

Antenatal interventions to address harmful behaviors and psychosocial risk factors in the prevention of low birth weight

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List of abbreviations used:

ANC - Antenatal care

CI - Confidence interval

ES - Effect size

FGR - Fetal growth restriction

GRADE - Grading of Recommendations Assessment, Development, and Evaluation

HIC - High-income country

IPV - Intimate partner violence

LIC - Low income country

LMIC - Low- and middle-income country

LBW - Low birth weight

NRT - Nicotine replacement therapy

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

PTB - Preterm birth

RCT - Randomized controlled trial

RR - Relative risk

SB - Stillbirth

SGA - Small for gestational age

WHO – World Health Organization

Abstract

Background: Risk factors related to the harmful behaviors, psychosocial wellbeing, and socio-economic circumstances in the lives of pregnant women can lead to adverse birth outcomes, including low birth weight (LBW).

Objective: This systematic search and review aims to provide a comparative evidence synthesis on the effect of eleven antenatal interventions targeted to address psychosocial risk factors on adverse birth outcomes.

Methods: We searched MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and CINAHL Complete between March 2020 and May 2020. We included randomized controlled trials (RCTs) and reviews of RCTs of eleven antenatal interventions for pregnant females reporting LBW, preterm birth (PTB), small-for-gestational-age or stillbirth as outcomes. For interventions where randomization was either not feasible or unethical, we accepted non-randomized controlled studies.

Results: Seven records contributed data to the quantitative estimates of the effect sizes and 23 contributed to narrative analysis. Psychosocial interventions for reducing smoking in pregnancy likely reduced the risk of LBW, and professionally provided psychosocial support for at-risk women possibly reduced the risk of PTB. Financial incentives or nicotine replacement therapy as smoking cessation aids, or virtually delivered psychosocial support did not appear to reduce the risk of adverse birth outcomes. The available evidence on these interventions was primarily from high-income countries. For other reviewed interventions (psychosocial interventions to reduce alcohol use, group based psychosocial support programs, intimate partner violence prevention interventions, antidepressant medication, and cash transfers) there was little evidence in any direction regarding the efficacy or the data was conflicting.

Conclusions: Professionally provided psychosocial support during pregnancy in general and specifically as a means to reduce smoking can potentially contribute to improved newborn health. The gaps in the investments for research and implementation of psychosocial interventions should be addressed to better meet the global targets in LBW reduction.

Key words

Low birth weight, preterm birth, antenatal care, pregnancy, psychosocial interventions, smoking, psychosocial support, low- and middle-income countries

Introduction

Exposure of a fetus to risk factors in nutritional, medical, environmental and socio-economic circumstances in a pregnant woman's life can lead to adverse birth outcomes, including low birth weight (LBW). An estimated 15 per cent of all births annually are LBW i.e., birth weight of less than 2500g, resulting from preterm birth (PTB, birth before 37 completed weeks of gestation), fetal growth restriction (FGR) that typically, but not always, presents as the newborn being small for gestational age (SGA, weight below the 10th percentile for the gestational age and sex), or both (1). LBW is a major predictor of newborn survival, childhood stunting, and various adverse adult-onset chronic conditions (1). PTB is considered the leading cause of death in children under 5 years of age globally and SGA is also associated with markedly increased risk of death and other adverse outcomes (2–5). Hence, addressing risk factors with effective interventions to prevent LBW, PTB, or SGA can lead to substantial and long-lasting improvements in birth outcomes and the health of newborns.

There is an increasing recognition of the importance of looking beyond medical and obstetrics factors towards also detecting psychosocial risk factors in antenatal period. Known psychosocial factors associated with a range of pregnancy complications and adverse birth outcomes such as LBW and PTB (**Figure 1**) include prenatal smoking (6), alcohol use (7), depression (8), stress (9,10), and intimate partner violence (IPV) (11). Lack of psychosocial support further increases the impact of stress and depression on pregnant women (**8,12,13**). Poverty and social disadvantage can be seen as underlying societal factors contributing to the risk of LBW. More than 90% of the LBW births take place in low- and middle-income countries (LMICs) (1). In high-income countries (HICs), deprived populations with lower levels of socio-economic status or employment have the highest odds for adverse birth outcomes (**14,15**).

There is a wide range in the prevalence rates of central antenatal psychosocial risk factors in different countries, however these factors tend to be interconnected in many ways. For instance, women who experience deprivation, depression, abuse, or limited support are more likely to engage in risky behaviors during pregnancy, such as smoking and alcohol use (16–18). Moreover, the effect of these risk factors outspreads to medical and nutritional domains: they affect the ability of women to seek and adhere to care and access nutrition (8,19,20) which in turn may cause further accumulation of risk factors for LBW. Hence, responding to these social risks is paramount to achieve the global targets in LBW reduction (21) and it is particularly important in areas where the burden of LBW is greatest.

There is scientific evidence on key psychosocial contributors that have been identified to contribute to adverse birth outcomes including LBW and PTB, and the burden of these risk factors in various populations. What is lacking is a systematic comparison of the most promising interventions that could be added to antenatal care (ANC) to reduce the global incidence of LBW and related outcomes. We aimed to fill this knowledge gap by providing an evidence synthesis on the impact of antenatal interventions targeted to address psychosocial risk factors, with the intent to provide evidence-based insight for policy and practice. The aim of this article is to present a summary of published literature on eleven interventions addressing harmful behaviors, psychosocial risks and unfavorable socioeconomic factors in pregnancy to reduce LBW and related adverse birth outcomes.

Methods

This article reports a part of an evidence synthesis on a range of antenatal interventions that could be used to reduce the incidence of LBW, PTB, SGA, and stillbirth (SB) globally. Out of the 46 studied antenatal interventions, the current review focuses on eleven antenatal interventions that aim to address harmful behaviors, psychosocial risks, and socioeconomic factors in pregnancy. The interventions related to maternal nutrition, infection control, and environmental exposures are reported elsewhere (22–24).

For the literature search, study selection, and evidence synthesis, we used a recently described novel systematic search and review method, the modular review, that allows concomitant review of multiple interventions (25). The modular review consists of a streamlined process to evaluate, synthesize, summarize and categorize evidence optimized to inform decision-making, policy and program planning. While the design of the method, particularly its ability to review multiple interventions simultaneously, precluded the registration of the study in prospective registers of systematic reviews of single interventions, an a priori protocol was used, and the method was published in detail (25).

Full details of the method are provided in Supplementary methods. In brief, we performed four systematic searches in MEDLINE (OvidSP), Embase (OvidSP), Cochrane Database of Systematic Reviews (Wiley Cochrane Library), Cochrane Central Register of Controlled Trials (Wiley Cochrane Library), CINAHL Complete (EbscoHOST) between 17 March 2020 and 26 May 2020.

We included English-language studies that were relevant to population, intervention, study design and outcomes. The population of interest was pregnant females, irrespective of gestational age. The interventions were 1) psychosocial interventions, 2) nicotine replacement therapy (NRT), and 3) financial incentives to reduce smoking in pregnancy; 4) psychosocial

interventions to reduce alcohol use in pregnancy; 5) health professional provided psychosocial support; 6) virtual support; 7) group program based psychosocial support; 8) antidepressant medication for pregnant women with depression; 9) intimate partner violence (IPV) prevention interventions; as well as 10) conditional and 11) unconditional cash transfers to pregnant women (search terms are listed in Supplementary data 1-11).

To our knowledge, there is no pooled data on the prevalence of psychosocial risk factors in pregnancy at the LMIC level, the estimated prevalence rates of single risk factors range from 1.3% to 92% (**Table 1**). However, many of the studied interventions are particularly relevant to LMICs. For instance, the prevalence of antenatal depression is higher in LMICs than in HICs (8,26) and while global prevalence rates of smoking are decreasing, tobacco industry increasingly targets especially young women in Africa and elsewhere in LMICs (27,28) where the implementation of global tobacco control policies tends to remain slower than in HICs (29). The implementation of these interventions is not currently explicitly recommended by World Health Organization (WHO) although screening of the risk factor may be so. However, the international research community has considered these interventions as potential tools to reduce the burden of LBW, because they address relevant, potentially modifiable social risk factors for LBW, PTB, or FGR.

As study designs, we primarily included randomized controlled trials (RCTs) and reviews of RCTs. For interventions, where randomization was either not feasible or unethical, we accepted non-randomized controlled studies. The included studies had to report at least one of the following outcomes: LBW, PTB, SGA, or SB. While LBW was the starting point of our project, PTB and SGA indicate the two main pathways that lead to it and SB is an extreme outcome that often results from the same processes that limit fetal growth or shorten the duration of pregnancy. Thus, all four outcomes can be partially attributed to the same antecedents (30).

For each intervention, we sought the best estimate of effect size (ES) from the included studies. ES documents consisted of the most recent quantitative evidence, with reviews of reviews (umbrella reviews, meta-reviews, reviews of (systematic) reviews) constituting the highest level of evidence. Next level consisted of reviews from the Cochrane collaboration followed by high quality systematic reviews with or without meta-analyses. If there were no reviews available, we used peer-reviewed published RCTs to estimate the combined effect size. In the absence randomized studies, we reported non-randomized controlled studies. In addition to identifying the latest reviews as ES documents, we also identified RCTs published after the review as ES documents. In such case, results from the more recent RCTs were reported separately. In reporting of effect size, we used unadjusted relative risk (RR) or odds ratio with 95% or 90% confidence intervals (CI), stating the number of randomized participants.

In assessing the quality of evidence, we primarily accepted the assessment given in the Summary of Findings tables of the utilized ES documents that were reviews. Typically, the tables were produced according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process and they provided the quality of evidence rating for each outcome (31). In the older ES documents, the assessment was typically described to indicate the “quality” of evidence, whereas in the newer documents it was marked as the “certainty” of evidence. For individual RCTs, we assessed the risk of bias. This was converted into assessment of quality of evidence (detailed in Supplementary methods).

To interpret the impact of the interventions on each outcome, we sorted our findings into five categories based on the calculated effect size, the 95% or 90% CI, the number of studies and the quality of evidence. Each intervention was given standardized statement in relation to its effect on each outcome, accompanied by a color code (**Table 2**).

We utilized narrative reporting with no quantitative effect estimate for interventions for which there were no or only one published RCTs but there were controlled studies in which true randomization was not feasible or ethical; or in which no RCTs were representative of commonly accepted strategy to reduce LBW.

For reporting the results, we applied a modified the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 checklist (32). For each intervention, we report quantitative estimates on the size of effect of the intervention on LBW, PTB, SGA, and SB with an assessment of the quality of evidence.

1 **Results**

2 We found 8682 records across four searches. After electronic removal of duplicate records,
3 we screened 4948 records for eligibility and reviewed 998 full texts of which 87 records met
4 the inclusion criteria. Out of 87 records, seven records contributed data that could be used to
5 estimate the size of effect of antenatal interventions (ES documents). Out of 87 records and
6 14 additional records of non-randomized controlled studies where true randomization was not
7 feasible or ethical but that otherwise met the inclusion criteria, 23 records contributed to the
8 narrative analysis (**Figure 2**).

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Antenatal interventions addressing harmful behaviors in pregnant women

Two ES documents, both systematic reviews, covered interventions addressing harmful behaviors in pregnant women. The documents reported results from 30 RCTs published between 1984 and 2019. All the RCTs were conducted in HICs (**Table 3**).

A total of 23 RCTs, published between 1984 and 2015 and conducted in the USA (11) and the UK (6), others in Australia, Ireland, Netherlands, Norway and Sweden, contributed to the estimates on the size of effect of *psychosocial interventions to reduce smoking*. The target group included pregnant women who were current or recent smokers at recruitment.

However, the criteria utilized for making that assessment varied between studies. Eight of the RCTs focused on counselling. Other variations of the intervention included health education, feedback, incentives, social support and exercise. The number of studies (participants) reporting specific outcome data was 18 (N=9420) for LBW, 19 (N=9222) for PTB, and 8 (N=6170) for SB. The risk of LBW was lower among women who received psychosocial interventions to reduce smoking than among those who did not (RR: 0.83 [95% CI 0.72, 0.94]). In contrast, the risk of PTB (RR: 0.93 [95% CI 0.77, 1.11]) and SB (RR: 1.2 [95% CI 0.76, 1.9]) was not different among the groups. The quality of evidence was considered high for all reviewed outcomes (LBW, PTB, SB). A detailed summary of the impact of psychosocial interventions to reduce smoking is shown in Supplementary data 1.

Of the previously described 23 RCT, five published between 2012 and 2015 and conducted in the USA and the UK contributed to the estimates on the size of effect of *financial incentives to support smoking cessation in pregnancy*. Except for one marginally different program, financial incentives consisted of gradually increasing shopping vouchers conditional on the participants' engagement with the program's milestones and, ultimately, with smoking cessation. The number of studies (participants) reporting specific outcome data was 4 studies

(N=215) for LBW, 5 studies (N=753) for PTB. There was no difference in LBW (RR: 0.70 [95% CI 0.40, 1.23]) or PTB (RR: 1.15 [95% CI 0.73, 1.82]) prevalence between women in intervention and control arms. The quality of evidence was considered high for these outcomes (LBW, PTB). A detailed summary of the impact of financial interventions to reduce smoking is shown in Supplementary data 2.

Seven RCTs published between 2000 and 2019 and conducted primarily in the USA (4), others in Denmark, France and the UK contributed to estimates on the size of effect of *nicotine replacement therapy* (NRT). The NRT was provided in the form of patch, gum, lozenge or inhaler to pregnant women over 16 or 18 including women who self-identified as an ethnic minority (one study). The number of RCT (participants) reporting specific outcome data was 7 (N=2171) for LBW, 7 (N=2182) for PTB and 4 (N=1777) for SB. There was no difference on the risk of LBW (RR: 0.69 [95% CI 0.39, 1.20], PTB (RR: 0.81 [95% CI 0.59, 1.11]) or stillbirth (RR: 1.24 [95% CI 0.54, 2.84]) between the NRT group and placebo and non-placebo (behavioral support only) control. The quality of evidence was considered moderate (LBW, PTB, SB). A summary of the impact of NRT on birth outcomes is shown in Supplementary data 3.

No ES documents were identified on the impact of *psychosocial interventions to reduce alcohol use* on birth outcomes. The evidence was reported narratively. Four documents contributed to the analysis. The target populations were pregnant women who were screened positive for alcohol use risk. The evidence was limited, from HICs and inconsistent on the effect of psychosocial interventions on birth outcomes (Supplementary data 4).

In summary, there was high-quality evidence that psychosocial interventions to reduce smoking in pregnancy are likely to reduce the prevalence of LBW, but not that of PTB or SB. For financial incentives and NRT to reduce smoking or psychosocial interventions to reduce

alcohol use, there was either insufficient data or the evidence suggested no positive effect of the intervention (**Table 4**).

Antenatal interventions aimed at addressing psychosocial risk factors in pregnancy

Five ES documents (three reviews and two RCTs) covered interventions addressing psychosocial risk factors in pregnant women's lives. The documents reported results from 23 original studies (RCTs), published between 1986 and 2017. Most studies were conducted in HICs (**Table 5**).

A total of 16 RCTs covering 19 countries published between 1986 and 2014 contributed to the estimates on the size of effect of *professionally provided psychosocial support*. The RCTs were conducted in the USA (7) others in Argentina, Australia, Brazil, Cuba, France, Ireland, Mexico, South Africa and the UK. The target population included pregnant women assessed to be at high risk due to obstetric or social risk for giving birth to infants that are either preterm, LBW or both. Additional social support was provided by a nurse, midwife or social worker and considered broadly including emotional support, which gives a person a feeling of being loved and cared for, tangible/instrumental support, in the form of direct assistance/home visits, and informational support, through the provision of advice, guidance and counselling. The number of studies (participants) reporting specific outcome data was 13 (9341) for LBW and 12 (11036) for PTB.

There was no statistically significant difference in the risk of LBW between at-risk women who received additional professionally provided psychosocial support and women who received routine care (RR: 0.92 [CI 95% 0.83, 1.02]). In contrast, the risk of PTB was marginally lower among women who received the intervention than among those who did not (RR: 0.91 [CI 95% 0.83, 1.00; CI 90% 0.84, 0.99]). The quality of evidence was considered

moderate (LBW, PTB). A detailed summary of the impact of psychosocial support for at-risk women is shown in Supplementary data 5.

Four RCTs, published between 1991 and 2008, conducted in the US (2), Australia and the UK contributed to estimates on the size of effect of *virtual (non-face-to-face) psychosocial support*. The target group included pregnant women at risk for giving birth to infants that are preterm due to obstetrics or social risk factors, such nulliparity or low maternal age. The support was provided by a nurse or midwife via phone calls. The number of studies (participants) reporting specific outcome data was 3 (3862) for LBW and 4 (3992) for PTB. There was no statistically significant difference between intervention and control groups (standard care) in the risk of LBW (RR: 0.90 [95% CI 0.76, 1.07] or PTB (RR: 0.91 [95% CI 0.77, 1.08]). The quality of evidence was considered moderate (LBW, PTB). A detailed summary of the impact of virtual support by health professionals for pregnant women is shown in Supplementary data 6.

Two studies, conducted in France and Spain (2014) and China (2017) contributed to estimates on the size of effect of *antenatal psychosocial support provided in group programs* on birth outcomes. The target group included pregnant women who were at risk for developing obstetric complications and postpartum depression or postpartum depression only. The interventions consisted of six to ten antenatal sessions focusing on multiple aspects of mental wellbeing in pregnancy organized in groups with or without a partner. The number of studies (participants) reporting specific outcome data was one (N=349) for LBW and two (N=476) for PTB. There was no statistically different change in the risk of LBW between the intervention groups and the control (routine care) groups. The quality of evidence for the effect of the intervention was considered low on LBW and moderate on PTB, however the latter estimate had a wide confidence interval. A detailed summary of the impact of

psychosocial support for pregnant women provided in group programs is shown in Supplementary data 7.

One study, conducted in the US in 2010 contributed to estimate on the size of effect of *intimate partner violence (IPV) prevention*. The target group included African-American women who reported IPV victimization in the past year. The number of participants reporting specific outcome data was 306 for both LBW and PTB. There were no significant differences between intervention group which received individually-tailored counselling including safety planning and control group (standard care). The quality of evidence was considered low (LBW, PTB). A detailed summary can be found in Supplementary data 8.

We did not identify any RCTs on the impact of *antidepressant medication for pregnant women with depression*. In comparing treated and untreated depression in pregnancy, such design may include ethical issues. Eleven documents contributed to the analysis, which was reported narratively. The evidence consisted of non-randomized comparative studies conducted in HICs and showed mixed effect on LBW and PTB (Supplementary data 9).

In summary, evidence suggested that professionally provided psychosocial support, targeted to pregnant women at risk of giving birth to a LBW or preterm infant may reduce the risk of PTB but not that of LBW. Virtual psychological support for women at risk of giving birth to a preterm infant did not seem to reduce the risk of LBW or PTB. The evidence was inconclusive on the effect of psychosocial antenatal support provided in the group context for at-risk women. For all other interventions and outcomes, the evidence was insufficient to make conclusions **(Table 6)**.

Antenatal interventions aimed at addressing socioeconomic factors in pregnancy

No ES documents were identified on the impact of conditional and unconditional cash transfers to pregnant women. The evidence was reported narratively. Three and five documents contributed to the analyses on the effect of conditional cash transfers and unconditional cash transfers, respectively. There were limited data from RCTs. The results varied across the geographical contexts; depending on whether the transfer was universal or targeted; and contingent on the aspects of overall programming (Supplementary data 10 and 11). The evidence was insufficient to make conclusion on the impact on birth outcomes **(Table 7)**.

Discussion

This article aimed to synthesize existing scientific data on the effectiveness of eleven selected psychosocial antenatal interventions to reduce the risk of LBW and other adverse birth outcomes. Summarizing English-language literature on RCTs from five central databases, there was evidence that the use of psychosocial interventions to reduce smoking likely reduced the risk of LBW in infants of smoking women. Additionally, there was evidence that professionally provided psychosocial support for women at risk of giving birth to a LBW or preterm infant possibly reduced the risk of PTB. In contrast, financial incentives or NRT as smoking cessation aids, and virtually delivered psychosocial support were summarized to unlikely reduce the risk of adverse birth outcomes. The available evidence on these interventions was primarily from HICs. On the impact of six other interventions, there was little or conflicting RCT evidence. This group included psychosocial interventions to reduce alcohol use, group based psychosocial support programs, IPV prevention interventions, antidepressant medication, and conditional and unconditional cash transfers.

The validity of our findings could be compromised by our choice to focus on one risk factor at the time and birth outcomes being reported as secondary outcomes in some of the reviewed documents. While the novel modular review method was particularly suited to systematically provide comparable data on multiple interventions it was not geared towards making conclusions on “holistic” interventions that address multiple risk factors. Not all studies report secondary outcomes in their abstracts, which makes it difficult for them to be found in the title-abstract screen. For both reasons, it is possible that the review could have theoretically failed to find some of the relevant records. To address this potential pitfall, we reviewed the reference lists of identified eligible articles and conducted a comprehensive analysis to assess the possibility that the search and screening procedures might have missed

key articles (reported in (25)) and concluded that it is unlikely that this has happened.

Therefore, we consider our findings valid and representative of the published literature. Of the eleven reviewed interventions, psychosocial smoking cessation interventions and professionally provided psychosocial support may reduce the risk of adverse birth outcomes in relevant populations. The other reviewed interventions either appear not to be effective in preventing adverse birth outcomes or there is little evidence in any direction regarding the efficacy.

The findings of our review support the WHO recommendation on the screening for antenatal tobacco use (33), founded on the well-established harmful effects of tobacco use to the fetus, and reinforce the related recommendation that health providers offer advice and psychosocial interventions to support tobacco cessation. Besides tobacco use, WHO recommends screening for alcohol use and the possibility of IPV (33). Our findings support the notion that health providers should also inquire about the psychological wellbeing of pregnant women and the level and source of psychosocial support they are receiving. This highlights the importance of holistic, multiple risk factor addressing maternity care and aligns with the overall philosophy of WHO ANC recommendations, which call attention to a positive pregnancy experience underlining the importance of social, cultural, emotional, and psychological wellbeing for pregnant women (33).

We promote a broad understanding of barriers to maternal psychosocial wellbeing and coordinated effort in addressing them in the context of ANC. These barriers include stress and accumulation of psychosocial risk factors. The increased risk for adverse birth outcomes is not restricted to antenatal depression but may include anxiety and stress. Sub-clinical or symptomatic manifestations of these disorders have also been associated with PTB (34).

Whilst the association between psychological risk factors and adverse birth outcomes may be

more subtle than medical or nutritional risk factors, their absolute impact may be substantial in LMICs due to the high burden and limited access to care (8).

The analysis of the geographical context showed an asymmetry between research conducted on the prevention of LBW via addressing psychosocial risks and the burden of these risk factors in the regions that are most relevant for the prevention of LBW. Poverty, depression and IPV are highly prevalent in pregnancy in LMICs, but the literature was marked by a paucity of research on how to prevent or mitigate the effects of these risk factors. Similarly, the majority of RCTs contributing to the effect size estimates focused on the prevention of smoking in pregnancy. However, the prevalence of maternal smoking is very low in the regions with the highest prevalence of LBW; 1.2% in Southeast Asia and 0.8% in Africa (35). This is believed to be due to its cultural unacceptability in many countries and women's preference over more affordable and acceptable smokeless tobacco products (36). The solid evidence base on smoking cessation can be contrasted by the scarcity of research to reduce maternal antenatal alcohol use even though approximately 10% of women in Africa and globally are estimated to consume alcohol during pregnancy (37). Hence, improving the coverage of psychosocial interventions to reduce smoking may have limited public health impact.

Our focus on RCTs as study designs and pregnant women as the target group may limit what can be concluded about the efficacy of psychosocial interventions to prevent adverse birth outcomes. Other research designs, such as community based or cohort studies could, in some cases, have been informative in assessing the impact of, and the amount of evidence on some interventions. However, this would have affected our ability to compare interventions, not only in this article but across the series. We addressed this potential limitation by accepting non-randomized studies in categories where there was limited RCT data and introducing narrative reporting to facilitate a more descriptive analysis of the evidence. Many risk factors

for LBW can be addressed by primary prevention focusing on upstream factors around vulnerability and gender. This often requires intervention before the antenatal period. For instance, IPV programs have targeted adolescents, men and women in schools, families and communities (38). Nevertheless, pregnancy provides a critical opportunity for intervention since it is a time when many women access health services and seek care from health professionals (39). Finally, some of the interventions were successful in achieving their primary outcomes even if they did not significantly reduce the risk of adverse birth outcomes. This may be due to sample sizes that are inadequate to detect subtle differences.

A particular limitation stemming from outdated evidence was observed with virtual psychosocial support. While we searched for support delivered through any medium, we were only able to identify relatively old studies in which the support was provided via telephone conversations. Studies of electronically delivered support (for instance through smart phones or computers) tended to focus on mental health outcomes or feasibility and acceptability of the technology. However, the current technology now supports face-to-face interaction, and electronically delivered therapy has been considered to be at least as effective as in-person therapy (40). Hence, due to the chronic treatment gap combined with limited resources and access particularly prevalent in LMICs, further exacerbated by emerging challenges such as pandemics and conflicts, we consider virtual psychosocial support something that should be further explored in global PTB prevention.

This review provided a comparative synthesis on promising antenatal interventions that address harmful behaviors, psychosocial risks, and unfavorable socioeconomic factors. Investing in professionally provided psychosocial support during pregnancy in general and specifically as a means to reduce smoking in the relevant populations alongside the other antenatal interventions currently recommended by WHO, can potentially contribute to improved newborn health in LMICs. Our findings also highlighted some critical gaps in the

global research agenda. HIC, and particularly the US, centrality of the evidence means that the reviewed programs and activities may not always be transferable to other contexts. These gaps should be addressed to inform effective intervention strategies and culturally tailored implementation approaches that are integrated in ANC and responsive to those populations at greatest risk. Taking on this evidence-based agenda to direct attention, collaboration, and resources in areas of greatest need and impact has potential to contribute to reaching the global target of decreasing the rate of LBW by 30% and ultimately increase the chances of the small vulnerable babies to survive and thrive.

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Table 1. Reviewed antenatal interventions, associated risk factors with their prevalence in low income countries (LICs) and mechanism of action for the interventions

Antenatal interventions to address harmful behaviors in pregnancy			
Intervention	Risk factor	Prevalence of the risk factor in LICs	Assumed mechanism of action for the intervention
Psychosocial interventions to reduce smoking	Smoking	No prevalence data for LICs, 1.3% [95% CI: 0.9, 1.8] in LMICs (41) or 1.2% [95% CI: 0.7, 1.7] in the Southeast Asian Region, 0.8% [95% CI: 0.0, 2.2] in the African Region (35).	Psychosocial interventions are non-pharmacological, for instance counselling-based interventions which aim to increase the smokers' motivation or affective or emotional responses to smoking cessation and avoidance of relapse (42).
Financial incentives to reduce smoking	Smoking		Nicotine replacement therapy aims to replace the nicotine inhaled through tobacco smoking with nicotine in a medicinal form, such as patches (43).
Nicotine replacement therapy to reduce smoking	Smoking		Financial incentives aim to work by positively rewarding the cessation achieved at predefined stages, usually contingent on production of a biochemically-confirmed cessation outcome (44).
Psychosocial interventions to reduce alcohol use	Alcohol use	No prevalence data for LICs, 1.8% [95% CI: 0.9, 5.1] in the Southeast Asian Region 10% [95% CI: 8.5, 11.8] in the African Region (37).	Psychosocial interventions consist of non-pharmacological approaches, including e.g. alcohol brief interventions (a structured therapy of typically 5–30 minutes (45)) to support women to abstain from alcohol or reducing its consumption (46).
Antenatal interventions to address psychosocial risk factors in pregnancy			
Health professional provided psychosocial support	Elevated need for informational, psychosocial, or mental health support due to physical, emotional, or pregnancy related factor, distress, stress, harm, depression, or other mental health issue.	No prevalence data for antenatal stress in LIC. Antenatal stress is reported by a third to more than half (up to 92%) of respondents in healthy pregnant women in LMICs (47–52).	Psychosocial support is additional emotional, instrumental, or informational support which aims to mitigate or buffer against potential stress caused by for instance, social disadvantage or maternal mental health concerns (53).
Virtual psychosocial support	Elevated need for informational, psychosocial, or mental health support due to physical, emotional, or pregnancy related factor, distress,		Virtual psychosocial support is additional emotional, instrumental, or informational support which is not delivered face-to-face but over a medium such as telephone.

	stress, harm, depression, or other mental health issue.		
Group support program	Elevated need for informational, psychosocial, or mental health support due to physical, emotional, or pregnancy related factor, distress, stress, harm, depression, or other mental health issue.		Group programs vary greatly in purpose and execution, however generally their aim is that some of the support comes from peer involvement and collaborative participation of women (54).
Antidepressant medication	Depression	No prevalence data for LICs, 15—65% in LMICs (8).	Antidepressants aim to increase the availability of chemical messengers (neurotransmitters) such as serotonin in the brain (55).
Intimate partner violence prevention interventions	Intimate partner violence	No prevalence data for LICs. The prevalence of physical intimate partner violence in pregnancy was globally 9.2% [95% CI: 7.4, 11.1], and 16.3% [95% CI: 13.5, 19.6] for Africa and 9.0% [95% CI: 6.5, 12.3] for Asia (56).	Interventions against intimate partner violence aim to support women by screening, referral and supportive counselling to increase pregnant women's level of awareness and empowerment. Interventions can also include safety planning, home visitation, support from lay mothers, among others (57,58).
Antenatal interventions to address socioeconomic factors in pregnancy			
Conditional cash transfers	Poverty, social disadvantage, lack of agency	N/A	Conditional cash transfers are performance-based payments, which make cash payments to individuals (or households) contingent on behavioral requirements (59). Cash and in-kind transfers have been used to address risk factors related to maternal diet, antenatal care seeking, facility birth, intimate partner violence and women's empowerment (60–62).
Unconditional cash transfers	Poverty, social disadvantage, lack of agency	N/A	Unconditional cash transfers are a type of social protection intervention provided without obligation for reducing poverty and vulnerabilities (63).

CI = Confidence interval, LIC = Low income country, LMIC = Low and middle income country, N/A = Not applicable.

Table 2. Summary of categorization of the evidence in the evidence synthesis for reducing Low Birth Weight

Color	Interpretation	Criteria
Green	The intervention likely reduces the risk of the adverse outcome.	<ul style="list-style-type: none"> At least two moderate-to-high quality RCTs in a meta-analysis / IPD analysis, with 95% CI of the point estimate of the RR entirely below 1.
Yellow	The intervention may reduce the risk of the adverse outcome.	<ul style="list-style-type: none"> At least two RCTs in a meta-analysis / IPD analysis, where either the 95% CI of the point estimate of the RR is entirely below 1 but the quality of the evidence is low or the quality is moderate-to-high and the 90% CI of the point estimate of the RR entirely below 1. One moderate-to-high quality RCT, with 95% CI of the point estimate of the RR entirely below 1.
Red	The intervention is not likely to reduce the risk of the adverse outcome.	<ul style="list-style-type: none"> Situations that do not meet the requirements for other categories, including meta-analysis results suggestive of harm. In other words, there is sufficient evidence to conclude that the intervention is unlikely to have a positive effect on the outcome.
Grey	Inconclusive published research on the intervention's effect on the outcome.	<ul style="list-style-type: none"> At least two RCTs, 95% CI of the point estimate of the RR ranges from < 0.5 to > 2.
White	Insufficient published research on the intervention's effect on the outcome.	<ul style="list-style-type: none"> No RCTs or one low quality RCT (any result) One moderate-to-high quality RCT where 95% CI of the RR includes 1. Narrative reporting

CI= Confidence interval, IPD = Individual participant data, RCT = Randomized controlled trial, RR=Relative risk.

Table 3: Source documents for effect size estimates of antenatal interventions to address harmful behaviours in pregnancy

Antenatal interventions to address harmful behaviours in pregnancy							
Intervention	First author	Year	Study design	Country of data collection	Population	Description of Intervention	Description of Control
Psychosocial interventions to reduce smoking	Chamberlain (42)	2017	Systematic review and meta-analysis	Australia (2) Ireland (1) Netherlands (1) Norway (1) Sweden (1) UK (6) USA (11) Total: 23	Healthy pregnant women of 16 years and older who are current or recent smokers	Psychosocial interventions: counselling, health education, feedback, incentives, social support, exercise	Usual care or less intensive counselling/information intervention
Financial incentives to reduce smoking	Chamberlain (42)	2017	Systematic review and meta-analysis	UK (1) USA (4) Total: 5	Healthy pregnant women of 16 years or older who are current or recent smokers	Shopping vouchers	Routine care
Nicotine replacement therapy to reduce smoking	Claire (43)	2020	Systematic review and meta-analysis	Denmark (1) France (1) UK (1) USA (4) Total:7	Healthy pregnant women of 16 years or older who are current or recent smokers	Nicotine replacement therapy from patch, gum, lozenge or inhaler with behavioral support	Placebo nicotine replacement therapy product with behavioral support or behavioral support alone.

Table 4. The effect of antenatal interventions aimed at addressing harmful behaviours in pregnancy on birth outcomes.

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Psychosocial interventions to reduce smoking in pregnancy	Yes	No	Insufficient data	No
	RR: 0.83 [0.72, 0.94] (N=9420)	RR: 0.93 [0.77, 1.11] (N=9222)	N/A	RR: 1.2 [0.76, 1.9] (N=6170)
	HIGH	HIGH	N/A	HIGH
Financial incentive interventions to reduce smoking in pregnancy	No	No	Insufficient data	Insufficient data
	RR: 0.70 [0.40, 1.23] (N=215)	RR: 1.15 [0.73, 1.82] (N=753)	N/A	N/A
	HIGH	HIGH	N/A	N/A
Nicotine replacement therapy to reduce smoking in pregnancy	No	No	Insufficient data	No
	RR: 0.69 [0.39, 1.20] (N=2171)	RR: 0.81 [0.59, 1.11] (N=2182)	N/A	RR: 1.24 [0.54, 2.84] (N=1777)
	MODERATE	MODERATE	N/A	MODERATE
Psychosocial interventions to reduce alcohol use during pregnancy	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

N/A = Not applicable, RR=Relative risk.

95% confidence intervals in square brackets, number of participants in parentheses.

The result of the quality of evidence assessment is expressed as LOW-MODERATE-HIGH

Table 5 Source documents for effect size estimates of antenatal interventions to address psychosocial risk factors in pregnancy

Antenatal interventions aimed at addressing psychosocial risk factors in pregnancy							
Health professional provided psychosocial support in pregnancy	East (53)	2019	Systematic review and meta-analysis	Argentina (1) Australia (1) Brazil (1) Cuba (1) France (2) Ireland (1) Mexico (1) South Africa (2) UK (2) USA (7) Total:16 RCTs in 19 countries	Pregnant women at risk for giving birth to infants that are either preterm, low birth weight, or both, at birth due to obstetric or social risk.	Additional health professional-provided psychosocial support	routine care
Virtual psychosocial support from health professionals in pregnancy	Lavendar (64)	2013	Systematic review and meta-analysis	UK (1), US (2), Australia (1) Total: 4	Pregnant women at risk for giving birth to infants that are preterm due to obstetrics or social risk.	Additional psychosocial support via phone calls	routine care
Group based psychosocial support program in pregnancy	Zhao (65)	2017	RCT	China (1)	Pregnant women at risk for obstetric complications and at risk for postpartum depression	Group antenatal sessions in psycho-educational program	routine care
Group based psychosocial support program in pregnancy	Ortiz Collado (66)	2014	RCT	France + Spain (1) Total:1 RCT in 2 countries	Pregnant women considered to be at psychosocial risk via three factors: socioeconomic status, low social support, and the risk of postpartum depression	Group antenatal sessions based on psychosocial approach.	routine care
Intimate partner violence prevention intervention	Jahanfar (67)	2014	Systematic review and meta-analysis	USA (1)	African-American women who reported intimate partner violence victimization in the past year.	Individually tailored counselling	routine care

RCT = Randomized controlled trial.

Table 6 The effect of antenatal interventions aimed at addressing psychosocial risk factors in pregnancy

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Health professional provided psychosocial support for women at risk of giving birth to a LBW or preterm baby	No	Possibly	Insufficient data	Insufficient data
	RR: 0.92 [0.83, 1.02] (N=9341)	RR: 0.91 [0.83, 1.00] (N=11036)	N/A	N/A
	MODERATE	MODERATE	N/A	N/A
Virtual psychosocial support for women at risk of giving birth to preterm baby	No	No	Insufficient data	Insufficient data
	RR: 0.90 [0.76, 1.07] (N=3862)	RR: 0.91 [0.77, 1.08] (N=3992)	N/A	N/A
	MODERATE	MODERATE	N/A	N/A
Group based psychosocial support program for pregnant women at risk for obstetric complications and postpartum depression	Insufficient data	Inconclusive	Insufficient data	Insufficient data
	RR: 1.08 [0.49, 2.39] (N=349)	RR: 0.59 [0.15, 2.27] (N=476)	N/A	N/A
	LOW	MODERATE	N/A	N/A
Intimate partner violence prevention interventions for at risk pregnant women	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	RR: 0.74 [0.41, 1.32] (N=306)	RR: 0.69 [0.40, 1.20] (N=306)	N/A	N/A
	LOW	LOW	N/A	N/A
Antidepressant medication for pregnant women with depression	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

N/A = Not applicable, RR=Relative risk.

95% confidence intervals in square brackets, number of participants in parentheses.

The result of the quality of evidence assessment is expressed as LOW-MODERATE-HIGH

Table 7 The effect of antenatal interventions aimed at addressing socioeconomic risk factors in pregnancy

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Conditional cash transfers to pregnant women	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A
Unconditional cash transfers to pregnant women	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

N/A = Not applicable.

Figure legends:

Figure 1. Central psychosocial risk factors contributing to the risk of low birth weight and selected antenatal interventions deemed potentially helpful.

Figure 2. Summary flow diagram. Search and the selection process of antenatal interventions addressing harmful behaviors, psychosocial risks and unfavorable socioeconomic factors to prevent low birth weight. Adapted from Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 (32). Some records may appear more than once due to being relevant to more than one category.