DOI:
10.1098/rstb.2020.0028

Document Version
Peer reviewed version

Preventing postnatal depression: a causal mediation analysis of a 20-year preconception cohort

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Key words: postnatal depression; preconception; social support; maternal depression; antenatal; prospective

Acknowledgments and funding: We thank participants, collaborators and study teams of the Victorian Adolescent and Intergenerational Health Cohort Studies. This work was supported by the ARC (DP180102447), NHMRC, Australian Rotary Health, Colonial Foundation, Perpetual Trustees, Financial Markets Foundation for Children (Australia), Royal Children's Hospital Foundation and the Murdoch Children's Research Institute. GCP is supported by NHMRC (APP1117873), SJB by NHMRC (APP1103976), CAO by NHMRC

(APP1175086), MMB by ARC (DE190101326), KCT by the Canadian Institutes of Health Research (MFE158141), and LMH by the South London and Maudsley NHS Foundation Trust and King's College London NIHR (National Institute for Health Research) Biomedical Research Centre. Research and NIHR South London Applied Research Collaboration at the Murdoch Children's Research Institute is supported by the Victorian Government's Operational Infrastructure Program.

Author contributions: ES, GP, and EM conceived the paper. ES, MMB, MM, EM, CO and GP devised the analysis plan and all authors approved it. ES, MMB, MM and CG conducted the analysis. ES drafted the manuscript. MMB and MM contributed to drafting of the method section. CO contributed to drafting of the discussion section. All authors critically revised the manuscript. All authors approved the final version of the manuscript.

Data accessibility: Code for analysis from this paper may be accessed at https://osf.io/4h2xm/?view_only=868a559a861b466caaf50cdd4bdd1606. Ethics approvals for this study do not permit the data to be made publicly available, due to limitations of participant consent and concerns regarding potential re-identifiability. If required and upon request, the dataset subset can be made available to a named individual for the purpose of replication of research findings.

Conflicts of interest: Authors declare no competing interests.

Summary

Postnatal depression (PND) is common and predicts a range of adverse maternal and offspring outcomes. PND rates are highest amongst women with persistent mental health problems before pregnancy, and antenatal healthcare provides ideal opportunity to intervene. We examined antenatal perceived social support as a potential intervention target in preventing PND symptoms among women with prior mental health problems. A total of 398 Australian women (600 pregnancies) were assessed repeatedly for mental health problems before pregnancy (ages 14-29 years, 1992-2006), and again during pregnancy, 2 months postpartum, and 1 year postpartum (2006-2014). Causal mediation analysis found that intervention on perceived antenatal social support has the potential to reduce rates of PND symptoms by up to 3% (from 15% to 12%) in women with persistent preconception symptoms. Supplementary analyses found that the role of low antenatal social support was independent of concurrent antenatal depressive symptoms. Combined, these two factors mediated up to more than half of the association between preconception mental health problems and PND symptoms. Trialing dual interventions on antenatal depressive symptoms and perceived social support represents one promising strategy to prevent PND in women with persistent preconception symptoms. Interventions promoting mental health before parenthood may yield greater reduction in PND symptoms by disrupting a developmental cascade of risks via these and other pathways.

Introduction

Maternal postnatal depression (PND) is a global public health issue, with one in ten women reporting clinically significant levels of depression at one year postpartum in high income countries, and higher rates in developing countries [1–3]. The consequences for women and children are far-reaching [4]. For women, these can include reduced maternal capacity for sensitive and responsive caregiving [5], and symptom persistence or relapse beyond the postpartum [6]. Children exposed to maternal postpartum depression are at increased risk of emotional, behavioural and cognitive problems through childhood and into adulthood [4], even after accounting for genetic and other familial risks [7]. The economic costs of perinatal mental health problems are also substantial [8,9]. Prevention of PND is therefore a clinical and public health priority [10].

Social support is linked to depression across the life-course [11] and has received attention as a promising target for prevention of PND [12–14]. For parents of infants, supportive relationships are likely to assume particular importance, given heightened risk for mental health problems, sleep disruption, loss of income, employment changes and relationship pressures [15]. In high income countries, reduced connectedness of extended families, increasing work hours with both parents in the workforce, and a cultural emphasis on autonomy and intensive mothering can also exacerbate challenges of parenthood [14,16,17]. Women's perceptions that sufficient perinatal social support is available appear particularly important [14,18]. Low perceived social support during pregnancy predicts PND symptoms even after accounting for other perinatal risks [6,14,19]. Conversely, perceived support from partners, family or friends appears protective against perinatal symptoms [14,20].

For these reasons, preventative interventions to promote maternal social support have been trialed, often commencing in pregnancy when many parents have greater health system contact [21]. These often show little reduction in rates of PND when applied generally, but there is some indication that targeted intervention in women at heightened risk may yield greater benefits [10,22]. One of the strongest and most reliable pre-existing risk factors for PND is a history of mental health problems [13]. For many women, perinatal depression is a continuation of pre-existing mental health problems with onset well before pregnancy [23,24]. Women with preconception mental health problems are not only disproportionately

at risk of PND, but also may reap greater mental health benefits from antenatal intervention to promote social support. Persistent mental health problems may trigger social withdrawal limiting opportunities to form and maintain supportive relationships in the transition to parenthood [25]. Women with long-term mental health problems may also have altered perception and capacity to uptake available support, in turn exacerbating risk of symptom recurrence [25,26]. Further, lack of social support may also contribute to onset and maintenance of mental health problems before and during pregnancy. Targeted intervention to improve social support in women with a prior history of mental health problems may thus prevent a developmental cascade of risk for PND symptoms in this vulnerable group.

For women with prior mental health problems, evaluating the potential benefit of intervention on antenatal social support remains an important priority. From a policy perspective, such evaluation is most valuable if it identifies potential gains relative to other feasible intervention targets, allowing strategic investment of limited funds. These include most notably antenatal depressive symptoms, a key focus of current intervention strategies [10], and other risks including financial difficulties and low maternal-fetal attachment [13,14,27]. Another consideration is the primary focus of prior trials on peer support (informally from friends or formally from trained supporters) [22,28], despite observational evidence for the importance of partner support [6,14]. The relative potential benefit of interventions by source of support in women with preconception mental health problems is unclear.

The purpose of this study is therefore to examine the extent to which low perceived antenatal social support mediates associations between preconception mental health problems and PND symptoms. We use data from the Victorian Intergenerational Health Cohort Study (VIHCS), a unique cohort with prospective assessment of women before pregnancy, during pregnancy, and postnatally. Specifically, we examine the relative potential benefit of intervening on a) perceived antenatal *overall social support* as compared to other potentially modifiable antenatal intervention targets; and b) perceived *partner support*, compared to *friend/family support*.

Methods

Participants

The Victorian Intergenerational Health Cohort Study (VIHCS) is an ongoing prospective intergenerational study of preconception predictors of infant and child health, described elsewhere [29]. It arose from a cohort study commencing in 1992 in the state of Victoria, Australia (The Victorian Adolescent Health Cohort Study; VAHCS). 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 three, two months postpartum and one 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.

Measures

Figure 1 portrays our conceptual model.

Preconception mental health problems (A) were assessed during VAHCS Waves 2-7 (participant ages 14-21 years) using the Revised Clinical Interview Schedule (CIS-R; range 0-56) [30], 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 [31]. At each wave, total score was dichotomised at ≥12 to identify mixed depression-anxiety symptoms at a level lower than major disorder, but which a general

practitioner would view as clinically significant [30]. At Waves 8 and 9 (participant ages 24 and 29), symptoms were assessed with the General Health Questionnaire (GHQ-12; range 0-12), a screening measure widely used to assess psychiatric illness in the general population. Total scores were dichotomised at ≥3, a validated threshold that also corresponds to CIS-R ≥12 [30,32]. We constructed variables denoting presence of preconception mental health problems at ≥1 adolescent wave (VAHCS Waves 2-6), and ≥1 young adult wave (VAHCS Waves 7-9). Continuity of preconception mental health problems was defined as 'none', 'transient' (present in adolescence or young adulthood, but not both), and 'persistent' (present in both adolescence and young adulthood).

Postnatal depressive (PND) symptoms (Y) were assessed at two months and one year postpartum, for each pregnancy, using the Edinburgh Postnatal Depression Scale (EPDS) [33]. The EPDS is a widely used 10-item scale that asks participants to rate frequency of past-week depressive symptoms, validated for ante- and postnatal use [34]. Total scores (range 0-30) were calculated at each postnatal timepoint, and dichotomised at a threshold (≥10) recommended for use in screening for mild to severe postnatal depression [35].

We included four potential *antenatal mediators (M)* assessed during trimester three of pregnancy: low perceived social support, high depressive symptoms, low income, and low maternal-fetal attachment. These were identified as associated with PND symptoms, screenable, potentially amenable to intervention, and measured in this study [12,13]. Other periconceptional/pregnancy factors associated with PND symptoms but considered less amenable to intervention were included as covariates (*L*; see below). We dichotomised mediators for translatability to policy settings. To compare mediators at a level denoting relatively high vulnerability, we applied consistent thresholds of ≤10th percentile, except for low income where a policy-relevant threshold is predefined.

- *Maternal perceived social support* was assessed using the six-item Maternity Social Support Scale [36]. Response options ranged from 0 (never) to 4 (always). We defined *low overall social support* as overall mean score ≤10th percentile, *low partner support* as mean score ≤10th percentile for the four partner items ('My husband/partner helps me a lot', 'There is conflict with my husband/partner', 'I feel controlled by my husband/partner' and 'I feel loved by my husband/partner'), and *low*

friend/family support as mean score ≤10th percentile for the two friend/family items ('I have good friends who support me' and 'My family is always there for me'). These thresholds corresponded to mean score ≤2 ('some of the time') in our sample. The scale has shown good reliability and predictive utility [36,37].

- *Depressive symptoms* were assessed and dichotomised as per the postnatal waves, using the EPDS at ≥10 (corresponding to ≤10th percentile in our sample) [33].
- *Low income* was reported as total household income and dichotomised at ≤$50,000 per year, approximating Australian poverty line at the data-collection midpoint [38].
- *Maternal fetal attachment* was assessed using six items from the Maternal Fetal Attachment Scale [39]. Response options ranged from 0 (almost never) to 3 (almost always). Low maternal-fetal attachment was defined as ≤10th percentile. This scale has shown good reliability [40].

Our conceptual model included diverse potential *preconception confounders (C),* based on prior evidence, to maximise plausibility of exchangeability assumptions [41,42]. We also considered potential *periconceptional and pregnancy confounders (L)* of the associations between antenatal factors and PND symptoms. Confounders are listed in Figure 1, and described in detail in the Supplementary Appendix.

Statistical analysis

Estimating the strength of the hypothesised pathways

We first investigated the strength of the hypothesised pathways from preconception mental health problems to PND symptoms via low social support by estimating the unadjusted and adjusted relative risk of a) low antenatal *overall*, *partner*, and *friend/family support* in women with persistent or transient versus no preconception mental health problems, and b) PND symptoms in women with versus without low antenatal social support. We used Poisson regression with robust standard errors to account for within-family clustering.

In supplementary analyses we evaluated correlations between low *overall*, *partner*, and *friend/family support* and the other antenatal mediators in our conceptual model, estimated as the unadjusted relative risk of high antenatal depressive symptoms, low maternal-fetal

attachment, and low income, stratified by low antenatal social support. We also examined the strength of associations between low antenatal *overall*, *partner*, and *friend/family support* and PND symptoms in women with persistent preconception mental health problems, with and without adjustment for the other antenatal factors.

Mediation analysis

We then estimated the potential reduction in PND symptoms in women with prior mental health problems achievable by intervention on antenatal *overall social support* versus other putative antenatal mediators, and on *friend/family* versus *partner support*. We extended a recent method for causal mediation with multiple interdependent mediators that extends previous approaches [43,44] to emulate the effects that would be obtained in a hypothetical randomized trial with interventions both on the exposure and each of a set of interdependent mediators [41]. For this question, we took two approaches. We first estimated a) a 'best case scenario' intervention effect, estimating the potential reductions in PND symptoms in the exposed group if *all risk due to the given mediators* were eliminated. We then estimated b) a more 'pragmatic scenario', using a realistic benchmark estimable from the dataset, by estimating the potential reductions in PND symptoms in the exposed if *the increased risk of the given mediators attributable to prior mental problems* were eliminated. Models included the exposure, mediators, outcome, and all baseline and postexposure confounders. We did not additionally include interaction terms due to sample size and dimensionality of the problem.

We estimated each of the following mediation effects on the risk difference scale, expressed as a marginally adjusted *difference* in risk of PND symptoms, adjusted for pre- and peri-conceptional confounders via a g-computation procedure:

- *Interventional indirect effect via mediator k (IIE_k)*: The reduction in risk of PND symptoms in those with persistent preconception mental health problems achievable by intervention to a) set mediator *k* under exposure to be absent, effectively eliminating all risk due to mediator *k*; or b) shift their mediator distribution to the levels in those without persistent preconception problems, in both cases leaving other interdependent mediator distributions unchanged. The latter amounts to setting the mediator under exposure to a random draw from the distribution under no exposure.

- *Interventional direct effect (IDE).* The remaining risk difference under intervention to a) set all mediators jointly to be absent, effectively eliminating all risk due to included mediators; or b) make the joint distribution of mediators in the exposed (i.e. levels of all the putative mediators and their correlations) to be as in the unexposed.
- *Total causal effect (TCE)*: The overall difference in risk of PND symptoms if all participants were set to be exposed (persistent preconception mental health problems) versus unexposed (no persistent preconception mental health problems). The TCE can be expressed as the sum of IIE_k, the IDE, and an effect that compares joint mediator intervention with the sum of individual interventions on each mediator (IIE_{int}).

All analyses included participants who responded in at least one preconception wave and at least one perinatal wave. Incomplete data were handled using multiple imputation under a fully conditional specification framework [45]. We imputed 35 complete datasets based on the proportion of records with any missing data. Parameter estimates were obtained by pooling results across imputed datasets using Rubin's rules. To assess potential for participation bias, we compared VIHCS participant characteristics with those in VAHCS who were either not screened for pregnancies due to prior study withdrawal, or were screened and eligible but did not participate. We used Stata 16 [46]. Code for analysis from this paper may be accessed at https://osf.io/4h2xm/?view_only=868a559a861b466caaf50cdd4bdd1606

Results

The flow of participants through the study is in Supplementary Figure 1. The initial sample of adolescents recruited to VAHCS in 1992 included 1000 females. Fourteen years and nine waves later, at the start of VIHCS screening and perinatal data collection, 885 (88%) women were available for screening. During VIHCS screening, 465 women reported pregnancies and were thus eligible to participate in VIHCS. Of these, 398 women participated with 600 pregnancies. Women who were screened, identified as eligible, and participated in VIHCS were broadly representative of the original VAHCS cohort on measured baseline demographic, mental health and health risks [29].

Supplementary Table 1 summarises participant characteristics using observed data, and proportions of missing data. Preconception mental health problems were reported in 27% of pregnancies, corresponding to 24% of women. Low perceived overall, family/friend, and partner support were reported in 11%, 9% and 8% of pregnancies respectively. Of those women who participated with more than one pregnancy, few (13-14%) had discordant support ratings across pregnancy (normative/high in one pregnancy, and low in another). Rates of PND symptoms were similar at two months (7%) and one year (8%) postpartum. The cumulative rate of PND symptoms across timepoints was 13%, with 5% reporting symptoms at two months postpartum only, 6% reporting symptoms at one year postpartum only, and 2% reporting symptoms at both timepoints.

Table 1 shows estimated associations of women's preconception mental health problems with low antenatal *overall*, *partner*, and *friend/family support*. Rates of each type of support were higher amongst those with preconception mental health problems, and highest amongst those with persistent symptoms (Supplementary Table 2). After adjustment, persistent preconception mental health problems were associated with increased risk of low *overall* (adjusted risk ratio (aRR) 3.8, 95%CI 1.6, 9.2) and *partner support* (aRR 3.6, 95%CI 1.2, 11.0). Associations with low *friend/family support* were smaller, and attenuated after adjustment (aRR 1.6, 95%CI 0.7, 3.9).

– Insert Table 1 –

Table 2 shows estimated associations of low antenatal *overall*, *partner*, and *friend/family support* support with PND symptoms at two months and one year postpartum. Risk of PND symptoms was consistently higher amongst those with low *overall support*; associations were most pronounced at two months postpartum with an almost fourfold increase in risk, and remained after adjustment. Low *partner support* was associated with a threefold increase in risk of PND symptoms at both two months and one year postpartum after adjustment. Associations between *family/friend support* and PND symptoms were evident at one year postpartum only, and attenuated somewhat after adjustment.

– Insert Table 2 –

Supplementary Tables 3 and 4 show estimated unadjusted associations between low *overall*, *partner*, and *friend/family support* and the other concurrently assessed antenatal mediators in our conceptual model, and estimated associations between low antenatal social support and PND symptoms after adjustment for the other antenatal mediators in women with preconception mental health problems. Risk of antenatal depressive symptoms was higher in those with each type of low antenatal support compared to those with normal/high social support. There was weak evidence of an association between low social support and low income, and little evidence of an association with low maternal-fetal attachment. Despite the correlations between mediators, observed associations between low antenatal *overall* or *partner* support and PND symptoms remained after adjustment for other potential antenatal mediators, albeit with wider confidence intervals (two months postpartum: aRR 3.5, 95%CI 1.0, 12.4; one year postpartum: aRR 2.2, 95%CI 0.7, 6.6).

Table 3 displays the results from the first mediation analysis, examining the reduction in PND symptoms that might be achieved by intervening on low antenatal *overall support*, relative to other potential antenatal mediators. Estimated risks of PND symptoms were higher in women with persistent preconception symptoms than those without at both two months (15.0% vs. 3.2%; total causal effect [TCE] 11.8%) and one year (16.2 vs. 2.7%; TCE 13.5%) postpartum.

At 2 months postpartum, the estimated reduction in PND rates achievable by intervention on *low overall social support* was 2.3% (20% of TCE) under a pragmatic intervention scenario,

and 3.0% (26% of TCE) under a best-case intervention scenario. At 1 year postpartum, the estimated reduction by intervention on low overall social support was 1.1% (8% of TCE; pragmatic scenario) and 1.5% (11% of TCE; best-case scenario).

Considering the other potential intervention targets, the estimated reduction in PND rates achievable by intervention on antenatal depressive symptoms was 3.9% (33% of TCE) under a pragmatic intervention scenario, and 4.9% (42% of TCE) under a best-case intervention scenario, at 2 months postpartum. At 1 year postpartum, the estimated reduction was 4.7% (35% of TCE; pragmatic scenario) and 6.3% (47% of TCE; best-case scenario). In contrast, aside from small risk reductions under a best-case scenario at 2 months postpartum, the roles of income and maternal-fetal attachment were negligible (<0.5% combined). The proportion of TCE via the mediators' interdependence (IIE_int) was negative, as expected because summing the effects overestimates what is achievable due to between-mediator correlations.

When considered together, under a best case intervention scenario eliminating all risk of PND symptoms due to all mediators, the remaining risk difference was 23% at 2 months postpartum and 45% at one year postpartum. Under a more pragmatic intervention scenario lowering the distribution of all mediators to those in the unexposed, the remaining risk difference was 52% at 2 months postpartum and 59% at 1 year postpartum.

– Insert Table 3 –

In the second mediation analysis (Supplementary Table 5), we compared the potential effects of intervention on low antenatal *friend/family support* versus low antenatal *partner support*. We estimated that, aside from a small risk reduction evident under a best case intervention scenario at 1 year postpartum (1.2%; 9% of TCE), intervention to reduce low *family/friend support* yielded negligible reductions in PND symptoms. The estimated potential impact of intervention on antenatal *partner support* was greater, reducing rates of PND symptoms among women with preconception mental health problems by 1.6% (14% of TCE) under a pragmatic scenario and 2.0% (17% of TCE) under a best case scenario at two months postpartum, and by 1.8 (13% of TCE) under a pragmatic scenario and 2.3% (17% of TCE) under a best-case scenario at one year postpartum.

Discussion

Women with a long-term history of mental health problems before pregnancy were at substantially increased risk of PND symptoms, with estimated rates of 15-16% in this group compared to 3% in women without a prior history. The overall proportion of preconception associations mediated by included antenatal factors was 41-77%, driven almost entirely by antenatal social support and depressive symptoms. Interventions on antenatal social support in women with persistent pre-pregnancy mental health problems have the potential to reduce rates of PND symptoms by up to 3% (from 15% to 12%), in a best-case scenario where all mediator risk is eliminated. Importantly, a more conservative target of ~~lowering~~ raising levels of social support to those seen in women without prior mental health problems could also yield comparable gains (up to 2.3%, from 15% to 12.7%). Interventions on antenatal depressive symptoms directly also had the potential to reduce PND symptoms by up to 6.3%. Nonetheless, associations between antenatal social support and PND were robust to adjustment for antenatal depressive symptoms, suggesting an independent role of social support. Findings support a role of antenatal social support, as well as highlighting the likelihood of multiple, complex pathways from preconception to postpartum mental health problems.

Prospectively, women with persistent preconception mental health problems were more than three times more likely to report low antenatal support, a finding consistent with prior retrospective reports [26]. Our findings suggest a role of low antenatal *overall* and *partner-specific* social support in mediating associations between preconception mental health problems and PND symptoms. This may reflect both greater support needs and difficulties in eliciting and maximising support [25,26], increasing risk of symptom recurrence. Negative attribution style is a further potential explanation. Global perceived support may reflect a stable view of the social environment, shaped by lifelong experience [47]. Attachment and trauma models emphasise family of origin legacies in increasing risk of depression, social difficulties, and perceived unavailability of a reliable attachment figure [48]. Nonetheless, partner-specific perceived support is likely to reflect not only general interpersonal disposition but also qualities of the couple's relationship [47]. *Partner support* is a broad construct, and our measure may also capture general partner dissatisfaction and intimate partner violence and abuse, both also risk factors for PND [13,49].

Our finding of a negligible role of *family/friend support* aligns with prior evidence that associations between women's peer networks during pregnancy and PND symptoms may reflect underlying risks, and partially explain the limited efficacy of peer support interventions [14,50]. Aggregation of friend/family support may also mask more specific roles, such as the maternal grandmother. Evidence on family support is mixed, with suggestion that increases to retirement age and distances between extended family members impact grandparental availability [51].

Strengths and limitations

VIHCS is a unique, population-based prospective study of adolescent health with rich developmental data on diverse mental health and behavioural outcomes, spanning two generations. Our use of recent causal mediation methods represents an advance over prior methods, by quantifying the potential relative benefit of interventions at a population level considering multiple interdependent mediators, and by providing best-case versus more realistic estimates of potential intervention effects. However, limitations common to mature cohorts should be considered. Attrition was low in VAHCS, with little evidence that those participating in VIHCS differed from the eligible or baseline VAHCS sample. However, there remains potential for selection bias due to differences on unmeasured characteristics.

Options for data linkage in Australia preclude prospective identification of new pregnancies to an existing longitudinal cohort. Therefore, participants were contacted every six months and invited to join the study if they were pregnant. This makes our study one of very few internationally with antenatal survey data on a long-term preconception cohort. The higher missingness at this wave reflects the logistical challenge of detecting all pregnancies in this way before the birth of the child. When the study detected a new pregnancy after the child was born, we included that child in the VIHCS sample from the postnatal waves onwards, to minimise bias due to selective recruitment. We then used multiple imputation data with a rich imputation variable set to minimise potential for biases due to missing data as far as possible. Nonetheless, as with all cohort studies, potential for bias due to missing data remains. We note that rates of adolescent and young adult mental health problems in our sample were

similar to those reported in other prospective cohorts [52]. Rates of ante- and postnatal depressive symptoms were at the lower end of previously reported meta-analytic bounds [53].

This study included Australian women aged 29-36 years, maximising recruitment within a discrete window around peak maternal age at birth in Australia [54]. Future research should explore associations in younger and older parents given different risk profiles. The role of social support is also influenced by culture, community and policy [14]; for example, Australia's paid parental leave scheme provides financial context for our findings, suggesting a need to explore these questions across political, socio-economic and cultural settings.

Measures were self-reported which opens the possibility of shared method variance. However, perceived sufficiency of support with respect to felt need has intrinsic value, strong predictive validity, and is easily screened [14,18]. Further, associations of low antenatal social support with PND were not explained by concurrent low mood. Our social support measure was brief to reduce participant burden, so that we were able to investigate the high-level categories of *partner* versus *family/friend support*. Our findings were consistent with prior observational evidence of the relatively small role of *family/friend* as compared to *partner support* during pregnancy. However, future research may investigate the role of more specific sources and types of support (including emotional, practical, informational or other types of support) [55,56]. The breadth of the VIHCS dataset and use of new methods enabled adjustment for many potential preconception and periconceptional confounders. Potential for unmeasured confounding remains. Future directions include the preventative role of antenatal social support in women with additional vulnerabilities, such as intimate partner violence.

Conclusions

Even though women with preconception mental health problems are at substantially increased risk of perinatal depression, evidence of effective strategies to prevent symptom recurrence has been limited. Our findings highlight two avenues for research and practice. First, we observed a role of low perceived social support over and above antenatal depressive symptoms, with these two factors accounting for most of the mediated effect. Thus, our findings support a focus on trialling dual intervention on these two factors specifically for women with a background of persistent problems [57]. Prior trials have predominantly focussed on peer support [21,28]. Our findings suggest potential promise of intervention on

perceived *overall* and *partner support* in women with prior mental health problems. These may include efforts to address underlying attributional and interpersonal processes [58], and greater emphasis on family-focussed, partner-inclusive care and consideration of the social context in perinatal mental health strategies [59–61].

Secondly, our findings support calls to evaluate the potential benefit of preventative efforts before pregnancy [62,63]. We found that a substantial proportion of the associations between preconception and postnatal symptoms were not mediated by low social support or the other included antenatal factors, highlighting the likelihood of multiple, complex pathways. Preconception care is increasingly recognised as a critical element of healthcare for women of reproductive age, benefitting women across the life-course and into future pregnancies, should they occur [64]. Such strategies may include focussed preconception care for women with long-term mental health problems, given the complexity and treatment lag times of intervention on socio-emotional health and partner relationships. Prevention strategies from adolescence may have broader benefits in limiting symptom persistence and intergenerational impacts. Adolescence is a critical window of socio-emotional development, commonly marked by the shift from parent to peer as primary support as well as first romantic or sexual relationships [65]. Strengthening investment in adolescent mental health, including healthy and supportive relationship patterns, may thus yield multiple cascading benefits for women that also extend into future pregnancies [66].

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Table 1. Relative risk of low social support during pregnancy, by preconception mental health problems (N=600 pregnancies)

	Low antenatal social support								
	Low overall support			Low friend/family support			Low partner support		
Preconception mental health problems	RR[1]	95% CI[1]	*p*	RR[1]	95% CI[1]	*p*	RR[1]	95% CI[1]	*p*
Unadjusted									
None	ref			ref			ref		
Transient	3.4	(1.4 8.2)	0.006	2.2	(1.0 4.9)	0.060	2.9	(1.1 8.1)	0.036
Persistent	4.3	(1.8 10.2)	0.001	2.6	(1.2 5.9)	0.018	3.5	(1.2 10.3)	0.021
Adjusted for preconception characteristics[2]									
None	ref			ref			ref		
Transient	2.7	(1.1 6.7)	0.033	1.5	(0.7 3.5)	0.332	2.8	(1.0 7.9)	0.052
Persistent	3.8	(1.6 9.2)	0.004	1.6	(0.7 3.9)	0.262	3.6	(1.2 11.0)	0.022

1. RR = relative risk, 95% CI = 95% confidence intervals
2. Adjusted for mother's family of origin, adolescent and young adult preconception characteristics.

Table 2. Relative risk of postnatal depression (PND) symptoms, by low social support during pregnancy (N=600 pregnancies)

	PND[1] symptoms					
	2 months postpartum			1 year postpartum		
Low antenatal social support	RR[1]	95% CI[1]	*p*	RR[1]	95% CI[1]	*p*
Unadjusted						
Low overall support	3.8	(2.0 7.2)	<0.001	2.9	(1.4 6.1)	0.005
Low friend/family support	1.6	(0.6 4.0)	0.325	2.7	(1.3 5.7)	0.007
Low partner support	3.6	(1.7 7.4)	0.001	2.9	(1.2 7.1)	0.017
Adjusted for pre- and periconceptional characteristics [2]						
Low overall support	4.3	(1.8 10.4)	0.001	2.8	(1.2 6.6)	0.020
Low friend/family support	1.1	(0.4 3.0)	0.795	1.8	(0.8 4.0)	0.132
Low partner support	3.4	(1.4 8.5)	0.008	3.5	(1.4 8.6)	0.008
Further adjusted for preconception mental health problems [3]						
Low overall support	3.7	(1.6 8.6)	0.003	2.4	(1.0 5.4)	0.042
Low friend/family support	1.1	(0.4 2.9)	0.822	1.8	(0.8 4.0)	0.157
Low partner support	2.9	(1.2 7.0)	0.017	3.0	(1.2 7.2)	0.015

1. PND = postnatal depression; RR = relative risk, 95% CI = 95% confidence intervals
2. Adjusted for mother's family of origin, adolescent and young adult pre- and periconception characteristics.
3. Adjusted for mother's family of origin, adolescent and young adult pre- and periconception characteristics, and preconception mental health problems.

Table 3. Estimated reduction in rates of postnatal depression (PND) symptoms achieved by intervention on the preconception exposure (TCE) and antenatal mediators (IIE), in women with persistent preconception symptoms (N=600 pregnancies).

	PND[1] symptoms									
	2 months postpartum					1 year postpartum				
	Risk reduction (%)	95% CI	*p*	Proportion of TCE (%)	Risk remaining in exposed (%)	Risk reduction (%)	95% CI	*p*	Proportion of TCE (%)	Risk remaining in exposed (%)
Risk of PND symptoms under exposure (no intervention)	-	-	-	-	15.0	-	-	-	-	16.2
Total causal effect of the preconception exposure (TCE)[2]	11.8	(4.5 , 19.0)	0.002	100	3.2	13.5	(5.9 , 21.1)	0.000	100	2.7
Estimated effects of hypothetical intervention on the mediators										
Scenario 1: Best case intervention *eliminating all mediator risk*										
Interventional indirect effects via mediators (IIE)[3]										
IIE1 (antenatal low social support)	3.0	(-0.3 , 6.3)	0.073	26	12.0	1.5	(-1.8 , 4.7)	0.376	11	14.7
IIE2 (antenatal depressive symptoms)	4.9	(1.0 , 8.8)	0.015	42	10.1	6.3	(2.2 , 10.4)	0.003	47	9.9
IIE3 (antenatal low maternal-fetal attachment)	1.3	(-1.2 , 3.9)	0.304	11	13.7	<1	(-3.0 , 1.7)	0.601	-5	16.8
IIE4 (antenatal low income)	1.9	(-0.6 , 4.3)	0.130	16	13.1	<1	(-1.1 , 2.9)	0.380	7	15.3
IIE_int (mediators' interdependence)	-2.1	(-4.4 , 0.2)	0.073	-18	-	<1	(-2.7 , 1.6)	0.625	-4	-
Interventional direct effect not via mediators (IDE)[4]	2.7	(-2.9 , 8.4)	0.341	23	-	6.0	(-1.2 , 13.3)	0.104	45	-
Scenario 2: Pragmatic intervention *lowering mediator levels to those in the unexposed*										
Interventional indirect effects via mediators (IIE)[5]										
IIE1 (antenatal low social support)	2.3	(-0.4 , 5.0)	0.094	20	12.7	1.1	(-1.5 , 3.8)	0.394	8	15.1
IIE2 (antenatal depressive symptoms)	3.9	(0.5 , 7.3)	0.025	33	11.1	4.7	(1.2 , 8.3)	0.009	35	11.5
IIE3 (antenatal low maternal-fetal attachment)	<1	(-1.2 , 1.3)	0.934	<1	14.9	<1	(-1 , 0.8)	0.883	<1	16.3
IIE4 (antenatal low income)	<1	(-1.3 , 2.1)	0.638	4	14.6	<1	(-0.9 , 1.2)	0.805	1	16.1
IIE_int (mediators' interdependence)	-1.0	(-2.6 , 0.6)	0.217	-9	-	<1	(-2 , 1.2)	0.653	-3	-
Interventional direct effect not via mediators (IDE)[6]	6.1	(0.2 , 19.0)	0.002	52	-	7.9	(1.1 , 14.7)	0.023	59	-

1. PND = postnatal depression. All models adjusted for mother's family of origin, adolescent and young adult preconception and periconceptional characteristics.
2. Risk difference comparing exposed vs unexposed
3. Set given mediator under exposure to zero (no risk)
4. Risk difference comparing exposed vs unexposed under intervention setting all mediators to zero (no risk)
5. Set given mediator under exposure to a random draw from its distribution under no exposure
6. Risk difference comparing exposed vs unexposed under intervention jointly lowering all mediators to those in unexposed

Figure 1. Directed acyclic graph portraying the assumed causal structure, showing the pathways from preconception mental health problems (A) to postpartum depressive symptoms (Y) via the four antenatal mediators (M1-4), after accounting for potential baseline (C) and post-exposure (L) confounding factors. In this conceptual model we are agnostic about the directionality of causal influences between mediators, as indicated using dotted undirected arrows.