BMJ Open

Fast-track referral for health interventions during pregnancy: study protocol of a randomised pragmatic experimental study to reduce low birth weight in Portugal (STOP LBW)

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To cite: Barros H, Baia I, Monjardino T, *et al*. Fast-track referral for health interventions during pregnancy: study protocol of a randomised pragmatic experimental study to reduce low birth weight in Portugal (STOP LBW). *BMJ Open* 2022;**12**:e052964. doi:10.1136/bmjopen-2021-052964

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052964).

Received 29 April 2021
Accepted 16 February 2022

Check for updates

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ABSTRACT

Introduction Low birth weight (LBW) is associated with a wide range of short-term and long-term consequences and is related to maternal psychosocial and behavioural determinants. The objective of this study is to estimate the effect of implementing fast-track referral for early intervention on psychosocial and behavioural risk factors—smoking, alcohol consumption, depression and physical violence—in reducing the incidence of LBW.

Methods and analysis Parallel superiority pragmatic clinical trial randomised by clusters. Primary healthcare units (PHCU) located in Portugal will be randomised (1:1) to intervention or control groups. Pregnant women over 18 years of age attending these PHCU will be eligible to the study. Risk factors will be assessed through face-to-face interviews. In the intervention group, women who report at least one risk factor will have immediate access to referral services. The comparison group will be the local standard of care for these risk factors. We will use intention-to-treat analyses to compare intervention and control groups. We estimated a sample size of 2832 pregnant women to detect a 30% reduction in the incidence rate of LBW between the control and intervention groups. Secondary outcomes are the reduction of preterm births, reduction of the four risk factors and acceptance of the intervention.

Ethics and dissemination The study was approved by the Ethics Committee of the Public Health Institute of the University of Porto (no CE20140). The findings will be disseminated to the public, the funders, health professionals, health managers and other researchers.

Trial registration number NCT04866277.

Strengths and limitations of this study

- Pragmatic intervention using resources available in the healthcare system which favours immediate adoption if favourable results.
- Implementation of validated instruments for screening risk factors in all primary healthcare units participating in the study.
- Estimates of the prevalence of four psychosocial and behavioural risk factors, the women's acceptance of the intervention and the effects of the intervention on the prevalence of these risk factors.
- Possible under-reporting of risk factors assessed during the face-to-face interview with pregnant women leading to non-differential misclassification and underestimation of the effects between the groups.
- Possibility of contamination between groups, which could dilute the effect of the tested intervention.

INTRODUCTION

Low birth weight (LBW), defined by the WHO as weighing less than 2500 g regardless of gestational age, remains a major global public health concern, contributing disproportionately to high mortality rates and child morbidity.[1 2] It is estimated that 15%–20% of births worldwide are underweight, corresponding to more than 20 million births per year.[3] According to the study of the global burden of the disease in 2017, LBW was the second risk factor responsible for deaths and losses of years of healthy life in children under 5 years of age, contributing to more than one million deaths and to 20% of the total Disabled Adjusted Life Years worldwide.[4] LBW is also an important predictor of chronic non-communicable diseases in adulthood, such as type 2 diabetes mellitus, arterial hypertension and cardiovascular disease.[5 6]

In 2012, the 65th World Health Assembly approved the implementation of a comprehensive plan on maternal and child nutrition, defining six global targets by 2025, which include the goal of reducing LBW by 30% based on the prevalence estimate of 15% observed in 2012.[7] Achieving this goal implies the definition and adoption of cost-effective policies and interventions.[8] However, the

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progress has been slow and more than doubling current efforts will be needed.[3]

The prevalence of LBW varies widely with higher estimates in low-income and middle-income countries.[3] However, some high-income countries have a high prevalence of LBW. In the USA, LBW is responsible for about 20% of neonatal deaths, with a steady increase in the prevalence of LBW from 8.0% in 2014 to 8.3% in 2017.[9] In Japan, the LBW rate rose from 4.5% to 9.4%, between 1979 and 2017.[10] In Europe, characterised by heterogeneous estimates and temporal trends in the prevalence of LBW, Portugal represents a country of high and growing prevalence.[10] In 2017, the prevalence of LBW in Portugal was 8.9%, higher than the average point estimate of 6.5% observed among the countries of the Organisation for Economic Cooperation and Development, in 2017, with only Greece (9.3%) and Japan (9.4%) having higher estimates.[10] It is expected that LBW disproportionately affects more vulnerable populations, such as migrants, who currently represent 13% of births in Portugal.[11 12]

LBW is a complex problem that includes preterm births (before 37 weeks of gestation), newborns small for gestational age, and the overlap of these two situations—preterm newborns small for gestational age—which typically present worse health outcomes.[13]

Several risk factors contribute to LBW.[14] Maternal factors have the strongest associations with LBW and can generally be grouped into: (1) demographic factors (eg, belonging to a minority, being a teenage or elderly mother, being single); (2) obstetric history (eg, very short or very long interval between pregnancies, maternal birth weight, having had a LBW in a previous birth, history of infertility, medically assisted reproduction treatments); (3) nutritional factors (eg, iron deficiency); (4) anthropometric factors (eg, low weight in early pregnancy); (5) clinical history and complications during pregnancy (eg, anatomical changes of the uterus and placenta, hypertension, premature rupture of membranes, infectious disease); (6) psychosocial factors (eg, depression during pregnancy); (7) lifestyles (eg, personal history of addictions, alcohol and tobacco use during pregnancy); (8) environmental factors (eg, passive exposure to tobacco smoke) and (9) maternal violence/abuse and trauma during pregnancy.[14] Among the large set of determinants of LBW there is increasing scientific evidence on the relevance of maternal psychosocial and behavioural risk factors that are susceptible to efficient interventions to support behavioural change.[15]

In Portugal, smoking, alcohol consumption, depression and interpersonal violence are psychosocial and behavioural determinants that could be intervened during pregnancy, taking into account the consistent associations with LBW[16–25] and its high frequency in the Portuguese population. Smoking in pregnancy is the most important preventable risk factor for LBW in developed countries.[14 15] There is also increasing evidence of the effect of passive exposure to tobacco smoke on increasing the risk of LBW.[26] In Portugal, estimates of the prevalence of tobacco use during pregnancy range from 10.0% in 2014/2015[27 28] and 20.9% in 2004/2005.[29] The prevalence of smoking during pregnancy is higher in native women (14%) than in long-term (8%) and short-term (4%) migrants.[30] Regarding alcohol consumption, several mechanisms have been proposed to explain the teratogenic effect in the developing fetus that can lead to LBW.[31] Prevalence studies in Portugal have described estimates of any alcohol consumption during pregnancy that vary between 13.3%[32] and 19%.[33] Prenatal depression can increase the risk of LBW by activating the hypothalamic–pituitary–adrenal axis and through inflammatory mechanisms.[34] Depression also determines the adoption of risky health behaviours such as substance abuse—tobacco, alcohol, medication—or inadequate nutrition, which are associated with an increased risk of LBW.[35] In Portugal, using different instruments to assess depressive symptoms, the prevalence of depression during pregnancy varied between 14.2%[36] and 20%.[37] The effects of interpersonal violence on adverse pregnancy outcomes can be direct, on a physical level, or indirect, through effects on mental health and behavioural change.[38] Prevalence rates of physical violence in Portugal ranged from 9.7%[39] to 21.9%,[40] depending on the studied population and the type of instrument used.

The main hypothesis of this protocol study is that early interventions in pregnancy, targeting maternal psychosocial and behavioural risk factors, may reduce the incidence of LBW. However, there are few intervention models with proven effectiveness to reduce these risk factors during pregnancy and the incidence of LBW. The most evident effect is that of strategies related to smoking cessation, including mainly behavioural interventions.[41 42] The evidence is scarce for alcohol consumption, but it suggests that educational and psychosocial actions[43] and behavioural change techniques[44] have a potential effect in reducing alcohol consumption during pregnancy. For depression in pregnancy and in the postpartum period, interventions that assess different outcomes in addition to reducing LBW, and which include physical activity, screening, counselling and cognitive–behavioural therapy, indicate beneficial effects.[45–48] For violence between intimate partners, the evidence is also not conclusive,[49 50] but it suggests that screening, referral and supportive counselling is likely to benefit women who experience domestic violence.[50]

The effect of interventions targeting several risk factors appears to be promising. In the USA, studies demonstrated the success of prenatal interventions aimed at various risk factors in reducing risk behaviours and consequently reducing LBW incidence[51] and the number of very preterm births.[52] These results highlight that psychobehavioural risk factors should not be treated separately, but be the target of well-planned multidisciplinary interventions taking into account the health status of the pregnant woman and her socioeconomic context in a syndemic approach.[15]

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Objectives

In this pragmatic randomised clinical trial, our primary goal is to estimate the effect of implementing fast-track referral for early intervention on psychosocial and behavioural risk factors—smoking, alcohol consumption, depression and physical violence—on reducing the incidence of LBW compared with the current standard of care. As secondary objectives, we aim to estimate: (1) the effect of the intervention on the incidence of preterm birth, (2) the effect of the intervention in reducing the prevalence of these four risk factors in pregnant women and (3) the rate of acceptance of the intervention.

METHODS

We used Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines[53] (online supplemental appendix 1).

Study design

Parallel superiority pragmatic clinical trial randomised by clusters allocating Primary Healthcare Units (PHCU) to either 'standard of care' arm or the intervention arm (1:1), where pregnant women with at least one risk factor (smoking, risk alcohol consumption, risk of depression and physical violence) will have fast-track referral to reference services.

Participants

Study setting

The study will be conducted in PHCU located in the metropolitan regions of Porto and Lisbon, in Portugal.

Eligibility criteria

All 236 PHCU, nested in 13 Primary Care Centres (PCC), will be considered eligible to inclusion (109 PHCU in 7 PCC in Porto; 127 PHCU in 6 PCC in Lisbon).

At each PHCU, all pregnant women, of any gestational age, over the age of 18, who are attending their first prenatal care visit during the study period, that currently reside in Portugal and plan to have a birth in Portugal will be considered eligible and invited to participate in the study. Exclusion criteria include pregnant women unable to answer the questionnaire in Portuguese (language barrier, deafness concomitant with blindness, etc) and/or unable to provide informed consent at the time of recruitment.

Recruitment

All eligible PHCU will be invited to participate in the study by sending email, phone calls and local meetings with the research coordinating team.

At each PHCU, health professionals providing prenatal care will be responsible for recruiting pregnant women at their first prenatal visit at the PHCU, obtaining informed consent (online supplemental appendix 2) and collecting data. Participation in the study is voluntary and non-participation in the study does not affect the routine healthcare provided. The recruitment of participants will last until the planned sample is reached (estimated period of 1 year).

Procedure

After being informed of the objectives of the study and giving informed and written consent, pregnant women who agree to participate will answer a face-to-face questionnaire. Data collection will take place in a private environment, that is, in a medical or nursing office, without the presence of other pregnant women, partners or family members, to ensure confidentiality, using an online link.

The electronic questionnaire includes sociodemographic characteristics (date of birth, nationality, marital status, education level, type of work) and risk assessment (smoking, alcohol consume, depression and physical abuse). The questionnaire also includes information about the COVID-19 tests and contact with positive cases, due to the SARS-CoV-2 pandemic and its potential negative effect on the development of the fetus. Pregnant women with at least one of the psychosocial or behavioural risk factors will be asked about chronic conditions, medication use, obstetric history, characteristics of the current pregnancy and anthropometry.

To assess smoking during pregnancy, we will use a set of questions including pre-pregnancy smoking and smoking during pregnancy (frequency, number of cigarettes per day, gestational month). In women who report smoking during pregnancy, we will assess smoking addiction using the Fagerström nicotine addiction test, validated in Portugal in an academic community of teachers and staff.[54] For alcohol consumption screening, we will use the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), a scaled-down version of the AUDIT,[55] which has a good performance in detecting risky consumption of alcohol during pregnancy.[56] To assess depression, we will use the Portuguese version of the Edinburgh Postpartum Depression Scale (EPDE)[57] with a 9-point cut-off.[58] To assess physical violence against pregnant women, we will use the Abuse Assessment Screen (AAS) instrument due to its reliability, validity and easiness of application by clinicians in the context of healthcare provision.[59]

Women with at least with one risk factor will be eligible to the intervention. The intervention is the fast-track referral to a reference service. In the intervention arm, women will receive a fast-track referral to reference services. In the 'standard of care' arm, women will receive the usual care provided in each PHCU.

Birth weight will be measured immediately after birth in maternity services and the information about the primary outcome (LBW) will be assessed during the first visit to the PHCU after birth. Secondary outcomes will be assessed 1 month after birth by telephone interview. Figure 1 describes the enrolment of PHCU and women, risk factor assessment, risk factor management and outcome assessment.

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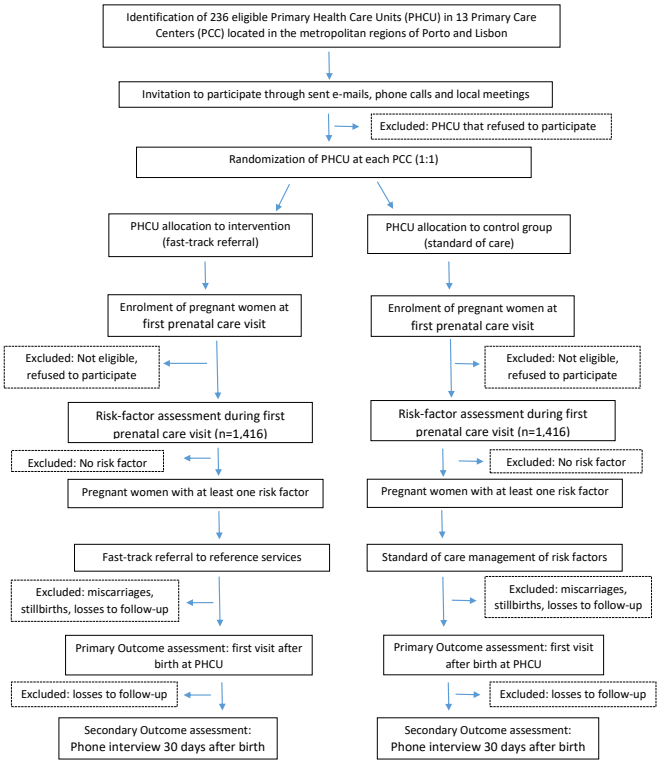

Figure 1 Flow diagram showing study design, measures and sample size.

Criteria for discontinuing or modifying allocated interventions

We have no reason to believe that the intervention will harm the participants. However, we will record all cases of miscarriage, stillbirths, neonatal death, birth defects or maternal death. Any potential damage resulting from the investigation will lead to the immediate suspension of part or all of it. Unless a participant withdraws from the study, they will be followed up for data collection regardless of their acceptance of referral and/or adherence to risk reduction services.

Interventions

Intervention arm

Women who present at least one of the risk factors will be eligible to receive the intervention. The intervention will be the activation of fast-track referral for specialised units and care programmes for the four psychosocial and behavioural risk factors under study. All pregnant women referred by the 'STOP LBW project' would have access to consultations or other health activities, such as counselling and group meetings, within a maximum of 7 days, in reference services available in each metropolitan area. The care provided in each reference service is the current practice in health services in Portugal and may vary between services. The activation of the fast-track referral will be the responsibility of the doctor/nurse who applies the questionnaires to identify the risk factors. The intervention ends with childbirth, miscarriage, termination of pregnancy or if the participant decides to abandon the study.

The intervention will have the following process:

(1). Any tobacco use during pregnancy → Activation of fast-track referral for smoking cessation consultation in Health Centre Units, Hospitals or other; and/or (2) Risk alcohol consumption (score ≥4 on the test AUDIT-C) → Activation of fast-track referral for consultation in support services for the cessation of alcoholic consumption in Health Centre Units, Hospitals, Division of Intervention in Addictive Behaviours and Dependencies, social service or other; and/or (3) Risk of depression (score ≥9 on the EPDE scale) → Activation of fast-track referral for psychology consultation at Health Centre Units, Hospital Psychiatry or other; and/or (4) Physical Violence (affirmative answer to the physical violence question in the AAS) → Activation of the fast-track referral for social service and/or psychological consultation in Health Centre Units, Psychiatry Hospitals or other.

'Standard of care' arm

In the standard of care arm, pregnant women with at least one of the four risk factors will be monitored according to the resources and care routines currently existing in each PHCU. The standard of care varies across the various PHCU and may include several approaches: care by the antenatal care provider; referral to other health professional in the same health unit; and referral to other health services, with the time elapsed for consultation depending on the health resources available in each area. In each PHCU, different standards of care may exist for each of the four risk factors.

Outcomes

The primary outcome is the incidence of LBW (objective of 30% reduction in the incidence of LBW, from 9.0% to 6.5%). The secondary outcomes are: (1) the incidence of preterm births (live births with less than 37 weeks of gestation); (2) the reduction of the prevalence of each of the four psychosocial and behavioural risk factors (smoking, alcohol consumption, depression and physical violence) when comparing the first prenatal visit and the period of 1 month after birth and (3) the proportion of pregnant women with adherence to care programmes targeted at psychosocial and behavioural risk factors and description of the determinants of adherence.

Sample size

We calculated the sample size considering the use of bilateral tests, for a significance level of 5% and statistical power of 80%, in order to compare the intervention and control groups in relation to the primary outcome defined in the main objective of the study. We assume that the intervention can reduce the incidence of LBW by about 30%, that is, from 9.0% to 6.5%. Estimating an institutional adherence rate of 50%, using an intracluster correlation coefficient of 0.01 (estimated from perinatal health studies in primary healthcare)[60] and estimating a size variation of 20% in clusters (variation in the number of eligible pregnant women in each PHCU), we calculated a sample

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size of 1416 participants per intervention/control group, in a total of 2832 participants with at least one risk factor.

Randomisation

Sequence generation, allocation and blinding

We will use the PHCU as units of randomisation and pregnant/newborn dyads as the unit of analysis. In each of the 13 PCC, all PHCU that adhere to the study will be randomised in a 1: 1 ratio for the intervention or control group and will belong to that group until the end of the study. A research team statistician will generate the randomisation sequence through Excel Office 365 and implement the random allocation sequence using sequentially numbered, opaque, sealed envelopes.

Due to the nature of the study, there will be no blinding of pregnant women, health professionals or members of the research team after assignment of the intervention. However, those involved in the outcome assessment and data analysis will be blinded as there will be no identification of the intervention group.

Data management

All questionnaires will be coded using an alphanumeric unique code to ensure confidentiality and anonymity. Clinical and sociodemographic data will be stored in a Limesurvey server from the Institute of Public Health of the University of Porto, to which only two members of the research team will have access (IB and PP). The access to the dataset is private and will only be available by using a specific user account and password. This repository uses digital certificates that guarantee the security of all the communications and traceability. Datasets will be extracted to a SPSS software V.26.0 for analysis and report.

Data collection and analysis

Adherence to the study protocol will be fostered using different strategies including information to pregnant women, project communication through the creation and maintenance of a website, involvement of health professionals during the planning and monitoring phases, and close monitoring of the intervention by the research team. Data collection will be weekly monitored comparing women attended in the first prenatal consultation, women invited to participate and women included in the study. This efforts aim to prevent empty clusters and ensure that the inclusion process of pregnant women is independent of the allocation process.

Information on birth weight, gestational age and type of delivery will be obtained from the child health records at the first appointment of the newborn at the PHCU. Since 2016, all newborns in Portugal are assigned to a family doctor at the PHCU right after birth, usually the same PCHU where the woman was followed during prenatal care. The baby's first consultation takes place in the first week of life and the child is monitored throughout the first year of life free of charge.

The research team will conduct a telephone interview in the first month after birth, using the same screening questionnaire used in the first interview, to assess tobacco and alcohol consumption, the presence of depressive symptoms and exposure to interpersonal violence. We will also measure adherence to care programmes aimed at the four risk factors and the determinants of adherence and other strategies used by the pregnant woman to control these risk behaviours. Adherence will be measured during the telephone interview, when women will be asked if they were referred to a referral service, if they attended the referral service and followed its recommendations, what barriers and facilitators they faced to attend these services and if they used other strategies for dealing with the risk factors. We will also assess adherence at the referral services, where we will check if the women attended the service within 7 days after referral and if they attended the following consultations.

We will conduct an intention-to-treat analysis to compare the results between the intervention and control groups using random effects models that take into account the cluster effect.[60] We will consider pregnant women who have miscarriages; termination of pregnancy; stillbirths; early neonatal deaths without information on birth weight; and pregnant women included in the study who decided to leave the study or who became inaccessible by the research team as lost to follow-up. The missing data for individual variables will be described and techniques to deal with missing values will be used when the missing data is >5%. The technique to be used will depend on the pattern of missingness.

Characteristics of included women vs losses to follow-up and potential impact on results will be described, with use of statistical techniques, if necessary, to address selection bias. Differences in LBW incidence between the intervention group and the control group clusters will be tested using the χ^2 or Fisher's exact test, as appropriate. Adjusted analysis will be conducted to control the effect of potential confounders if maternal characteristics such as age, education, chronic conditions, marital status, type of pregnancy (single or multiple), type of delivery, among others are misbalanced between groups.

Most women in Portugal start prenatal care during the first trimester of gestation. However, we plan to conduct a sensitivity analysis to assess the effect of gestational age on the outcome LBW, if a large proportion of women are included in the study after the first trimester of pregnancy. We also plan to conduct a post hoc power analysis to assess the study power to detect differences in LBW in the intervention and control groups.

We conducted a pilot study from 8 January 2020 to 18 June 2020 in ten PHCU including 142 pregnant women (1 refusal, 0.7%). The average gestational age was 19 weeks and 28.2% had at least one of the four risk factors: 14.8% reported smoking during pregnancy, 0.7% had high alcohol consumption, 16.9% had depressive symptoms and 1.4% reported at least one episode of physical abuse during pregnancy.

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We had planned to start the clinical trial immediately after the pilot study but it had to be stopped because of the COVID-19 pandemic. The study will be resumed in 2021.

Patient and public involvement

Patients and public were not involved in the definition of research questions, outcome measures and design of the study. During the interviews, women will be asked about the burden of the intervention and their acceptance. We intend to involve patients and the public in the plan to disseminate the study results.

DISCUSSION

Portugal has one of the highest prevalence of LBW among OECD countries,[10] with possible consequences for child health. Based on previous studies,[27–30 32 33 36 37 39 40] we can estimate that the prevalence of modifiable risk factors is high in the country, which we also observed in the pilot study, especially for smoking and depression.

This study will provide evidence of the effects of a pragmatic intervention to reduce the prevalence of LBW in Portugal. The proposed intervention, a fast-track access to health resources, was based on previous experiences of fast-tracking referrals to reduce mortality in patients with myocardial infarction.[61] Pregnancy has a short duration, with a small window of opportunity for intervention in modifiable risk factors. Therefore, this study will verify whether shortening the period of referral to reference services that already exist in the Portuguese health system, under its usual operating conditions, can result in better perinatal outcomes.

The study will also provide updated estimates on the prevalence of four psychosocial and behavioural risk factors—smoking, alcohol consumption, depression and physical abuse—in Portuguese pregnant women attending the Portuguese primary care services in the two most populous regions of the country. We will also assess women's acceptance of the intervention and the effects of the intervention on the prevalence of the four risk factors.

Our primary outcome was defined in line with international goals of reducing LBW by 30%.[7] This is an audacious goal, considering the mixed existing evidence on the effects of early interventions in pregnancy aimed at behavioural and psychosocial risk factors addressed in this study.[41–52] However, even if we detect a minor or no effect in reducing the frequency of LBW, the reduction in the prevalence of risk factors can contribute to the health promotion in this group of women with benefits that go beyond the perinatal period.

The study will use the resources already available in the Portuguese National Health System, which are public and free of charges, which we believe will facilitate the implementation of the intervention. The only exception will be the use of standardised screening tools for risk assessment, as currently the PHCU assess risk factors in different and non-standardised ways. The implementation of a valid screening tool in all PHCU will allow a more reliable assessment of these risk factors and future comparisons of prevalence rates in different regions of the country.

Currently, 13% of pregnant women in Portugal are foreign women, which may have higher risk of LBW. However, nearly 70% of these women are from Portuguese-speaking countries.[62] Therefore, we do not expect exclusion of large numbers of women due to language barriers. We have excluded teenage pregnancies and the results will not apply to this group of women. However, in Portugal, they represent less than 1% of pregnancies.

We will obtain information on risk factors during the face-to-face interview with pregnant women and underreporting is possible, as these are sensitive topics. However, we will assess all risk factors before the outcomes occur and, if any misclassification occurs, it will be non-differential, probably leading to underestimation of the effects between the groups.

The use of the PHCU as a randomisation unit aimed to reduce contamination, since all pregnant women in each health service will be allocated to the same intervention/control group. However, the sharing of information between health professionals and pregnant women can occur and lead to contamination, which could dilute the effect of the tested intervention. Therefore, the estimated effects of the intervention will be conservative.

The results of this study will contribute to inform health decision makers in Portugal about the effectiveness of the tested intervention and its potential benefit in comparison to the standard of care currently existing in primary healthcare services. The study will use resources already available in the Portuguese Health System, which we believe will contribute to its sustainability, since the intervention does not entail additional costs for health services. We hope that the study will promote the strengthening of network including primary care services and referral services, which will facilitate the referral of high-risk women to referral health facilities.

Countries with national health systems, based on primary care services, could also benefit from these results. However, we have prioritised four modifiable risk factors that are relevant to the Portuguese context. Other factors, such as nutritional factors, were not included and may be relevant to other contexts.

Acknowledgments We would like to thank all health professionals, healthcare managers and pregnant women that agreed to participate in the pilot study.

Contributors HB: conceptualisation, Supervision, writing—review and editing. IB, TM, AA, AS and PP: writing—review and editing. RD: conceptualisation, original draft preparation, writing—review and editing. All authors read and approved the final manuscript.

Funding This project was funded by the Calouste Gulbenkian Foundation under the Knowledge Challenge 'The Importance of the Right Weight at Birth'. Sponsor contact information: HB. ISPUP. hbarros@med.up.pt.

Disclaimer The funding source had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Competing interests The authors declare no conflict of interests

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

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INFORMED CONSENT FOR PARTICIPATION IN THE STUDY "STOP LOW BIRTHWEIGHT"

Please carefully read the following information. If there is something incorrect or not clear, do not hesitate to ask for more information using the e-mail: desafiobaixopeso@ispup.up.pt

If you accept to participate in this study, we ask you to give your consent, by signing the final document.

Your participation in this study is entirely voluntary. Besides, if you want, you can participate in only a part of the study, as well as you can withdraw at any time, without any consequence for you, just by contacting the responsible researcher using the e-mail above.

1. INFORMATION ABOUT THE STUDY

Title: Fast-track referral for health interventions during pregnancy: a randomized pragmatic experimental study to reduce low birthweight in Portugal - STOP Low birthweight.

Responsible Institution: Instituto de Saúde Pública da Universidade do Porto (ISPUP) and Calouste Gulbenkian Foundation

Principal Researcher: Henrique Barros

Aim of the study: To estimate the effect of implementing fast-track referral for early intervention on psychosocial and behavioural risk factors - smoking, alcohol consumption, depression, and physical violence - in reducing the incidence of LBW.

2. DATA PROTECTION

Study Background: In the last decades, there has been an increase in the number of infants born with low birthweight (less than 2,5 kg) in Portugal, reaching in 2018 one of the highest prevalence in Europe (9.0%), which increases the risk of health problems at the beginning of life and even death, long hospitalizations, and infants' susceptibility to special needs. Therefore, personal data collected in this study will be essential to contribute to new and relevant scientific knowledge around maternal and infant's care to inform health decisions about the best interventions to reduce low birthweight.

Personal data: Eligible pregnant women will be invited to participate in the study by a healthcare professional during antenatal consultations at the primary care unit. This professional will explain the study to you and, after your consent, will apply a questionnaire containing social and demographic information (birth date, country of birth, nationality, marital status, level of education, professional status); information about COVID-19; risk factors such as smoking, alcohol consumption, depressive symptoms and interpersonal violence; as well as clinical and obstetric history (gestational age, parity, number of antenatal appointments). The collected information will be reported to the health professional that is following you at the health unit, to promote the best care for you. If any risk factor is detected, your medical doctor will propose a referral to a specialized health unit with specific interventions target to psychosocial and behavioral risk factors. You may agree or not to this referral. After birth, if you consent, we will collect data about your delivery and your baby (type of delivery, birth date, sex, gestational age, birthweight).

Goal of Data Collection and Processing: Data will be analysed according to the national and European applicable legislation and will only be used to scientific research purposes, namely, to understand if early interventions in pregnancy for specific risk factors, such as smoking, alcohol, depression and violence, are relevant to reduce low birthweight.

Data Protection Manager: Instituto de Saúde Pública da Universidade do Porto (ISPUP), Rua das Taipas, nº 135, 4050-600 Porto, Portugal.

Personal Data Recording: Participants' contact data will be kept during the strictly needed period of the time which is estimated to be a maximum of 2 years to conclude the questionnaire fulfillment regarding behaviors during pregnancy, delivery and your baby. Clinical and sociodemographic data will be kept by a maximum of 3 years to allow the analysis of data until the end of the study. After this deadlines data will be deleted.

Data Protection Measures: Data collected through medical records will be performed by a health professional and analyzed by the ISPUP team. This information, as well as data collected using the questionnaire, will be exclusively accessible to the research team. Paper identified documents (with name and contacts) will be kept in a locked room, apart from the other documents. Databases (quantitative and qualitative) will be stored online and in a computer at ISPUP, both protected by a password only known by the reached team. To allow pseudonymization, each participant will be identified by an alphanumeric unique code.

Personal Data Sharing: Data will not be shared to other institutions. Only aggregated data will be published, guaranteeing participants' confidentiality and privacy.

THIS DOCUMENT HAS TWO PAGES AND IS DUPLICATED: ONE FOR THE RESEARCHER, ANOTHER FOR THE PERSON WHO IS GIVING CONSENT

Rights of the Data Holder: You have the following rights as a data holder: information, access, rectification, erasing, portability, and limitation of treatment. To exercise any of these rights please use the following e-mail: desafiobaixopeso@ispup.up.pt.
The exercise of these rights may be removed or limited, in compliance with the terms and conditions provided for in the applicable national and EU legislation, to the extent that such exercise is likely to make it impossible or seriously harm the achievement of the purposes of the research, but only to the extent necessary for the pursuit of those purposes. The law also gives you the right to present complaints at an European Supervisory Authority, and in Portugal the competent Authority is the CNPD (www.cnpd.pt).

Manager of Data Protection: To any questions, exercise of rights of the data holder, complaints or requests regarding data protection and treatment, please, contact the Manager of Data Protection, by the e-mail: dpo@ispup.pt.

3. INFORMED CONSENT

1. I read and understood the information about the study, including the identity of the manager, the type of data collected, the aim of, analysis and storage of personal data, as well as, for how long data will be kept.	☐
2. I had the chance to ask questions and clarify all my doubts regarding the study.	☐
3. I understand that I can withdraw my participation in the study at any time, without giving explanations and without any penalty or questions about my reasons.	☐
4. I authorize collection of information to identify risk factors, using a questionnaire applied by a health professional.	☐
5. I authorize personal data collection by the research team from ISPUP.	☐
6. I authorize collection of information about the delivery and my baby.	☐
7. If any risk factor will be identified I authorize the referral for specialized health units and care programs.	☐
8. I authorize the collection of information from medical records at the Electronic Health Registry, by a health professional to complete data collection.	☐

Researcher/ Health professional:

Name: … … … … … … … ..... … … … ..... … … … … … … … … … … … … …. …

Signature: … … … … … … … ..... … … … … … … … … … … … … … … … … … … Date: …… /…… /…….

Participant:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered satisfactorily. I consent voluntarily to participate as a participant in this research, and I voluntarily allow the use of my personal data.

Name: … … … … … … … ..... … … … ..... … … … … … … … … … … … … … Birth date …… /…… /…….

Signature: … … … … … … … ..... … … … … … … … … … … … … … … … … … Date: …… /…… /…….

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Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	No
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	Na

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug	10

		dose change in response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned	13

		restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15,16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15,16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13, 19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups	19

		(eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental appendix 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA