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

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Data

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Code for analysis from this paper may be accessed at

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Conflict of interest

I/We declare we have no competing interests

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60 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.

81 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 can also exacerbate challenges of parenthood [14,16]. Women's perceptions that sufficient perinatal social support is available appear particularly important [14,17]. Low perceived social support during pregnancy predicts PND symptoms even after accounting for other perinatal risks [6,14,18]. Conversely, perceived support from partners, family or friends appears protective against perinatal symptoms [14,19].

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 [20]. 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 [10,21]. 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 [22,23]. Women with preconception mental health problems are not only disproportionately

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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 [24]. 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 [24,25]. 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 [13,14,26]. Another consideration is the primary focus of prior trials on peer support (informally from friends or formally from trained supporters) [21,27], 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.

2 3	143	Methods
4 5 7 8 9 10	144	
	145	Participants
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	147	The Victorian Intergenerational Health Cohort Study (VIHCS) is an ongoing prospective
12	148	intergenerational study of preconception predictors of infant and child health, described
13 14	149	elsewhere [28]. It arose from a cohort study commencing in 1992 in the state of Victoria,
15 16	150	Australia (The Victorian Adolescent Health Cohort Study; VAHCS). Briefly, a close-to-
17	151	representative sample of 1943 Victorian mid-secondary school students (1000 female) were
18 19	152	selected via a two-stage cluster sampling design and assessed six-monthly during adolescence
20 21	153	(VAHCS Waves 1-6: mean age 14.9-17.4 years), and three times in young adulthood
22 23	154	(VAHCS Waves 7-9: 20.7, 24.1 and 29.1 years). VIHCS began in 2006 during the ninth
24	155	wave of VAHCS. Between 2006 and 2013 (participant age 29-35 years, encompassing
25 26	156	median maternal and paternal age for Australian births (Australian Bureau of Statistics,
27 28	157	2013)), VAHCS participants were screened six-monthly for pregnancies via SMS, email, and
29	158	phone calls. Participants reporting a pregnancy or recently born infant were invited to
31	159	participate in VIHCS, and asked to complete telephone interviews in trimester three, two
32 33	160	months postpartum and one year postpartum for each infant born during VIHCS screening.
34 35	161	Participants' parents or guardians provided informed written consent at recruitment into
36 27	162	VAHCS, and participants provided informed verbal consent at every subsequent wave.
38	163	Protocols were approved by the human research ethics committee at the Royal Children's
39 40	164	Hospital, Melbourne.
41 42	165	
43 44 45	166	Measures
	167	
46 47	168	Figure 1 portrays our conceptual model.
48 49 50 51 52 53 54 55	169	
	170	Preconception mental health problems (A) were assessed during VAHCS Waves 2-7
	171	(participant ages 14-21 years) using the Revised Clinical Interview Schedule (CIS-R; range
	172	0-56) [29], a structured psychiatric interview designed to assess symptoms of anxiety and
	173	depression in community samples. The CIS-R has been validated for use with adolescent
50 57	174	populations [30]. At each wave, total score was dichotomised at \geq 12 to identify mixed
58 59	175	depression-anxiety symptoms at a level lower than major disorder, but which a general
60		6

practitioner would view as clinically significant [29]. 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 \geq 3, a validated threshold that also corresponds to CIS-R \geq 12 [29,31]. 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) [32]. 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 [33]. 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 [34]. 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 [35]. Response options ranged from 0 (never) to 4 (always). We

defined *low overall social support* as overall mean score $\leq 10^{\text{th}}$ percentile, *low partner* support as mean score $\leq 10^{\text{th}}$ 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

2		
3 4 5 6 7	209	<i>friend/family support</i> as mean score $\leq 10^{\text{th}}$ percentile for the two friend/family items
	210	('I have good friends who support me' and 'My family is always there for me').
	211	These thresholds corresponded to mean score ≤ 2 ('some of the time') in our sample.
o 9	212	The scale has shown good reliability and predictive utility [35,36].
10 11	213	• <i>Depressive symptoms</i> were assessed and dichotomised as per the postnatal waves,
12	214	using the EPDS at ≥ 10 (corresponding to $\leq 10^{\text{th}}$ percentile in our sample) [32].
14 15 16	215	• Low income was reported as total household income and dichotomised at \leq \$50,000
	216	per year, approximating Australian poverty line at the data-collection midpoint [37].
17 19	217	• Maternal fetal attachment was assessed using six items from the Maternal Fetal
19	218	Attachment Scale [38]. Response options ranged from 0 (almost never) to 3 (almost
20 21	219	always). Low maternal-fetal attachment was defined as $\leq 10^{\text{th}}$ percentile. This scale
22 23	220	has shown good reliability [39].
24	221	
25 26	222	Our conceptual model included diverse potential preconception confounders (C), based on
27 28	223	prior evidence, to maximise plausibility of exchangeability assumptions [40,41]. We also
29	224	considered potential periconceptional and pregnancy confounders (L) of the associations
30 31	225	between antenatal factors and PND symptoms. Confounders are listed in Figure 1, and
32 33	226	described in detail in the Supplementary Appendix.
34 35	227	
35 36	228	Statistical analysis
38	229	
39 40 41	230	Estimating the strength of the hypothesised pathways
	231	
43	232	We first investigated the strength of the hypothesised pathways from preconception mental
44 45 46 47 48 49 50	233	health problems to PND symptoms via low social support by estimating the unadjusted and
	234	adjusted relative risk of a) low antenatal overall, partner, and friend/family support in women
	235	with persistent or transient versus no preconception mental health problems, and b) PND
	236	symptoms in women with versus without low antenatal social support. We used Poisson
51 52	237	regression with robust standard errors to account for within-family clustering.
53 54	238	
55	239	In supplementary analyses we evaluated correlations between low overall, partner, and
50 57	240	friend/family support and the other antenatal mediators in our conceptual model, estimated as
58 59	241	the unadjusted relative risk of high antenatal depressive symptoms, low maternal-fetal
60		0

Mediation analysis

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.

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 [42,43] 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 [40]. 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 periconceptional 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 [44]. 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 [45]. Code for analysis from this paper may be accessed at https://osf.io/4h2xm/?view only=868a559a861b466caaf50cdd4bdd1606

2 3	295	Results
4 5 7 8 9 10	296	ixesuits
	297	The flow of participants through the study is in Supplementary Figure 1. The initial sample of
	298	adolescents recruited to VAHCS in 1992 included 1000 females. Fourteen years and nine
	299	waves later, at the start of VIHCS screening and perinatal data collection, 885 (88%) women
11 12	300	were available for screening. During VIHCS screening, 465 women reported pregnancies and
13 14	301	were thus eligible to participate in VIHCS. Of these, 398 women participated with 600
15 16 17 18 19	302	pregnancies. Women who were screened, identified as eligible, and participated in VIHCS
	303	were broadly representative of the original VAHCS cohort on measured baseline
	304	demographic, mental health and health risks [28].
20 21	305	
21 22 23 24 25 26 27 28 29	306	Supplementary Table 1 summarises participant characteristics using observed data, and
	307	proportions of missing data. Preconception mental health problems were reported in 27% of
	308	pregnancies, corresponding to 24% of women. Low perceived overall, family/friend, and
	309	partner support were reported in 11%, 9% and 8% of pregnancies respectively. Of those
	310	women who participated with more than one pregnancy, few (13-14%) had discordant
30 31	311	support ratings across pregnancy (normative/high in one pregnancy, and low in another).
32 33	312	Rates of PND symptoms were similar at two months (7%) and one year (8%) postpartum.
34 35	313	The cumulative rate of PND symptoms across timepoints was 13%, with 5% reporting
36	314	symptoms at two months postpartum only, 6% reporting symptoms at one year postpartum
37 38	315	only, and 2% reporting symptoms at both timepoints.
39 40	316	
41 42	317	Table 1 shows estimated associations of women's preconception mental health problems with
43	318	low antenatal overall, partner, and friend/family support. Rates of each type of support were
44 45	319	higher amongst those with preconception mental health problems, and highest amongst those
46 47	320	with persistent symptoms (Supplementary Table 2). After adjustment, persistent
48 ⊿q	321	preconception mental health problems were associated with increased risk of low overall
50	322	(adjusted risk ratio (aRR) 3.8, 95%CI 1.6, 9.2) and partner support (aRR 3.6, 95%CI 1.2,
51 52	323	11.0). Associations with low friend/family support were smaller, and attenuated after
53 54	324	adjustment (aRR 1.6, 95%CI 0.7, 3.9).
55	325	
57	326	– Insert Table 1 –
58 59	327	
60		11

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,

1 2		
2 3 4 5 6 7 8 9	361	and 3.0% (26% of TCE) under a best-case intervention scenario. At 1 year postpartum, the
	362	estimated reduction by intervention on low overall social support was 1.1% (8% of TCE;
	363	pragmatic scenario) and 1.5% (11% of TCE; best-case scenario).
	364	
10	365	Considering the other potential intervention targets, the estimated reduction in PND rates
12	366	achievable by intervention on antenatal depressive symptoms was 3.9% (33% of TCE) under
13 14	367	a pragmatic intervention scenario, and 4.9% (42% of TCE) under a best-case intervention
15 16 17 18 19	368	scenario, at 2 months postpartum. At 1 year postpartum, the estimated reduction was 4.7%
	369	(35% of TCE; pragmatic scenario) and 6.3% (47% of TCE; best-case scenario). In contrast,
	370	aside from small risk reductions under a best-case scenario at 2 months postpartum, the roles
20 21	371	of income and maternal-fetal attachment were negligible (<0.5% combined). The proportion
22 23 24 25 26 27 28	372	of TCE via the mediators' interdependence (IIE_int) was negative, as expected because
	373	summing the effects overestimates what is achievable due to between-mediator correlations.
	374	
	375	When considered together, under a best case intervention scenario eliminating all risk of
29	376	PND symptoms due to all mediators, the remaining risk difference was 23% at 2 months
30 31 32 33 34 35 36 37 38 39 40	377	postpartum and 45% at one year postpartum. Under a more pragmatic intervention scenario
	378	lowering the distribution of all mediators to those in the unexposed, the remaining risk
	379	difference was 52% at 2 months postpartum and 59% at 1 year postpartum.
	380	
	381	– Insert Table 3 –
	382	
41 42	383	In the second mediation analysis (Supplementary Table 5), we compared the potential effects
43	384	of intervention on low antenatal <i>friend/family support</i> versus low antenatal <i>partner support</i> .
44 45	385	We estimated that, aside from a small risk reduction evident under a best case intervention
46 47	386	scenario at 1 year postpartum (1.2%; 9% of TCE), intervention to reduce low family/friend
48 49	387	support yielded negligible reductions in PND symptoms. The estimated potential impact of
50	388	intervention on antenatal partner support was greater, reducing rates of PND symptoms
51 52	389	among women with preconception mental health problems by 1.6% (14% of TCE) under a
53 54	390	pragmatic scenario and 2.0% (17% of TCE) under a best case scenario at two months
55 56	391	postpartum, and by 1.8 (13% of TCE) under a pragmatic scenario and 2.3% (17% of TCE)
57	392	under a best-case scenario at one year postpartum.
58 59 60		

394 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 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.

³⁴ 412

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 [25]. 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 [24,25], 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 [46]. Attachment and trauma models emphasise family of origin legacies in increasing risk of depression, social difficulties, and perceived unavailability of a reliable attachment figure [47]. Nonetheless, partner-specific perceived support is likely to reflect not only general interpersonal disposition but also qualities of the couple's relationship [46]. 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 [13,48].

2		
3 4	427	
5 6 7 8 9	428	Our finding of a negligible role of <i>family/friend support</i> aligns with prior evidence that
	429	associations between women's peer networks during pregnancy and PND symptoms may
	430	reflect underlying risks, and partially explain the limited efficacy of peer support
10 11	431	interventions [14,49]. Aggregation of friend/family support may also mask more specific
12	432	roles, such as the maternal grandmother. Evidence on family support is mixed, with
13 14	433	suggestion that increases to retirement age and distances between extended family members
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33	434	impact grandparental availability [50].
	435	
	436	Strengths and limitations
	437	
	438	VIHCS is a unique, population-based prospective study of adolescent health with rich
	439	developmental data on diverse mental health and behavioural outcomes, spanning two
	440	generations. Our use of recent causal mediation methods represents an advance over prior
	441	methods, by quantifying the potential relative benefit of interventions at a population level
	442	considering multiple interdependent mediators, and by providing best-case versus more
	443	realistic estimates of potential intervention effects. However, limitations common to mature
	444	cohorts should be considered. Attrition was low in VAHCS, with little evidence that those
34	445	participating in VIHCS differed from the eligible or baseline VAHCS sample. However,
35 36	446	there remains potential for selection bias due to differences on unmeasured characteristics.
37 38	447	
39 40	448	Options for data linkage in Australia preclude prospective identification of new pregnancies
41	449	to an existing longitudinal cohort. Therefore, participants were contacted every six months
42 43	450	and invited to join the study if they were pregnant. This makes our study one of very few
44 45	451	internationally with antenatal survey data on a long-term preconception cohort. The higher
46	452	missingness at this wave reflects the logistical challenge of detecting all pregnancies in this
47 48	453	way before the birth of the child. When the study detected a new pregnancy after the child
49 50	454	was born, we included that child in the VIHCS sample from the postnatal waves onwards, to
51 52	455	minimise bias due to selective recruitment. We then used multiple imputation data with a rich
53	456	imputation variable set to minimise potential for biases due to missing data as far as possible.
54 55	457	Nonetheless, as with all cohort studies, potential for bias due to missing data remains. We
56 57 58 59	458	note that rates of adolescent and young adult mental health problems in our sample were
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15

similar to those reported in other prospective cohorts [51]. Rates of ante- and postnatal depressive symptoms were at the lower end of previously reported meta-analytic bounds [52]. This study included Australian women aged 29-36 years, maximising recruitment within a discrete window around peak maternal age at birth in Australia [53]. 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 [14,17]. 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) [54]. 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 [55]. Prior trials have predominantly focussed on peer support [20,27]. Our findings suggest potential promise of intervention on

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493 perceived *overall* and *partner support* in women with prior mental health problems. These
494 may include efforts to address underlying attributional and interpersonal processes [56], and
495 greater emphasis on family-focussed, partner-inclusive care and consideration of the social
496 context in perinatal mental health strategies [57–59].

Secondly, our findings support calls to evaluate the potential benefit of preventative efforts before pregnancy [60,61]. 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 [62]. 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 [63]. 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 [64].

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

				Low ant	enatal socia	l support			
	L	ow overall sup	oport	Low fi	riend/family	support	Lo	w partner sup	port
Preconception mental health problems	RR^1	95% CI ¹	р	RR^1	95% CI ¹	р	RR^1	95% CI ¹	р
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)

<u>2</u> 3 1		PND¹ symptoms								
5		2 r	nonth	s postj	partum	1	year postpa	rtum		
7 3	Low antenatal social support	RR^1	95%	6 CI ¹	р	RR^1	95% CI ¹	р		
) 10	Unadjusted									
10	Low overall support	3.8	(2.0	7.2)	< 0.001	2.9	(1.4 6.1)	0.005		
12	Low friend/family support	1.6	(0.6	4.0)	0.325	2.7	(1.3 5.7)	0.007		
3 4	Low partner support	3.6	(1.7	7.4)	0.001	2.9	(1.2 7.1)	0.017		
5	Adjusted for pre- and periconceptional characteristics ²									
6	Low overall support	4.3	(1.8	10.4)	0.001	2.8	(1.2 6.6)	0.020		
7	Low friend/family support	1.1	(0.4	3.0)	0.795	1.8	$(0.8 \ 4.0)$	0.132		
8 9	Low partner support	3.4	(1.4	8.5)	0.008	3.5	(1.4 8.6)	0.008		
0	Further adjusted for preconception mental health problems ³									
1	Low overall support	3.7	(1.6	8.6)	0.003	2.4	(1.0 5.4)	0.042		
2	Low friend/family support	1.1	(0.4	2.9)	0.822	1.8	(0.8 4.0)	0.157		
4	Low partner support	2.9	(1.2	7.0)	0.017	3.0	(1.2 7.2)	0.015		
.5										

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 mon	tpartum		1 year postpartum					
	Risk reduction (%)	95% CI	р	Proportion of TCE (%)	Risk remaining in exposed (%)	Risk reduction (%)	95% CI	р	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 <i>eliminating all mediator risk</i> 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 <i>lowering mediator levels to those in the</i> Interventional indirect effects via mediators (IIE) ⁵	unexposed									
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

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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.

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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 (M_{1-4}), 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.

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10	1	Preventing postnatal depression: a causal mediation analysis of a 20-year preconception
11 12	2	cohort
13	3	
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44	27	
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60	Summary
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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 2.33% (from 15% to 12.7%) in women with persistent preconception symptoms. Supplementary analyses found that the role of low antenatal social support was independent of concurrent antenatal depressive symptoms., where intervention could reduce PND symptoms by up to 4.7%. 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 commona 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 estimated at over \$7 billion per annum in Australia and are similarly high in other high income countriesalso 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 a context of heightened risk for mental health problems, substantial 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 can also exacerbate challenges of parenthood [14,16]. Women's perceptions that sufficient perinatal social support is available appear particularly important for mental health [14,17]. Low perceived social support during pregnancy predicts PND symptoms even after accounting for other perinatal risks [6,14,18]. Conversely, perceived support from partners, family or friends appears protective against perinatal symptoms [14,19].

For these reasons, a number of preventative interventions to promote maternal social support have been trialed, often commencing in pregnancy when many parents have greater health system contact [20]. However, these often show little reduction in rates of PND [8,19]. 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 [10,21]. One of the strongest and most reliable pre-existing risk factors for PND is a history

of mental health problems [13]. One reason may be that for many, For many women, perinatal

depression is a continuation of pre-existing, entrenched mental health problems with an-onset well before pregnancy [22,23]. Women with preconception mental health problems thus represent a vulnerable group who are not only disproportionately at risk of PND, but also may reap greater mental health benefits from antenatal intervention to promote social support. Preconception mental health problems are one of the strongest and most reliable predictors for PND [11]. Persistent mental health problems may trigger social withdrawal limiting opportunities to form and maintain supportive relationships in the transition to parenthood [24]. 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 [24,25]. 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. Women with preconception mental health problems thus represent a vulnerable group who are not only disproportionately at risk of PND, but also may reap greater mental health benefits from antenatal intervention to promote social support.

For women with preconception history ofprior 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 fundsas an alternative to, or in addition to, other potentially modifiable intervention targets remains an important priority. These include most notably antenatal depressive symptoms, a key focus of current preventive-intervention strategies [10], as well asand mitigation of other risks including financial difficulties and low maternal-fetal attachment [13,14,26]. An additionalAnother consideration is the primary focus of prior intervention trials on peer support (informally from friends or formally from trained supporters) [21,27], 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.

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9 10	146	The purpose of this study is therefore to examine the extent to which low perceived antenatal
11	147	social support mediates associations between preconception mental health problems and PND
13	148	symptoms. whether perceived antenatal social support has the potential to be a useful target
14	149	in preventing postnatal depressive symptoms amongst women with prior mental health
15	150	problems. We use data from the Victorian Intergenerational Health Cohort Study (VIHCS), a
16 17	151	unique cohort with prospective assessment of women before pregnancy, during pregnancy,
18	152	and postnatally. repeated prospective assessment of 1000 Australian women from
19	153	adolescence in 1992 (Generation 1), and prospective assessment of their offspring during the
20 21	154	third trimester of pregnancy, and at 2 months and 1 year postpartum from 2006 (Generation
21	155	2). Specifically, we examine ÷
23	156	
24	157	1 The extent to which low perceived antenatal social support mediates associations
25 26	158	hetween preconception mental health problems and PND symptoms.
20	159	2tThe relative potential henefit of intervening on a)
28	160	perceived antenatal overall social support as compared to other potentially modifiable
29	161	antenatal intervention targets:- and h)
30 31	162	\Rightarrow perceived partner support compared to friend/family support
32	102	percerved partner support, compared to prenarganity support.
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10	163	Methods
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12	165	Participants
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15	167	The Victorian Intergenerational Health Cohort Study (VIHCS) is an ongoing prospective
16	168	intergenerational study of preconception predictors of infant and child health described
17	169	elsewhere [28] It arose from a cohort study commencing in 1992 in the state of Victoria
19	170	Australia (The Victorian Adolescent Health Cohort Study: VAHCS) Briefly a close-to-
20	171	representative sample of 1943 Victorian mid-secondary school students (1000 female) were
21	172	selected via a two-stage cluster sampling design and assessed six-monthly during adolescence
23	173	(VAHCS Wayes 1-6: mean age 14.9-17.4 years) and three times in young adulthood
24	174	(VAHCS Waves 7-9: 20.7. 24.1 and 29.1 years). VIHCS began in 2006 during the ninth
25 26	175	wave of VAHCS Retween 2006 and 2013 (participant age 20.35 years, encompassing
20	176	median maternal and naternal age for Australian hirths (Australian Bureau of Statistics
28	177	2012)) VAHCS participants were screened six monthly for pregnancies via SMS email and
29	170	where calls. Derticipants reporting a programmy or recently have infant were invited to
30 21	178	phone calls. Participants reporting a pregnancy or recently born infant were invited to
32	179	participate in VIHCS, and asked to complete telephone interviews in trimester three, two
33	180	months postpartum and one year postpartum for each infant born during VIHCS screening.
34	181	Participants' parents or guardians provided informed written consent at recruitment into
35	182	VAHCS, and participants provided informed verbal consent at every subsequent wave.
36	183	Protocols were approved by the human research ethics committee at the Royal Children's
38	184	Hospital, Melbourne.
39	185	
40	186	Measures
41 42	187	
43	188	Figure 1 portrays our conceptual model.

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) [29], 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 [30]. 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 [29]. 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 \geq 3, a validated threshold that also corresponds to CIS-R \geq 12 [29,31]. 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).

206Postnatal depressive (PND) symptoms (Y) were assessed at two months and one year207postpartum, for each pregnancy, using the Edinburgh Postnatal Depression Scale (EPDS)208[32]. The EPDS is a widely used 10-item scale that asks participants to rate frequency of209past-week depressive symptoms, validated for ante- and postnatal use [33]. Total scores210(range 0-30) were calculated at each postnatal timepoint, and dichotomised at a threshold211(\geq 10) recommended for use in screening for mild to severe postnatal depression [34].

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 $\leq 10^{th}$ 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 [35]. 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*

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10	229	<i>friend/family support</i> as mean score $\leq 10^{\text{th}}$ percentile for the two friend/family items
11	230	('I have good friends who support me' and 'My family is always there for me').
13	231	These thresholds corresponded to mean score ≤ 2 ('some of the time') in our sample.
14	232	The scale has shown good reliability and predictive utility [35,36].
15	233	Depressive symptoms were assessed and dichotomised as per the postnatal waves
16	200	s = Depressive symptoms were assessed and denotoninsed as per the positiatian waves,using the EPDS at >10 (corresponding to <10th paraentile in our semple) [22]
1/	234	using the EPDS at ≥ 10 (corresponding to $\geq 10^{-6}$ percentine in our sample) [52].
10	235	• Low income was reported as total household income and dichotomised at \leq \$50,000
20	236	per year, approximating Australian poverty line at the data-collection midpoint [37].
21	237	• Maternal fetal attachment was assessed using six items from the Maternal Fetal
22	238	Attachment Scale [38]. Response options ranged from 0 (almost never) to 3 (almost
23	239	always). Low maternal-fetal attachment was defined as ≤10 th percentile. This scale
24 25	240	has shown good reliability [39].
26	241	
27	241	Our concentual model included diverse notential presencentian confoundary (C) based on
28	242	prior avidence, to maximize plausibility of avokangeability assumptions [40,41]. We also
29	243	prior evidence, to maximise plausionity of exchangeability assumptions [40,41]. We also
30 31	244	considered potential <i>periconceptional and pregnancy confounders</i> (L) of the associations
32	245	between antenatal factors and PND symptoms. Confounders are listed in Figure 1, and
33	246	-described in detail in the Supplementary Appendix.
34	247	
35	248	Statistical analysis
36 37	249	
38	250	Estimating the strength of the hypothesised pathways
39	251	
40	252	We first investigated the strength of the hypothesised pathways from preconception mental
41 42	253	health problems to PND symptoms via low social support by estimated estimating the
42	254	unadjusted and adjusted relative risk of a) low antenatal <i>antenatal</i> -overall, partner, and
44	255	friend/family support social support in women with persistent or transient versus no
45	256	preconcention mental health problems and b) PND symptoms in women with versus without
46	250	low entended social support. We used Deisson regression with robust standard errors to
47 48	237 hro	ow antenatal social support, we used i ofsson regression with robust standard effors to
49	258	account for within-family clustering. The aim was to provide an idea of the strength of the
50	259	nypothesised pathways from preconception mental health problems to PND symptoms via
51	260	low social support.
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In supplementary analyses we evaluated correlations between low *antenatal overall, partner*, and friend/family support social 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, in women with versus withoutstratified by low antenatal social support. We also examined the strength of associations between low antenatal overall, partner, and friend/family support antenatal social 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 used extended a recent method of for causal mediation with multiple interdependent mediators that extends previous approaches [42,43] 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 [40]. 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 periconceptional 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

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9 10	bor	aliminating all risk due to mediator k or intervention to b) shift their mediator
11	295	<u>entimating an risk due to mediator k, or intervention to or</u> sufficient mediator
12	296	distribution to the levels in those without persistent preconception problems, in both
13	297	cases leaving other interdependent mediator distributions unchanged. <u>This The latter</u>
14 15	298	case amounts to setting the mediator under exposure to a random draw from the
16	299	distribution under no exposure.
17	300	• Interventional direct effect (IDE). The <u>remaining</u> risk difference that would remain if
18	301	we could interveneunder intervention to a) set all mediators jointly to be absent.
19	302	effectively eliminating all risk due to included mediators; or b) make the joint
20 21	303	distribution of mediators in the exposed-group (i.e. levels of all the putative mediators
22	304	and their correlations) to be as in the unexposed group.
23	 305	• Total causal effect (TCE): The overall difference in risk of PND symptoms if all
24	306	participants were set to be exposed (persistent preconception mental health problems)
25 26	207	versus unsurposed (no persistent preconception mental health problems). The TCE con
20 27	307	versus unexposed (no persistent preconception mental health problems). The TCE can
28	308	be expressed as the sum of IIE_k , the IDE, and an effect that compares joint mediator
29	309	intervention with the sum of individual interventions on each mediator $(IIE_{int})_{z}$.
30	310	
31	311	All analyses included participants who responded in at least one preconception wave and at
33	312	least one perinatal wave. Incomplete data were handled using multiple imputation under a
34	313	fully conditional specification framework [44]. We imputed 35 complete datasets based on
35	314	the proportion of records with any missing data. Parameter estimates were obtained by
36	315	pooling results across imputed datasets using Rubin's rules. To assess potential for
37 38	316	participation bias, we compared VIHCS participant characteristics with those in VAHCS who
39	317	were either not screened for pregnancies due to prior study withdrawal, or were screened and
40	818	eligible but did not participate. We used Stata 165 [45] Code for analysis from this paper
41	319	may be accessed at https://osf.io/4b2vm/2view_only=868a559a861b466caaf50cdd4bdd1606
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10	321	Results							
11	322								
12	323	The flow of participants through the study is in Supplementary Figure 1. The initial sample of							
14	324	adolescents recruited to VAHCS in 1992 included 1000 females. Fourteen years and nine							
15 16	325	waves later, at the start of VIHCS screening and perinatal data collection, 885 (88%) women							
17	326	were available for screening. During VIHCS screening, 465 women reported pregnancies and							
18	327	were thus eligible to participate in VIHCS. Of these, 398 women participated with 600							
19 20	328	pregnancies. Women who were screened, identified as eligible, and participated in VIHCS							
20 21	329	were broadly representative of the original VAHCS cohort on measured baseline							
22	330	demographic, mental health and health risks [28].							
23	331								
24 25	332	Supplementary Table 1 summarises participant characteristics using observed data, and							
26	333	proportions of missing data. Preconception mental health problems were reported in 27% of							
27	334	pregnancies, corresponding to Women-24% of womenreported persistent preconception							
28 29	335	mental health problems for 27% of pregnancies. Low perceived overall, family/friend, and							
30	336	partner support were reported in 11%, 9% and 8% of pregnancies respectively. Of those							
31	337	women who participated with more than one pregnancy, few (13-14%) had discordant							
32 33	338	support ratings across pregnancy (normative/high in one pregnancy, and low in another).							
34	339	Rates of PND symptoms were similar at two months (7%) and one year (8%) postpartum.							
35	340	The cumulative rate of PND symptoms across timepoints was 13%, with 5% reporting							
36 37	341	symptoms at two months postpartum only, 6% reporting symptoms at one year postpartum							
38	342	only, and 2% reporting symptoms at both timepoints.							
39	343								
40 41	344	Table 1 shows estimated associations of women's preconception mental health problems with							
41	345	low antenatal overall, partner, and friend/family supportperceived antenatal social support.							
43	346	Rates of low perceived antenatal socialeach type of support were higher amongst those with							
44	347	preconception mental health problems, and highest amongst those with persistent symptoms							
45 46	348	(Supplementary Table 2). After adjustment, persistent preconception CMD symptoms mental							
47	349	health problems were associated with increased risk of low overall (adjusted risk ratio (aRR)							
48	350	3.8, 95%-CI 1.6, 9.2) and partner support (aRR 3.6, 95%-CI 1.2, 11.0)-compared to those							
49 50	351	without preconception symptoms. Associations with low friend/family support were smaller,							
51	352	and attenuated after adjustment (aRR 1.6, 95%-CI 0.7, 3.9).							

52 353

– Insert Table 1 –

Table 2 shows estimated associations of low antenatal overall, partner, and friend/family support perceived antenatal social support with PND symptoms at two months and one year postpartum. Risk of PND symptoms was consistently higher amongst those with low overall antenatal social support; associations were most pronounced at two months postpartum with an almost fourfold increase in risk, and remained after adjustment. Low perceived 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 2-3 and 4 shows estimated unadjusted associations between low overall, partner, and friend/family support perceived social support and the other potential concurrently assessed antenatal mediators in our conceptual model, assessed concurrently in trimester three (high depressive symptoms, low maternal-fetal attachment, and low income), 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 three to four times higher in those with each type of low antenatal support compared to those with normal/high social support. There was some weak evidence of an association between low income and low social support and low income, and no-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). Associations between low antenatal social support and PND symptoms in women with persistent preconception mental health problems were similar before and after adjustment for the other potential antenatal mediators, albeit with wider confidence intervals (Supplementary Table 3; two months postpartum: aRR 3.3, 95% CI 1.0, 11.5; one year postpartum: aRR 2.2, 95% CI 0.7, 6.4).

Table 3 displays the results from the first mediation analysis, examining the reduction in PND symptoms that might be achieved by intervening on perceived antenatallow antenatal overall social support, relative to other potential antenatal mediators, and after adjustment for a broad range of preconception and periconceptional factors. Estimated rates risks of PND symptoms were higher in women with persistent preconception symptoms than those without at both two months (15.0% vs. 3.2%; TCE total causal effect [TCE] 11.8%) and one year (16.2 vs. 2.7%; TCE 13.5%) postpartum. At two months postpartum, around half (48%) of the TCE was mediated by the four antenatal factors and their interdependence, leaving a remaining between-group difference (IDE) of 6.1%. The proportion mediated by the four antenatal factors and their interdependence reduced slightly to 41% at one year postpartum, with a remaining between-group difference (IDE) of 7.9%. Almost all of the mediated effect was via two factors: antenatal depressive symptoms, and low perceived antenatal social support. 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.

Commented [MMB1]: Again I would focus more on the fact tat these were the factors with most impact

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. We estimated that the greatest impact would be achieved by intervention on antenatal depressive symptoms (IIE2), reducing rates of PND symptoms in those with persistent preconception mental health problems by 3.9and% (from 15% to 11.1%) at two months postpartum (33% of the mediated effect, IIE) and by 4.7and% (from 16% to 11.2%) at one vear postpartum (35% of IIE). Antenatal low social support (IIE1) was the second largest highest-impact mediator, reducing rates of PND symptoms in those with a preconception history by 2.3and% (from 15% to 12.7%) at two months postpartum (20% of the mediated effect, IIE) and by 1.1amd% (from 16% to 14.9%) at one year postpartum (8% of IIE). The roles of income and maternal-fetal attachment (IIE3-4) were negligible (<0.5% combined). The proportion of TCE via the mediators' interdependence (IIE int) was negative, as expected because summing the indirect effects can overestimates what is achievable due to between-mediator correlations.

– Insert Table 3 –

In the second mediation analysis (Supplementary Table 54), we compared the potential effects of intervention on low antenatal friend/family support versus low antenatal partner support. In the risk difference scale, with marginal adjustment, weWe 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._at either two months (risk difference = 0.1%) or one year postpartum (risk difference = 0.6%). The estimated potential impact of intervention on antenatal partner support was greater, accounting for 13% of the mediated effect (IIE) at both outcome timepoints and reducing rates of PND symptoms among women with preconception CMD historymental health problems by 1.6% (14% of TCE) under a pragmatic scenario and toand2.05% (17% of TCE) under a best case scenario (from 15% to 13.5%) at two months postpartum, and by 1.8 (13% of TCE) under a pragmatic scenario toand 2.3% (17% of TCE) under a best-case scenario (from 16% to 14.2%) at one year

postpartum. The total proportion of the TCE at two months postpartum mediated by low *friend/family* and/or *partner support* in Supplementary Table 4 was slightly lower than that
mediated by *overall social support* in Table 3; the reverse was true at one year postpartum.
This is due to different impacts via the correlation between mediators at each timepoint.

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457 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 4041-5077%, 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 2.33% (from 15% to 12.7%), in this group in a best-case scenario where all mediator risk is eliminated. Importantly, a more conservative target of lowering 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%). The role of antenatal social support was robust to adjustment for antenatal depressive symptoms, where interventionInterventions on antenatal depressive symptoms directly also had the potential to reduce PND symptoms by up to 4.76.3%. Nonetheless, associations between antenatal social support and PND were robust to adjustment for antenatal depressive symptoms, suggesting an independent role of social support. These Ffindings support a modest role of antenatal social support, as well as highlighting the likelihood of multiple, complex pathways from preconception to postpartum mental health problems.

Rates of adolescent and young adult mental health problems in our sample were similar to
those previously reported in other prospective cohorts [44]. Likewise, rates of ante- and
postnatal depressive symptoms were similar to those previously reported for high income
countries, though at the lower end of previously reported meta-analytic bounds [45].

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 [25]. 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 [24,25], 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 [46]. Attachment and

trauma models emphasise family of origin legacies in increasing risk of depression, social difficulties, and perceived unavailability of a reliable attachment figure [47]. Nonetheless, partner-specific perceived support is likely to reflect not only general interpersonal disposition but also qualities of the couple's relationship [46]. 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 [13,48].

Our finding of a negligible role of *family/friend support* aligns with prior suggestion-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 [14,49]. 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 [50].

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 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 characteristicssamples may differ on unmeasured characteristics.

Response 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. rates were high preconception and postnatally, but lower antenatally due to challenges of prospectively identifying pregnancies. We used multiple imputation to minimise potential biases. RWe note that rates of adolescent and young adult mental health problems in our sample were similar to those reported in other prospective cohorts [51]. Rates of ante- and postnatal depressive symptoms were at the lower end of previously reported previously reported meta-analytic bounds [52]. This study included Australian women aged 29-36 years, maximising recruitment within a . 536 discrete window around peak maternal age at birth in Australia [53]. 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 [14,17]. 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, and future. 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 nuanced types of support. specific sources and types of support (including emotional, practical, informational or other types of support) [54]. The breadth of the VIHCS . 553 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 additionalvulnerabilities, such as intimate partner violence.

558 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 modest role of low perceived social support over and above antenatal depressive symptoms, with these two factors combined mediating up to almost half of the association of preconception mental health problems with PND symptoms 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 [55]. Prior trials have predominantly focussed on peer support [20,27]. Our findings suggest greater 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 [56], and greater emphasis on family-focussed, partner-inclusive care and consideration of the social context in perinatal mental health strategies [57-59]53,54.

Secondly, our findings support calls to evaluate the potential benefit of preventative efforts before pregnancy [60,61]. 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 [62]. 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. Further, up to half of associations between preconception and postnatal symptoms were not mediated by included antenatal factors, highlighting the likelihood of multiple, complex pathways. 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

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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										
	Lo	ow overall sup	oport	Low fi	riend/family	support	Low partner support				
Preconception mental health problems	RR^1	95% CI ¹	р	RR^1	95% CI ¹	р	RR^1	95% CI ¹	р		
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.

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 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	р	RR^1	95% CI ¹	р			
nadjusted									
Low overall support	3.8	(2.0 7.2)	< 0.001	2.9	(1.4 6.1)	0.005			
ow 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			
ljusted 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			
ow friend/family support	1.1	(0.4 3.0)	0.795	1.8	$(0.8 \ 4.0)$	0.132			
ow partner support	3.4	(1.4 8.5)	0.008	3.5	(1.4 8.6)	0.008			
or ther 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	29	(1.2 7.0)	0.017	3.0	(1272)	0.015			

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 mon	ths pos	tpartum		1 year postpartum							
	Risk reduction (%)	95% CI	р	Proportion of TCE (%)	Risk remaining in exposed (%)	Risk reduction (%)	95% CI	р	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 <i>eliminating all mediator risk</i> Interventional indirect effects via mediators (IIE) ³	2.0		0.072		12.0	1.5	(10, 47)	0.27(11	14.7			
IIE1 (antenatal low social support)	3.0	(-0.3, 0.3)	0.073	26	12.0	1.5	(-1.8, 4.7)	0.3/6	11	14./			
IIE2 (antenatal low maternal fetal attachment)	4.9	(1.0, 8.8)	0.015	42	13.7	0.5 <1	(2.2, 10.4)	0.003	-5	9.9			
IIE4 (antenatal low income)	1.5	(-1.2, 5.9)	0.130	16	13.1	<1	(-3.0, 1.7)	0.380	-5	15.3			
IIE int (mediators' interdenendence)	-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 <i>lowering mediator levels to those in the</i> Interventional indirect effects via mediators (IIE) ⁵	unexposed												
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.

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