.*, 2017). Brain regions
413 integral to stress response regulation and susceptible to excess exposure to maternal hormones
414 are identifiable by eight weeks gestation (Gunnar and Davis, 2013). Similarly, preconception
415 mental health problems may also be linked to infant emotional reactivity through increased risk of
416 other exposures during pregnancy and postpartum, including health-related behaviours such as
417 maternal substance use or diet, or social factors such as perceived social support, maternal
418 attachment style, partner relationship quality and conflict, or family violence (Howard *et al.*, 2014).

420

421 A final possibility is that persistent maternal mental health problems prior to pregnancy might
422 directly affect the maternal germline with persisting effects on offspring stress response and
423 reactivity (Chan *et al.*, 2017). The epigenetic profile of gamete DNA can be altered by parental
424 exposure to stress (Klengel *et al.*, 2015) but until recently these alterations were thought to be
425 completely erased during embryonic development. There is now evidence that some epigenetic
426 marks persist after fertilisation (Klengel *et al.*, 2015). Animal data support the intergenerational
427 transfer of stress-related behaviours through epigenetic modifications to the paternal germline
428 (Klengel *et al.*, 2015). Though studies of maternal germline transmission are limited, evidence is
429 emerging that stress reactivity traits may also be maternally transmitted by epigenetic
430 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
431 proteins in oocyte cytoplasm, may also influence fetal development and offspring phenotype
432 (Kovalchuk, 2012).

434

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 one 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, Hartman and Belsky, 2018, Slagt *et al.*, 2016).

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 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;

470 however, around one third of antenatal interviews were missed due to difficulties in detecting
471 eligible pregnancies. We addressed potential biases due to missing data using multiple imputation.
472 We also only included infants born to women aged 29-36 years. This included the median maternal
473 age at birth in Australia and maximised the number of included births, but it remains possible that
474 the risk profiles of older and younger mothers may differ from those in focus in this study.

475

476 Finally, infant emotional reactivity was assessed by maternal report and usefully draws on a
477 mother's knowledge of her baby's usual behaviour across contexts, particularly relevant for the
478 study of phenotypic traits such as emotional reactivity (Bates *et al.*, 2014, Shiner and Caspi, 2003).
479 Maternally reported infant reactivity predicts later child social and emotional problems, with effect
480 sizes similar to studies of independently assessed infant reactivity (Kagan *et al.*, 1999, Sayal *et al.*,
481 2013). However, maternal report of infant outcomes may be affected by a mother's mental state
482 such that depressed mothers perceive their infant as more reactive (Luoma *et al.*, 2004, Najman *et al.*, 2001). We investigated this possibility by including maternal depressive symptoms at the time
483 of the outcome in our mediation model. The association between preconception maternal mental
484 health and offspring infant emotional reactivity was overwhelmingly independent of maternal
485 depressive symptoms at the time of the outcome, suggesting minimal role of maternal reporting
486 bias due to concurrent depression. These findings align with previous research indicating that
487 depression-related biases explain only a small proportion of variance in maternally reported child
488 behavioural traits (Bagner *et al.*, 2013, Goodman *et al.*, 2011, Rothbart and Bates, 2006).

490

491 **Conclusion**

492

493 Maternal mental health problems remain one of the most significant early life risk factors for
494 childhood emotional and behavioural problems. The current findings do not detract from the
495 importance of antenatal and infancy phases as intervention points for both mothers and offspring,
496 to improve mental health outcomes for infants higher in emotional reactivity (Belsky, 2005, Boyce
497 and Ellis, 2005, Slagt *et al.*, 2016). Indeed, highly reactive children encountering few challenges
498 may have a lower likelihood of externalising problems, and greater prosocial behaviours, school
499 engagement and cognitive competence than low-reactive children (Obradović *et al.*, 2010, Slagt *et al.*, 2016). Yet the current study suggests that intervention in the perinatal period alone is unlikely
500 to be sufficient to eliminate risks for the offspring of women with persistent mental health
501 problems prior to pregnancy. It is perhaps one reason why the effects of existing postnatal
502 interventions on maternal depression have been mixed (Poobalan *et al.*, 2007, Stein *et al.*, 2018).
503 There is now a need to further explore whether the effects of maternal preconception mental
504

505 health problems extend to higher rates of emotional and behavioural problems in later childhood,
506 as well as understand the processes whereby preconception exposure leads to heightened infant
507 reactivity. Even so, the current findings suggest that a reorientation of clinical services and public
508 health responses to the years prior to pregnancy is warranted. Current approaches to
509 preconception care, for example, have largely focused on contraception (Patton *et al.*, 2018) with
510 little attention to maternal mental health. The growing calls for preconception health care around
511 other aspects of health and health risk (Barker *et al.*, 2018) should also extend to mental health
512 (Wilson *et al.*, 2018). It is likely that the benefits will extend beyond women themselves to their
513 children's emotional development.
514

515 **Acknowledgments**

516 The authors would like to thank the families who have participated in the Victorian Adolescent
517 Health Cohort Study, the Victorian Intergenerational Health Cohort Study, the Australian
518 Temperament Project and the ATP Generation 3 Study for their invaluable contributions, as well as
519 all collaborators and the study teams involved in the data collection and management. Further
520 information on the studies is available at <https://www.melbournechildrens.com/vihcs/> and
521 <https://www.melbournechildrens.com/atp/> . The VAHCS, VIHCS, ATP and ATPG3 studies are
522 located at The Royal Children's Hospital Melbourne. The ATP and ATPG3 are a collaboration
523 between Deakin University, The University of Melbourne, The Australian Institute of Family
524 Studies, The University of New South Wales, The University of Otago (NZ), and the Royal Children's
525 Hospital. We acknowledge all collaborators who have contributed to the Australian Temperament
526 Project, especially Professors Ann Sanson, Margot Prior, Frank Oberklaid, and Dr Diana Smart.

527
528 **Financial support**

529 This work was supported by the Australian Research Council (DP180102447). Data collection for
530 VIHCS was supported by the National Health and Medical Research Council; Australian Rotary
531 Health; Colonial Foundation; Perpetual Trustees; Financial Markets Foundation for Children
532 (Australia); Royal Children's Hospital Foundation; and the Murdoch Children's Research Institute.
533 Data collection for the ATPG3 was supported by the Australian Research Council. LMH receives
534 salary support for an NIHR Research Professorship in maternal mental health to LMH (NIHR-RP-R3-
535 12-011). LMH is also affiliated with the NIHR Mental Health Biomedical Research Centre at South
536 London and Maudsley NHS Foundation Trust and King's College London. JR is supported by an
537 NHMRC Dementia Research Leader Fellowship (APP1135727). GP is supported by an NHMRC
538 Senior Principle Research Fellowship (APP1117873). Research at the Murdoch Children's Research
539 Institute is supported by the Victorian Government's Operational Infrastructure Program.

540
541 **Conflict of interest**

542 None.

543

544 References

- 545 **Antony, M. M., Bieling, P. J., Cox, B. J., Enns, M. W. & Swinson, R. P.** (1998). Psychometric
546 properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical
547 groups and a community sample. *Psychological assessment* **10**, 176.
- 548 **Australian Bureau of Statistics** (2013). 3301.0 - Births, Australia, 2012 (Latest issue 24/10/2013).
- 549 **Bagner, D. M., Pettit, J. W., Lewinsohn, P. M., Seeley, J. R. & Jaccard, J.** (2013). Disentangling the
550 temporal relationship between parental depressive symptoms and early child behavior problems: a
551 transactional framework. *J Clin Child Adolesc Psychol* **42**, 78-90.
- 552 **Barker, D. J.** (1990). The fetal and infant origins of adult disease. *British Medical Journal* **301**, 1111-
553 1111.
- 554 **Barker, M., Dombrowski, S. U., Colbourn, T., Fall, C. H. D., Kriznik, N. M., Lawrence, W. T., Norris,
555 S. A., Ngaiza, G., Patel, D., Skordis-Worrall, J., Sniehotta, F. F., Steegers-Theunissen, R., Vogel, C.,
556 Woods-Townsend, K. & Stephenson, J.** (2018). Intervention strategies to improve nutrition and
557 health behaviours before conception. *The Lancet* **391**, 1853-1864.
- 558 **Bates, J. E., Schermerhorn, A. C. & Petersen, I. T.** (2014). Temperament concepts in developmental
559 psychopathology. In *Handbook of developmental psychopathology*, pp. 311-329. Springer.
- 560 **Belsky, J.** (2005). Differential susceptibility to rearing influence. In *Origins of the social mind:
561 Evolutionary psychology and child development* (ed. B. J. Ellis and D. F. Bjorklund), pp. 139-163.
562 Guilford Press: New York, NY.
- 563 **Bergink, V., Kooistra, L., Lambregtse-van den Berg, M. P., Wijnen, H., Bunevicius, R., van Baar, A.
564 & Pop, V.** (2011). Validation of the Edinburgh Depression Scale during pregnancy. *Journal of
565 Psychosom Research* **70**, 385-9.
- 566 **Bodner, T. E.** (2008). What improves with increased missing data imputations? *Structural Equation
567 Modeling* **15**, 651-675.
- 568 **Boyce, W. T. & Ellis, B. J.** (2005). Biological sensitivity to context: I. An evolutionary–developmental
569 theory of the origins and functions of stress reactivity. *Development and psychopathology* **17**, 271-
570 301.
- 571 **Bruder-Costello, B., Warner, V., Talati, A., Nomura, Y., Bruder, G. & Weissman, M.** (2007).
572 Temperament among offspring at high and low risk for depression. *Psychiatry research* **153**, 145-
573 151.
- 574 **Bylsma, L. M., Morris, B. H. & Rottenberg, J.** (2008). A meta-analysis of emotional reactivity in
575 major depressive disorder. *Clinical Psychology Review* **28**, 676-91.
- 576 **Chan, J. C., Nugent, B. M. & Bale, T. L.** (2017). Parental advisory: maternal and paternal stress can
577 impact offspring neurodevelopment. *Biological Psychiatry*.
- 578 **Cox, J. L., Holden, J. M. & Sagovsky, R.** (1987). Detection of postnatal depression. Development of
579 the 10-item Edinburgh Postnatal Depression Scale. *The British Journal of Psychiatry* **150**, 782-786.
- 580 **Curran, P. J. & Hussong, A. M.** (2009). Integrative data analysis: The simultaneous analysis of
581 multiple data sets. *Psychological methods* **14**, 81.
- 582 **Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicx-Demet, A. & Sandman, C. A.** (2007).
583 Prenatal Exposure to Maternal Depression and Cortisol Influences Infant Temperament. *Journal of
584 the American Academy of Child & Adolescent Psychiatry* **46**, 737-746.
- 585 **Davis, E. P., Snidman, N., Wadhwa, P. D., Glynn, L. M., Schetter, C. D. & Sandman, C. A.** (2004).
586 Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy*
587 **6**, 319-331.
- 588 **de Figueiredo, F. P., Parada, A. P., Cardoso, V. C., Batista, R. F. L., da Silva, A. A. M., Barbieri, M.
589 A., de Carvalho Cavalli, R., Bettiol, H. & Del-Ben, C. M.** (2015). Postpartum depression screening
590 by telephone: a good alternative for public health and research. *Archives of women's mental health*
591 **18**, 547-553.
- 592 **Donath, S.** (2001). The validity of the 12-item General Health Questionnaire in Australia: a
593 comparison between three scoring methods. *Australasian Psychiatry* **35**, 231-235.

Fullard, W., McDevitt, S. C. & Carey, W. B. (1984). Assessing temperament in one- to three-year-old children. *Journal of Pediatric Psychology* **9**.

Gibson, J., McKenzie-McHarg, K., Shakespeare, J., Price, J. & Gray, R. (2009). A systematic review of studies validating the Edinburgh Postnatal Depression Scale in antepartum and postpartum women. *Acta Psychiatrica Scandinavica* **119**, 350-64.

Gluckman, P. D. & Hanson, M. A. (2004). Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. *Pediatric research* **56**, 311-317.

Gluckman, P. D., Hanson, M. A., Bateson, P., Beedle, A. S., Law, C. M., Bhutta, Z. A., Anokhin, K. V., Bougnères, P., Chandak, G. R. & Dasgupta, P. (2009). Towards a new developmental synthesis: adaptive developmental plasticity and human disease. *The Lancet* **373**, 1654-1657.

Goldberg, D. P., Gater, R., Sartorius, N., Ustun, T. B., Piccinelli, M., Gureje, O. & Rutter, C. (1997). The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychological Medicine* **27**, 191-7.

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M. & Heyward, D. (2011). Maternal depression and child psychopathology: a meta-analytic review. *Clin Child Fam Psychol Rev* **14**, 1-27.

Gunnar, M. R. & Davis, E. P. (2013). The Effects of Stress on Early Brain and Behavioral Development. 447-465.

Hartman, S. & Belsky, J. (2018). Prenatal programming of postnatal plasticity revisited-And extended. *Development and Psychopathology* **30**, 825-842.

Hofer, S. M. & Piccinin, A. M. (2009). Integrative data analysis through coordination of measurement and analysis protocol across independent longitudinal studies. *Psychological methods* **14**, 150.

Howard, L. M., Molyneaux, E., Dennis, C.-L., Rochat, T., Stein, A. & Milgrom, J. (2014). Non-psychotic mental disorders in the perinatal period. *The Lancet* **384**, 1775-1788.

Huot, R., Brennan, P., Stowe, Z., Plotsky, P. & Walker, E. (2004). Negative affect in offspring of depressed mothers is predicted by infant cortisol levels at 6 months and maternal depression during pregnancy, but not postpartum. *Annals of the New York Academy of Sciences* **1032**, 234-236.

Hutchinson, D. M., Silins, E., Mattick, R. P., Patton, G. C., Fergusson, D. M., Hayatbakhsh, R., Toumbourou, J. W., Olsson, C. A., Najman, J. M. & Spry, E. (2015). How can data harmonisation benefit mental health research? An example of the Cannabis Cohorts Research Consortium. *Australian & New Zealand Journal of Psychiatry* **49**, 317-323.

Kagan, J., Snidman, N., Zentner, M. & Peterson, E. (1999). Infant temperament and anxious symptoms in school age children. *Development and psychopathology* **11**, 209-224.

Keenan, K., Hipwell, A. E., Class, Q. A. & Mbayiwa, K. (2018). Extending the developmental origins of disease model: Impact of preconception stress exposure on offspring neurodevelopment. *Developmental Psychobiology* **60**, 753-764.

Klengel, T., Dias, B. G. & Ressler, K. J. (2015). Models of intergenerational and transgenerational transmission of risk for psychopathology in mice. *Neuropsychopharmacology* **41**, 219-31.

Kovalchuk, I. (2012). Transgenerational epigenetic inheritance in animals. *Frontiers in genetics* **3**, 76.

Kuzawa, C. W. & Quinn, E. A. (2009). Developmental origins of adult function and health: Evolutionary hypotheses. *Annual Review of Anthropology* **38**, 131-147.

Letcher, P., Sanson, A., Smart, D. & Toumbourou, J. W. (2012). Precursors and correlates of anxiety trajectories from late childhood to late adolescence. *Journal of Clinical Child and Adolescent Psychology* **41**, 417-32.

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.

Lovibond, S. & Lovibond, P. (1995). Manual for the Depression Anxiety Stress Scale, Sydney: The Psychological Foundation of Australia. Inc.

Luciano, M., Hagenaars, S. P., Davies, G., Hill, W. D., Clarke, T.-K., Shiral, M., Harris, S. E.,
 Marioni, R. E., Liewald, D. C. & Fawns-Ritchie, C. (2018). Association analysis in over 329,000
 individuals identifies 116 independent variants influencing neuroticism. *Nature genetics* **50**, 6.
 Luoma, I., Kaukonen, P., Mäntymaa, M., Puura, K., Tamminen, T. & Salmelin, R. (2004). A
 longitudinal study of maternal depressive symptoms, negative expectations and perceptions of
 child problems. *Child Psychiatry and Human Development* **35**, 37-53.
 McAdams, T., Rijdsdijk, F., Neiderhiser, J., Narusyte, J., Shaw, D., Natsuaki, M., Spotts, E., Ganiban,
 J., Reiss, D. & Leve, L. (2015). The relationship between parental depressive symptoms and
 offspring psychopathology: evidence from a children-of-twins study and an adoption study.
Psychological Medicine **45**, 2583-2594.
 Meaney, M. J. & Szyf, M. (2005). Environmental programming of stress responses through DNA
 methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues*
in clinical neuroscience **7**, 103.
 Mitchell, E., Klein, S. L., Argyropoulos, K. V., Sharma, A., Chan, R. B., Toth, J. G., Barboza, L.,
 Bavley, C., Bortolozzi, A. & Chen, Q. (2016). Behavioural traits propagate across generations via
 segregated iterative-somatic and gametic epigenetic mechanisms. *Nature communications* **7**,
 11492.
 Moog, N. K., Buss, C., Entringer, S., Shahbaba, B., Gillen, D. L., Hobel, C. J. & Wadhwa, P. D.
 (2016). Maternal exposure to childhood trauma is associated during pregnancy with placental-fetal
 stress physiology. *Biological psychiatry* **79**, 831-839.
 Moog, N. K., Entringer, S., Rasmussen, J. M., Styner, M., Gilmore, J. H., Kathmann, N., Heim, C.
 M., Wadhwa, P. D. & Buss, C. (2018). Intergenerational effect of maternal exposure to childhood
 maltreatment on newborn brain anatomy. *Biological psychiatry* **83**, 120-127.
 Moreno-Betancur, M. & Carlin, J. B. (2018). Understanding Interventional Effects: A More Natural
 Approach to Mediation Analysis? *Epidemiology* **29**, 614-617.
 Murray, D. & Cox, J. L. (1990). Screening for depression during pregnancy with the edinburgh
 depression scale (EDDS). *Journal of Reproductive and Infant Psychology* **8**, 99-107.
 Najman, J. M., Williams, G. M., Nikles, J., Spence, S., Bor, W., O'Callaghan, M., Le Brocque, R.,
 Andersen, M. J. & Shuttlewood, G. (2001). Bias influencing maternal reports of child behaviour
 and emotional state. *Social psychiatry and psychiatric epidemiology* **36**, 186-194.
 Newland, R. P., Parade, S. H., Dickstein, S. & Seifer, R. (2016). The association between maternal
 depression and sensitivity: Child-directed effects on parenting during infancy. *Infant Behavior and*
Development **45**, 47-50.
 Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S. & Devlin, A. M. (2008).
 Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor
 gene (NR3C1) and infant cortisol stress responses. *Epigenetics* **3**, 97-106.
 Obradović, J., Bush, N. R., Stamperdahl, J., Adler, N. E. & Boyce, W. T. (2010). Biological sensitivity
 to context: The interactive effects of stress reactivity and family adversity on socioemotional
 behavior and school readiness. *Child development* **81**, 270-289.
 Ord, J., Fazeli, A. & Watt, P. J. (2017). Long-Term Effects of the Periconception Period on Embryo
 Epigenetic Profile and Phenotype: The Role of Stress and How This Effect Is Mediated. In
Periconception in Physiology and Medicine, pp. 117-135. Springer.
 Patton, G. C., Coffey, C., Posterino, M., Carlin, J. B., Wolfe, R. & Bowes, G. (1999). A computerised
 screening instrument for adolescent depression: population-based validation and application.
Social Psychiatry and Psychiatric Epidemiology **34**, 166-172.
 Patton, G. C., Coffey, C., Romaniuk, H., Mackinnon, A., Carlin, J. B., Degenhardt, L., Olsson, C. A.
 & Moran, P. (2014). The prognosis of common mental disorders in adolescents: a 14-year
 prospective cohort study. *The Lancet* **383**, 1404-11.
 Patton, G. C., Olsson, C. A., Skirbekk, V., Saffery, R., Wlodek, M. E., Azzopardi, P. S., Stonawski,
 M., Rasmussen, B., Spry, E. & Francis, K. (2018). Adolescence and the next generation. *Nature* **554**,
 458.

697 **Patton, G. C., Romaniuk, H., Spry, E., Coffey, C., Olsson, C., Doyle, L. W., Oats, J., Hearps, S.,**
 698 **Carlin, J. B. & Brown, S.** (2015). Prediction of perinatal depression from adolescence and before
 699 conception (VIHCS): 20-year prospective cohort study. *The Lancet* **386**, 875-83.
 700 **Pearson, R. M., Evans, J., Kounali, D., Lewis, G., Heron, J., Ramchandani, P. G., O'Connor, T. G. &**
 701 **Stein, A.** (2013). Maternal depression during pregnancy and the postnatal period: risks and
 702 possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* **70**, 1312-9.
 703 **Poobalan, A. S., Aucott, L. S., Ross, L., Smith, W. C. S., Helms, P. J. & Williams, J. H.** (2007). Effects
 704 of treating postnatal depression on mother-infant interaction and child development: systematic
 705 review. *The British Journal of Psychiatry* **191**, 378-386.
 706 **Prior, M., Sanson, A., Smart, D. & Oberklaid, F.** (2000). *Pathways from infancy to adolescence*.
 707 Australian Institute of Family Studies: Melbourne, Australia.
 708 **Prior, M. R., Sanson, A. V. & Oberklaid, F.** (1989). The Australian temperament project.
 709 **Quay, H. C. & Peterson, D. R.** (1987). *Manual for the Revised Behavior Problem Checklist* Quay &
 710 Peterson: Miami.
 711 **Reynolds, C. R. & Richmond, B. O.** (1978). What I think and feel: A revised measure of children's
 712 manifest anxiety. *Journal of abnormal child psychology* **6**, 271-280.
 713 **Rothbart, M. K. & Bates, J. E.** (2006). Temperament. In *Handbook of child psychology: Vol. 3.*
 714 *Social, emotional, and personality development* (ed. H. Grotevant, W. Damon and N. Eisenberg).
 715 Wiley: New York.
 716 **Rouse, M. H. & Goodman, S. H.** (2014). Perinatal depression influences on infant negative
 717 affectivity: timing, severity, and co-morbid anxiety. *Infant Behavior and Development* **37**, 739-751.
 718 **Rubin, D. B.** (1987). Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, Inc.:
 719 Hoboken, NJ, USA.
 720 **Sandman, C. A., Davis, E. P. & Glynn, L. M.** (2011). Prescient Human Fetuses Thrive. *Psychological*
 721 *Science* **23**, 93-100.
 722 **Sayal, K., Heron, J., Maughan, B., Rowe, R. & Ramchandani, P.** (2013). Infant temperament and
 723 childhood psychiatric disorder: longitudinal study. *Child Care Health Dev.*
 724 **Sayal, K., Heron, J., Maughan, B., Rowe, R. & Ramchandani, P.** (2014). Infant temperament and
 725 childhood psychiatric disorder: longitudinal study. *Child: Care, Health & Development* **40**, 292-297.
 726 **Sheriff, M. J., Bell, A., Boonstra, R., Dantzer, B., Lavergne, S. G., McGhee, K. E., MacLeod, K. J.,**
 727 **Winandy, L., Zimmer, C. & Love, O. P.** (2017). Integrating ecological and evolutionary context in
 728 the study of maternal stress. *Integrative and comparative biology* **57**, 437-449.
 729 **Shiner, R. & Caspi, A.** (2003). Personality differences in childhood and adolescence: Measurement,
 730 development, and consequences. *Journal of Child Psychology and Psychiatry* **44**, 2-32.
 731 **Slagt, M., Dubas, J. S., Deković, M. & van Aken, M. A. G.** (2016). Differences in sensitivity to
 732 parenting depending on child temperament: A meta-analysis. *Psychological Bulletin* **142**, 1068-
 733 1110.
 734 **StataCorp** (2015). Stata Statistical Software: Release 15. StataCorp LP: College Station, TX.
 735 **Stein, A., Netsi, E., Lawrence, P. J., Granger, C., Kempton, C., Craske, M. G., Nickless, A., Mollison,**
 736 **J., Stewart, D. A. & Rapa, E.** (2018). Mitigating the effect of persistent postnatal depression on
 737 child outcomes through an intervention to treat depression and improve parenting: a randomised
 738 controlled trial. *The Lancet Psychiatry* **5**, 134-144.
 739 **Stein, A., Pearson, R. M., Goodman, S. H., Rapa, E., Rahman, A., McCallum, M., Howard, L. M. &**
 740 **Pariante, C. M.** (2014). Effects of perinatal mental disorders on the fetus and child. *The Lancet* **384**,
 741 1800-1819.
 742 **Swanson, J. D. & Wadhwa, P. M.** (2008). Developmental origins of child mental health disorders.
 743 *Journal of Child Psychology and Psychiatry* **49**, 1009-1019.
 744 **Turner, N., Joinson, C., Peters, T. J., Wiles, N. & Lewis, G.** (2014). Validity of the Short Mood and
 745 Feelings Questionnaire in late adolescence. *Psychological assessment* **26**, 752.
 746 **Vansteelandt, S. & Daniel, R. M.** (2017). Interventional Effects for Mediation Analysis with
 747 Multiple Mediators. *Epidemiology* **28**, 258-265.

748 **White, I. R., Royston, P. & Wood, A. M.** (2011). Multiple imputation using chained equations:
749 issues and guidance for practice. *Statistics in medicine* **30**, 377-399.
750 **Wilson, C., Howard, L. M., Reynolds, R. M., Simonoff, E. & Ismail, K.** (2018). Preconception health.
751 *The Lancet* **392**, 2266-2267.
752 **Woody, C. A., Ferrari, A. J., Siskind, D. J., Whiteford, H. A. & Harris, M. G.** (2017). A systematic
753 review and meta-regression of the prevalence and incidence of perinatal depression. *Journal of*
754 *Affective Disorders* **219**, 86-92.
755 **Yehuda, R. & Meaney, M. J.** (2018). Relevance of Psychological Symptoms in Pregnancy to
756 Intergenerational Effects of Preconception Trauma. *Biological psychiatry* **83**, 94-96.
757 **Zaidan, H., Leshem, M. & Gaisler-Salomon, I.** (2013). Prereproductive stress to female rats alters
758 corticotropin releasing factor type 1 expression in ova and behavior and brain corticotropin
759 releasing factor type 1 expression in offspring. *Biological psychiatry* **74**, 680-687.

760

761

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

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

	VIHCS N=609		ATPG3 N=622		Combined N=1231	
<i>Preconception</i>	n	(%)	n	(%)	n	(%)
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)
Postnatal 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, sd)	2.46	(0.65)	2.64	(0.57)	2.54	(0.62)

Frequency estimates were calculated from imputed percentage estimates and total number of infants. VIHCS=The Victorian Intergenerational Health Cohort Study. ATPG3=The Australian Temperament Project, Generation 3. 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.

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	β	(95% CI)	p
Preconception[#]									
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
Antenatal[†]									
Adjusted for background characteristics	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
Postnatal[*]									
Adjusted for background characteristics	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

n¹ = number exposed; n² = number with exposure and outcome. Frequency estimates were calculated from imputed percentage estimates and total number of infants. Heightened infant reactivity at one year of age defined as unstandardised STST reactivity mean score ≥4. Linear regression estimates are presented as standardised mean score differences.

Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, and mother's adolescent smoking.

† 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.

* 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.

Table 3. Estimated direct and indirect pathways from persistent preconception maternal mental health problems to offspring infant emotional reactivity at one 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 _(interv)	0.37	(0.35 , 0.39)	88
Indirect effect _(interv)	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 _(interv)	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 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, S. and R. M. Daniel (2017)] which was very small in this study.

Supplementary Table 1. Sample descriptions and included assessment waves and ages

Parent Cohorts	ATP	VAHCS
Year commenced	1983	1992
Recruited sample	A representative sample of 2443 infants (1170 female) (aged 4-8 months) in the state of Victoria, Australia	A representative sample of 1943 (1000 female) mid-secondary school students (aged 14-15) in the state of Victoria, Australia
Adolescent assessment waves	Wave 10: 13-14 years Wave 11: 15-16 years Wave 12: 17-18 years	Wave 2: 15.4 years Wave 3: 15.9 years Wave 4: 16.3 years Wave 5: 16.8 years Wave 6: 17.4 years
Young adult assessment waves	Wave 13: 19-20 years Wave 14: 23-24 years Wave 15: 27-28 years	Wave 7: 20.6 years Wave 8: 24.0 years Wave 9: 29.0 years
Offspring Cohorts	ATPG3	VIHCS
Year commenced	2011	2006
Recruited sample	395 ATP women with 676 infants	398 VAHCS women with 609 infants
Perinatal assessment waves	Wave 1: Third trimester of pregnancy Wave 3: 1 year postpartum	Wave 1: Third trimester of pregnancy Wave 3: 1 year postpartum

Supplementary Figure 1. Sampling and ascertainment of VIHCS and the ATPG3

* Eligibility defined as all live births occurring during screening (VIHCS: September 2006 - June 2013; ATPG3: December 2011 - August 2018).

† Of the 120 VAHCS women who didn't participate for 1+ eligible VIHCS children, 68 were excluded and the remaining women were recruited to participate in the study with 1+ other child.

‡ In each study many parents participated with more than one child born during the recruitment phase.

ATPG3 1 year assessments ongoing until end 2019

Supplementary Table 2a. Comparison of baseline characteristics at VAHCS study recruitment in adolescence of a) VAHCS women screened and not screened for VIHCS eligibility and b) eligible women who did and did not participate in VIHCS.

	Comparison between the VAHCS women screened and not screened for VIHCS										
	All VAHCS women ^a			Screened ^b			Not screened ^c			Screened v. not screened	Screened v. all VAHCS women
	<i>N</i>	<i>n</i>	(%)	<i>N</i>	<i>n</i>	(%)	<i>N</i>	<i>n</i>	(%)	χ^2 <i>p</i> -value	χ^2 <i>p</i> -value
Baseline adolescent characteristics											
Adolescent common mental disorder (CIS-R $\geq$ 12)	1000	342	34	885	305	34	113	37	33	0.717	0.869
Regular cigarette smoking ($\geq$ daily)	1000	120	12	885	102	12	113	18	16	0.175	0.664
Regular cannabis use ($\geq$ monthly)	987	69	7	876	61	7	109	8	7	0.885	0.975
Frequent drinking (> 3 times per week)	1000	27	3	885	20	2	113	7	6	0.015	0.197
Family of origin demographic factors											
Parents divorced or separated	999	221	22	885	195	22	112	26	23	0.777	0.962
Neither parent completed high school	966	364	38	870	329	38	94	35	37	0.912	0.944
	Comparison between the eligible women participating and non-participating in VIHCS										
	All eligible women ^d			Participants ^e			Eligible non-participants ^f			Participants v. eligible non-participants	Participants v. all eligible women
	<i>N</i>	<i>n</i>	(%)	<i>N</i>	<i>n</i>	(%)	<i>N</i>	<i>n</i>	(%)	χ^2 <i>p</i> -value	χ^2 <i>p</i> -value
Baseline adolescent characteristics											
Adolescent common mental disorder (CIS-R $\geq$ 12)	466	146	31	398	121	30	68	25	37	0.296	0.699
Regular cigarette smoking ($\geq$ daily)	466	51	11	398	39	10	68	12	18	0.055	0.481
Regular cannabis use ($\geq$ monthly)	462	30	6	394	26	7	68	4	6	0.825	0.937
Frequent drinking (> 3 times per week)	466	8	2	398	7	2	68	1	2	0.866	0.928
Family of origin demographic factors											
Parents divorced or separated	466	89	19	398	79	20	68	10	15	0.319	0.704
Neither parent completed high school	459	184	40	393	152	39	66	32	49	0.132	0.565

^a. 1000 women originally recruited to VAHCS in adolescence

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

^c. 115 women lost to follow-up in VAHCS at VIHCS commencement, and not screened for VIHCS eligibility

^d. 466 women eligible to participate in VIHCS with one or more live-born children during VIHCS screening

^e. 398 women who participated in VIHCS with one or more live-born children

^f. 68 women eligible to participate in VIHCS with one or more live-born children during VIHCS screening, who refused all participation or were missed.

Supplementary Table 2b. Comparison of baseline characteristics at ATP study recruitment in infancy of a) ATP women screened and not screened for ATPG3 eligibility and b) eligible women who did and did not participate in ATPG3.

Comparison between the ATP women screened and not screened for ATPG3 eligibility								
	All ATP women^a		Screened^b		Not screened^c		Screened v. not screened	Screened v. all ATP women
	N=1171		N=851		N=320			
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	χ^2 <i>p</i> -value	χ^2 <i>p</i> -value
Family of origin demographic factors								
Mother didn't complete high school	831	71	593	70	238	74	0.019	0.224
Father didn't complete high school	599	51	422	50	177	55	0.004	0.143
Mother non-Australian born	236	20	145	17	91	28	<0.001	0.023
Father non-Australian born	297	25	187	22	110	34	<0.001	0.018
Comparison between eligible women participating and non-participating in ATPG3								
	All eligible women^d		Participants^e		Eligible non-participants^f		Participants v. eligible non-participants	Participants v. all eligible women
	N=447		N=395		N=52			
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	χ^2 <i>p</i> -value	χ^2 <i>p</i> -value
Family of origin demographic factors								
Mother didn't complete high school	314	70	271	69	43	83	0.027	0.372
Father didn't complete high school	207	46	179	45	28	54	0.170	0.596
Mother non-Australian born	65	15	58	15	7	13	0.850	0.877
Father non-Australian born	92	21	81	21	11	21	0.867	0.830

^a. 1171 women originally recruited to ATP in infancy

^b. 851 women active in ATP at ATPG3 commencement, and screened for ATPG3 eligibility

^c. 320 women lost to follow-up in ATP at ATPG3 commencement, and not screened for ATPG3 eligibility

^d. 447 women eligible to participate in ATPG3 with one or more live-born children during ATPG3 screening

^e. 395 women who participated in ATPG3 with one or more live-born children

^f. 52 women eligible to participate in ATPG3 with one or more live-born children during ATPG3 screening, who refused all participation or were missed.

Supplementary Table 3. Estimated associations of preconception and perinatal maternal mental health problems with infant emotional reactivity in the VIHCS and ATPG3 combined, using available case data.

Maternal mental health problems	N ¹	n ²	Offspring infant emotional reactivity							
			Logistic regression					Linear regression		
			n ³	%	OR	(95% CI)	p	β	(95% CI)	p
Preconception [#]										
Adjusted for background characteristics										
No waves (reference)										
Adolescent only	1090	266	65	24	1.1	(0.8 , 1.7)	0.508	0.05	(-0.12 , 0.22)	0.556
Young adult only	1090	123	33	27	1.4	(0.8 , 2.2)	0.232	0.18	(-0.04 , 0.40)	0.102
Adolescent and young adult	1090	251	94	37	2.1	(1.5 , 3.0)	0.000	0.34	(0.17 , 0.51)	0.000
Antenatal [†]										
Adjusted for background characteristics	680	85	36	42	2.2	(1.4 , 3.5)	0.001	0.37	(0.14 , 0.60)	0.001
Further adjusted for preconception mental health	680	85	36	42	1.8	(1.1 , 3.0)	0.017	0.27	(0.04 , 0.51)	0.023
Postnatal*										
Adjusted for background characteristics	1029	90	40	44	2.1	(1.4 , 3.3)	0.001	0.29	(0.07 , 0.50)	0.009
Further adjusted for preconception mental health	1029	90	40	44	1.8	(1.1 , 2.9)	0.013	0.21	(-0.01 , 0.42)	0.066
Further adjusted for antenatal mental health	1029	90	40	44	1.7	(1.1 , 2.7)	0.024	0.18	(-0.04 , 0.40)	0.108

N¹ = number with exposure and outcome data; n² = number exposed; n³ = number with exposure and outcome. Frequency estimates were calculated from imputed percentage estimates and total number of infants. Heightened infant reactivity at one year of age defined as unstandardised STST reactivity mean score ≥4. Linear regression estimates are presented as standardised mean score differences.

Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, and mother's adolescent smoking.

† 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.

* 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.

Supplementary Table 4a. Estimated associations of preconception and perinatal maternal mental health problems with infant emotional reactivity, in 609 infants of 398 women who participated in VIHCS.

Maternal mental health problems	n ¹	Offspring infant emotional reactivity								
		Logistic regression					Linear regression			
		n ²	%	OR	(95% CI)	p	β	(95% CI)	p	
Preconception [#]										
Adjusted for background characteristics										
No waves (reference)										
Adolescent only	144	30	21	1.2	(0.6 , 2.3)	0.590	0.12	(-0.14 , 0.38)	0.351	
Young adult only	67	19	28	1.8	(0.8 , 3.9)	0.150	0.24	(-0.09 , 0.57)	0.151	
Adolescent and young adult	157	53	34	2.4	(1.3 , 4.2)	0.003	0.40	(0.15 , 0.64)	0.002	
Antenatal [†]										
Adjusted for background characteristics	76	28	37	2.1	(1.1 , 4.2)	0.024	0.33	(0.04 , 0.62)	0.026	
Further adjusted for preconception mental health	76	28	37	1.7	(0.9 , 3.4)	0.129	0.24	(-0.07 , 0.54)	0.126	
Postnatal*										
Adjusted for background characteristics	49	21	42	2.5	(1.3 , 4.8)	0.008	0.23	(-0.09 , 0.55)	0.157	
Further adjusted for preconception mental health	49	21	42	2.0	(1.0 , 3.9)	0.054	0.12	(-0.20 , 0.45)	0.464	
Further adjusted for antenatal mental health	49	21	42	1.8	(0.9 , 3.6)	0.119	0.07	(-0.27 , 0.41)	0.689	

n¹ = number exposed; n² = number with exposure and outcome. Frequency estimates were calculated from imputed percentage estimates and total number of infants. Heightened infant reactivity at one year of age defined as unstandardised STST reactivity mean score ≥4. Linear regression estimates are presented as standardised mean score differences.

Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, and mother's adolescent smoking.

† 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.

* 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.

Supplementary Table 4b. Estimated associations of preconception and perinatal maternal mental health problems with infant emotional reactivity, in 622 infants of 358 women who participated in ATPG3.

Maternal mental health problems	n ¹	Offspring infant emotional reactivity							
		Logistic regression					Linear regression		
		n ²	%	OR	(95% CI)	p	β	(95% CI)	p
Preconception [#]									
Adjusted for background characteristics									
No waves (reference)									
Adolescent only	150	48	32	1.5	(0.8 , 2.7)	0.205	0.11	(-0.16 , 0.39)	0.417
Young adult only	73	17	23	0.9	(0.4 , 2.0)	0.825	0.08	(-0.25 , 0.41)	0.642
Adolescent and young adult	156	62	40	1.9	(1.1 , 3.4)	0.022	0.39	(0.11 , 0.66)	0.006
Antenatal [†]									
Adjusted for background characteristics	100	46	46	2.4	(1.2 , 4.9)	0.017	0.40	(0.13 , 0.68)	0.004
Further adjusted for preconception mental health	100	46	46	2.1	(1.0 , 4.5)	0.051	0.30	(0.01 , 0.60)	0.041
Postnatal*									
Adjusted for background characteristics	70	31	45	2.1	(1.1 , 4.2)	0.032	0.40	(0.09 , 0.70)	0.011
Further adjusted for preconception mental health	70	31	45	1.9	(1.0 , 3.8)	0.069	0.32	(0.01 , 0.63)	0.040
Further adjusted for antenatal mental health	70	31	45	1.7	(0.9 , 3.5)	0.132	0.27	(-0.04 , 0.59)	0.083

n¹ = number exposed; n² = number with exposure and outcome. Frequency estimates were calculated from imputed percentage estimates and total number of infants. Heightened infant reactivity at one year of age defined as unstandardised STST reactivity mean score ≥4. Linear regression estimates are presented as standardised mean score differences.

Background characteristics: cohort, mother's parents high school completion and divorce, mother's high school completion, and mother's adolescent smoking.

† 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.

* 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.