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Maternal positional therapy for fetal growth and customised birth weight centile benefit in a Bayesian reanalysis of a double-blind, sham-controlled, randomised clinical trial

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ABSTRACT

Objectives To update the Ghana PrenaBelt Trial's (GPT) primary outcome data with the latest fetal growth standard and reanalyse it. To estimate the posterior probability, under various clinically relevant prior probabilities, of maternal nightly positional therapy (PT) throughout the third-trimester having a beneficial effect on customised birth weight centile (CBWC) using Bayesian analyses.

Design A reanalysis of a double-blind, sham-controlled, randomised clinical trial.

Setting A single, tertiary-level centre in Accra, Ghana.

Participants Two-hundred participants entered, 181 completed and 167 were included in the final analysis. Participants were Ghanaian, healthy, aged 18–35 years, with low-risk, singleton pregnancies in their third-trimester, with Body Mass Index<35 kg/m^2 at the first antenatal appointment for the index pregnancy and without known fetal abnormalities, pregnancy complications or medical conditions complicating sleep.

Interventions Participants were randomised to receive treatment with either a PT or sham-PT device.

Primary and secondary outcome measures The primary outcome was the CBWC using the latest Perinatal Institute, Gestation-Related Optimal Weight calculator. Using Bayesian methods, posterior probabilities of achieving a greater than 0%, 5% and 10% benefit in CBWC with PT were estimated. There was no secondary outcome.

Results The median (IQR) CBWC was 42% (15–71) and 28% (9–52) in the PT and sham-PT groups, respectively (difference 8.4%; 95% CI −0.30 to 18.2; p=0.06). For achieving a >0%, >5% and >10% gain in CBWC with PT, the posterior probabilities were highly probable, probable and unlikely, respectively, given a range of prior probabilities reflecting varying degrees of pre-existing enthusiasm and scepticism.

Conclusions Maternal nightly PT throughout the third-trimester did not have a statistically significant effect on CBWC on a frequentist analysis using the latest fetal growth standard. However, from a Bayesian analysis, clinicians can infer that PT is likely to benefit fetal growth but with a modest effect size.

Trial registration number NCT02379728.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A reanalysis of a double-blind, sham-controlled, randomised clinical trial.
⇒ Used the latest Gestation-Related Optimal Weight standard to update the primary outcome using country-of-origin ethnicity coefficients and repeated the original frequentist analysis.
⇒ Completed a Bayesian analysis of the primary outcome, incorporating data from a recent meta-analysis and a range of representative clinical prior beliefs ranging from enthusiasm to scepticism, allowing for more meaningful interpretation of the trial results.
⇒ Results may not be generalisable to pregnancies with medical or pregnancy complications, non-Ghanaian ethnicity or living in other parts of the world.
⇒ All analyses were post hoc, so the results should be interpreted with caution.

INTRODUCTION

Background

The Russo–Williamson thesis states that a causal hypothesis can be established only by using both statistical evidence and evidence of mechanism.[1] In recent years, evidence of mechanism between maternal supine sleeping position after 28 weeks gestation, fetal growth restriction and late stillbirth has been mounting.[2–14] Biological plausibility likely stems from aortocaval compression in the supine position and resultant deleterious changes in maternal and fetal haemodynamics as well as the effect of the supine position on maternal respiratory parameters during pregnancy. Regarding statistical evidence, Owusu *et al* were the first to find an association between supine sleep and low birth weight, and hypothesised that this association may mediate the relationship between

supine sleep and stillbirth.[15] Several other case–control studies have been performed[16–20] culminating in two individual participant data (IPD) meta-analyses that showed the supine going-to-sleep position, when adopted after 28 weeks of pregnancy, is associated with giving birth to a small-for-gestational-age infant and/or having a stillbirth.[21 22] In 2021, the Royal College of Obstetricians and Gynaecologists with the National Institute for Health and Care Excellence analysed this evidence[23] and incorporated sleeping position recommendations into their antenatal care guideline.[24] Clinical standards have also been rewritten in Australia to include advice to settle to sleep on the side in pregnancy starting at 28 weeks.[25]

In 2013, the authors (JC, AK and JW) developed and tested a positional therapy (PT) device to minimise time spent sleeping in the supine position in pregnancy.[26–28] The device does not prevent the user from lying supine during sleep, but it has been shown to cause a significant reduction in the amount of time spent sleeping supine without demonstrable impact on sleep quantity or quality.[26 27] The Ghana PrenaBelt Trial (GPT),[28] was a double-blind, randomised, sham-controlled trial conducted by the authors (JC and AK) to investigate whether nightly use of this PT device by a group of healthy pregnant participants during sleep in the home setting throughout the third-trimester of pregnancy affected birth weight and customised birth weight centile (CBWC) when compared with a similar group who used a sham-PT device. The original publication of the GPT is open access and can be found online.[28]

In the GPT, the CBWC was calculated using the Gestation-Related Optimal Weight (GROW) standard by Gardosi *et al* (Perinatal Institute and Gestation Network, Birmingham, UK).[29 30] When the original GPT analysis was completed, the ethnicity coefficient used by the GROW calculator (V.6.7.8.1)[31] was a regional coefficient ('West African') because, at that time, country-of-origin specific coefficients for ethnicity were not available; however, since the GPT was published, the GROW calculator was updated (now version 8.0.6.2)[32] and now includes country-of-origin specific coefficients for ethnicity, including 'Ghanaian', which is the ethnicity of the GPT sample. Given the important contribution of maternal ethnicity to fetal growth,[33–35] the authors of this study contacted the GROW team about this update and were advised that the GPT CBWCs should be recomputed with the latest GROW calculator using country-of-origin ethnicity coefficients and reanalysed, which relates to the first objective of this study.

The authors of the GPT used a traditional frequentist analysis and were unable to reject the null hypothesis of no treatment effect of PT (on birth weight or CBWC) because the p-value for each of these outcomes (0.14 and 0.11, respectively) was greater than the commonly accepted cut-off of 0.05.[36] In the biomedical literature, trials analysed under the frequentist paradigm with p-values>0.05 are often labelled as 'negative'.[37 38] While this serves as the function of preventing future and futile investigations of completely ineffective interventions, it could also mean that the trial has low power against an important effect size. This often perpetuates the belief that the treatment under consideration is ineffective or does not work.[39] However, Bayesian analyses have been used on several such 'negative' studies since the early 2000s, which have clarified the results of clinical trials and conveyed more relevant and meaningful information to clinicians.[40 41] Furthermore, even in the frequentist paradigm, it is not uncommon to reanalyse results with updated methodologies (eg, adjusted analyses) and data sets, especially in the context of meta-analyses and for the results of these reanalyses to change clinical practice.[42 43] Here lies the second objective of this study.

See online supplemental file 1 for additional background information.

Objectives

Primarily, to recompute the CBWC values in the GPT using the updated GROW calculator (V.8.0.6.2) and repeat the frequentist analysis employed in the GPT to determine the effect, on CBWC, of use of PT during sleep in the home setting throughout the third-trimester of pregnancy in comparison with sham-PT. Secondarily, to make more clinically relevant use of the GPT data by performing a Bayesian reanalysis of the updated GPT CBWC data. Specifically, to determine the probability of PT benefiting the CBWC by achieving >0%, >5% and >10% improvement in comparison to sham-PT when used during sleep in the home setting throughout the third-trimester of pregnancy. These objectives were previously unplanned for the GPT.

METHODS

Trial design

This study is a reanalysis of the GPT, which was a single-centre, double-blind, randomised (one-to-one), sham-controlled, clinical trial conducted between September 2015 and March 2016.[28]

Patient and public involvement

Patients and the public were not involved in the development of the research question or outcome measures, nor in the design, recruitment, or conduct of the study.

Participants

The GPT recruited participants from antenatal care clinics at the Korle Bu Teaching Hospital (KBTH)—see the original GPT publication (open access) for full details regarding the study setting, eligibility criteria and number of trial participants assessed for eligibility, recruited, randomised and analysed.[28] The GPT was approved and monitored by the Ghana Food and Drugs Authority (Accra, Ghana; Clinical Trial Certificate FDA/CT/152).

Interventions

Each participant was instructed to use their assigned device (PT or sham-PT) every night from approximately

28 weeks' gestation through birth. The PT device was worn at the level of the waist and had two back pockets each containing two rigid, hollow, polyethylene balls held securely in place by a foam insert. The theoretical mechanism of the PT device is based on the tennis-ball technique of PT, which is a common treatment to reduce snoring in sleep medicine.[44] When supine, the balls apply pressure points across the user's lower back, prompting them to reposition themself in a lateral position to maintain comfort. The sham-PT device was identical in appearance, materials and construction to the PT device, but had soft foam balls instead of firm plastic balls and did not have foam inserts. See the original GPT publication for further details regarding the recruitment and follow-up processes.[28]

Outcomes

The primary outcomes for the GPT were birth weight (grams) and CBWC (%). To address the objectives of this study, we recompute and reanalyse only the CBWC in the frequentist paradigm because only the CBWC is affected by the new GROW calculator, and the birth weight values (and analysis) from the GPT are unchanged. In the Bayesian framework, we analyse only the CBWC because the CBWC, owing to its incorporation of the six main non-pathological factors impacting birth weight, is a much more accurate proxy for fetal growth in comparison to birth weight. For a full description of how the measurements composing the CBWC were taken in the GPT, including the study personnel responsible for collecting them, see the original publication.[28]

Sample size

The target sample size of the GPT was 200 participants (100 per group), which accounted for an expected 20%–30% lost-to-follow-up rate and assumed a 300 g difference in birth weight between the PT and sham-PT groups (with pooled SD of 643 g), power (β) 0.80, and type I error probability (α) of 0.05.[28]

Randomisation

Randomisation to either the PT or sham-PT group in the GPT included allocation concealment and followed a one-to-one, simple randomisation scheme.[28]

Blinding

Participants in the GPT remained blinded to the allocation until after study completion. Efforts to ensure that each participant did not know what the alternate device looked or felt like included conducting separate introduction sessions for each group and ensuring no balls or foam inserts were in the device (so it was configured neither as a PT nor sham-PT device) during demonstrations.

Statistical methods

In the GPT, all data were double-entered from scanned PDFs into Microsoft Excel and double-entry checked prior to the final analysis.[28] These data were provided by the principal investigator of the original study (JC). Analyses (below) were performed using the psych, nortest, bmrs, tidyverse and magrittr packages in the R statistical software package (V.4.2.2) and Bayesian inference was conducted using Stan probabilistic programming language via brms in R. The brms uses Stan and employs the Hamiltonian Monte Carlo algorithm to conduct Markov chain Monte Carlo (MCMC) sampling.[45] We used standard, validated, off-the-shelf, open-access MCMC software (ie, Stan) to ensure reproducibility of our study results.

Frequentist methods

We used the same data set and completed the same analysis (difference testing via Wilcoxon rank sum test) as in the original GPT, using the CBCW values from the GROW V.6.7.8.1 calculator, which specified the ethnicity coefficient as West African, and then repeated the same analysis using the GROW V.8.0.6.2 calculator and specifying the ethnicity coefficient as Ghanaian.

Bayesian methods

Bayesian methods focus on providing plausible values for the treatment effect that are compatible with both the observed data and prior knowledge or beliefs.[46] To guide statistical inference, Bayesian analysis enables the use of both non-informative (NI) priors that minimise the influence of priors on the statistical inference, and informative priors that are guided by existing evidence (eg, meta-analysis and literature) or a range of collective expertise from investigators regarding the belief or scepticism regarding treatment efficacy. Under the Bayesian framework, the posterior probabilistic summary of treatment efficacy (also known as an updated belief of treatment efficacy) is obtained by combining the prior beliefs (ie, prior probability distribution of the treatment effect parameter) and the observed data (ie, the likelihood distribution of the data specified with the treatment effect parameter). Thus, a Bayesian analysis of trials can leverage background information allowing the quantification of this information as priors to aid the interpretation of the trial results. Bayesian analyses are particularly appealing and beneficial when the study is underpowered, with a small sample size, through the incorporation of clinically relevant priors to improve estimation precision. See online supplemental file 2 for more details.

To aid the interpretation of prior and posterior probabilistic summaries of treatment efficacies, we provided the following probability perception scale: 'unlikely' indicates a probability ranging between 0 and 0.5; 'probable' indicates a probability ranging between 0.5 and 0.8; 'highly probable' indicates a probability ranging between 0.8 and 0.95 and 'almost certain' indicates a probability ranging between 0.95 and 1.00.[47]

Prior probabilities

The prior beliefs about the plausible range of values of the effect of PT on CBCW are represented by a probability density distribution ('prior probability')—see figure 1. The wider (more variance) this distribution, the

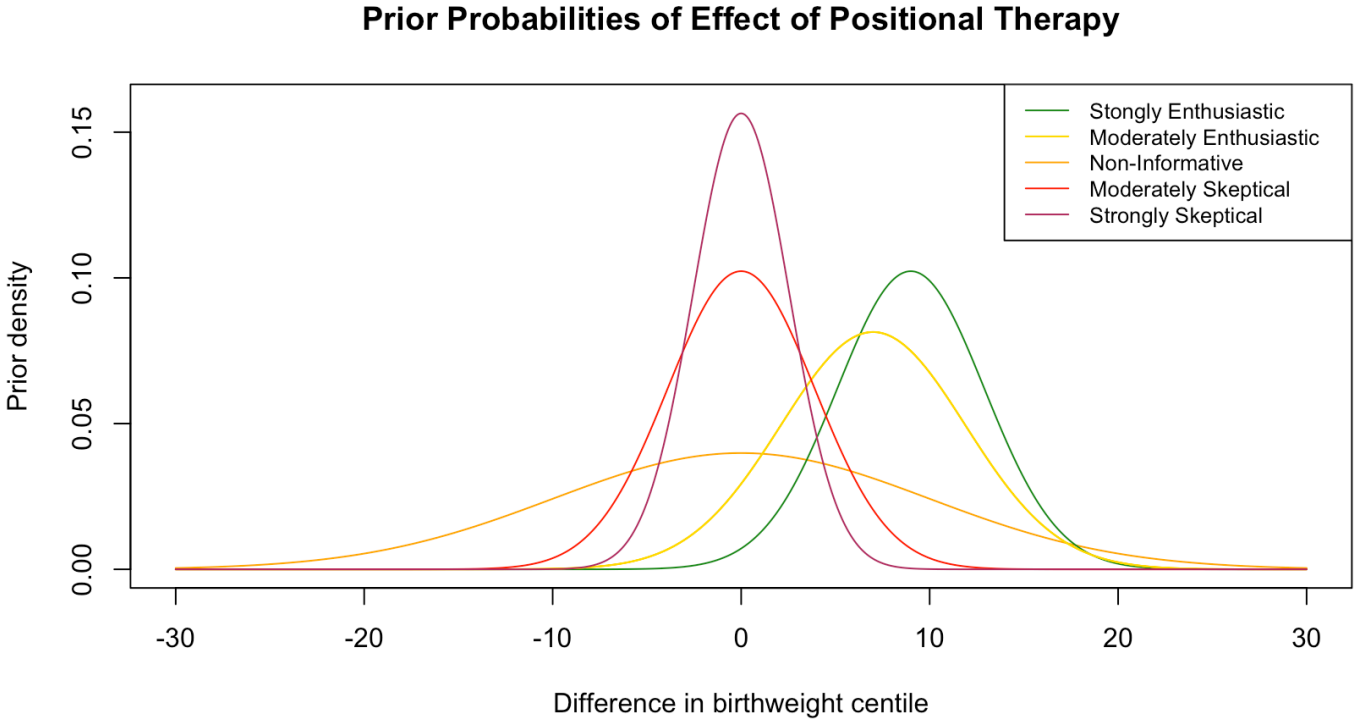

Figure 1 Probability density distributions of a range of priors selected in an effort to match the spectrum of belief in the clinical community about the plausible range of values for the treatment effect of PT on CBWC compared with sham-PT when used nightly across the third-trimester of pregnancy. CBWC, customised birth weight centile; PT, positional therapy.

less certainty about the treatment effect and the narrower (less variance) this distribution, the more certainty about the treatment effect. The area under the distribution and to the right of any given CBWC value is the probability that the treatment effect is greater than that value. To develop each statistical prior for this analysis, we used normal probability distribution defined by two values. The first value was the median gain in CBWC, μ, on which we centred the distribution, which reflects the value for the treatment effect that an enthusiast or a sceptic would assume to have a 50% probability of obtaining. The second value was the width of the distribution defined by a SD, σ, which reflects the magnitude of uncertainty about the plausible range of values for treatment effect.

Five priors were defined to typify varying degrees of enthusiasm and scepticism for the benefit of PT on CBWC consistent with pre-existing controversy in the literature about the association between supine sleeping position and adverse pregnancy outcomes.[23 48–51] These five archetypal beliefs are strongly enthusiastic (SE), moderately enthusiastic (ME), NI, moderately sceptical (MS) and strongly sceptical (SS), are depicted graphically via probability density distributions in figure 1, and were derived as follows.

Strongly enthusiastic prior

For our SE prior, we derived μ and σ from a recent IPD meta-analysis of four case–control studies, which included n=1760 participants.[22] For n=57 participants whose going-to-sleep position in the third-trimester was supine, their infant's mean (SE) CBWC was 40.7% (7.6). For n=1703 participants whose going-to-sleep position in the third-trimester was non-supine, their infant's mean (SE) CBWC was 49.7% (6.7). Comparing these two groups, the adjusted mean difference in CBWC was 9.0 (95% CI: 1.4 to 16.6). Therefore, we set μ=9.0 for our SE prior, and using the 95% CI, we derived σ to be 3.9 assuming a normal distribution. In summary, our SE prior favours a positive treatment effect of a 9% gain in CBWC with PT, and there is some uncertainty in this belief but not enough to make the 95% CI of the treatment effect cross zero.

Finally, to aid in understanding the strength of the enthusiasm or scepticism represented by the SE prior, we computed the probability that a person holding this level of belief (about the treatment effect) would observe PT achieving an average gain in CBWC greater than 0%, 5% and 10% compared with sham-PT on the probability scale. See online supplemental file 2 for these computations for the SE prior and each of the following priors.

Moderately enthusiastic prior

For our ME prior, we derived μ and σ from the original published GPT results in which the mean difference in CBWC between the PT and sham-PT groups was 7.0 (95% CI: −2 to 17). Therefore, we set μ=7.0 for our ME prior, and using the 95% CI, we derived σ to be 4.9 assuming a normal distribution. In summary, our ME prior favours a positive treatment effect of a 7% gain in CBWC with PT, but there is more uncertainty in this belief as this distribution is wider than our SE prior and the 95% CI of the treatment effect crosses zero.

Non-informative prior

A NI prior, tantamount to keeping an 'open mind', has little influence on the posterior distribution because it regards all possible treatment effect values to be equally likely. With an NI prior, minimal information is added to the study data in the Bayesian analysis, and the resulting posterior distribution is essentially dependent on the study data alone.[52] For our NI prior, we set μ=0 and σ=10, reflecting ignorance about the treatment effect of PT and sham-PT. As such, the 95% CI of our NI prior spanned −19.6 to +19.6. At this width, the level of uncertainty of our NI prior was more than double the uncertainty of our next most uncertain prior (ME prior, σ=4.9). In summary, being centred at 0%, our NI prior does not favour any treatment effect and there is much uncertainty in this belief as this distribution is very wide relative to our other priors.

Moderately sceptical prior

For our MS prior, we set μ=0, which does not favour a treatment effect, and σ=3.9, which just happens to be the same uncertainty level as our SE prior. The choice of σ was based on the notion that for a person who is MS, the width of the MS prior distribution should be set such that there is an approximate 10% probability of achieving a treatment effect as large or larger than the minimum clinically important difference (MCID), which we chose as a 5% gain in CBWC for the purposes of defining our priors—see online supplemental file 2. In summary, being centred at 0%, our MS prior does not favour any treatment effect and there is some uncertainty in this belief (the same level of uncertainty as in our SE prior).

Strongly sceptical prior

For our SS prior, we also set μ=0, which does not favour a treatment effect, but we reduced the width (uncertainty) of the distribution by setting σ=2.55. This time, the choice of σ was based on the notion that for a person who is strongly sceptical, the width of the SS prior distribution should be set such that there is very small probability (2.5% or less) of achieving a treatment effect as large or larger than the MCID. In summary, being centred at 0%, our SS prior does not favour any treatment effect and there is little uncertainty in this belief (this is our narrowest prior), reflecting that the sceptic is very confident that his/her belief that PT has no treatment effect is correct.

Posterior probabilities

MCMC modelling (with four chains, 5000 iterations burn-in and 5000 saved iterations per chain; see the Stan Reference Manual[45] for full details of the implementation and configuration of the MCMC algorithm) was used to fit Bayesian generalised linear models to derive estimates of the treatment effect and 95% credible intervals (CrI's) from the median 2.5th and 97.5th percentiles of each posterior distribution. Note that the 95% CrI is the interval that has a 95% probability of containing the true treatment effect.[53] Each of the prior distributions was updated by the study data (CBWC values from the GROW V.8.0.6.2 calculator) to estimate the posterior probabilities that the treatment effect of PT, in comparison to sham-PT, exceeds a range of thresholds for the MCID, namely, a >0%, >5% and >10% centile increase in the CBWC. In the Bayesian regression analysis, NI priors (ie, N(0,100) and Student-t(0,10, df=3)), were used for nuisance parameters including the regression intercept term and the variance term as these parameters do not quantify treatment effectiveness. Convergence of the Bayesian estimation is examined using trace plots and the R-hat convergence index (a cut-off of 1.01).[54]

RESULTS

Of two-hundred and seventy-six participants assessed for eligibility, 200 were recruited, and 167 (n=83 in the PT group, and n=84 in the sham-PT group) were included in the final analysis of the CBWC. See the original GPT publication for full details on excluded participants and sample characteristics.[28]

Frequentist analysis of customised birth weight centile

For the frequentist analysis of difference in CBWC between the PT and sham-PT groups with the GROW V.6.7.8.1 calculator and specifying the ethnicity coefficient as West African, we arrived at the same results presented in the GPT (see table 1). Repeating the same analysis with values from the GROW V.8.0.6.2 calculator and specifying the ethnicity as Ghanaian gave a similar result and the p-value (0.06) associated with the difference was close to what many frequentists would consider statistically significant. Note that while table 1 presents the unadjusted difference, the GROW centile is already

Table 1 Frequentist analysis of customised birth weight centile in the GPT

	Positional therapy (n=83)	Sham positional therapy (n=84)	Treatment—Sham difference (95% CI)	P value
GROW v6.7.8.1 centile (%)	43 (18 to 67)	31 (14 to 58)	6.8* (–1.7 to 16.6)	0.11
GROW v8.0.6.2 centile (%)	42 (15 to 71)	28 (9 to 52)	8.4* (–0.3 to 18.2)	0.06

Variables are non-normally distributed and presented as median (IQR).
*Wilcoxon rank sum test.
GPT, Ghana PrenaBelt Trial; GROW, Gestation-Related Optimal Weight.

Table 2 Bayesian analysis of customised birth weight centile in the GPT

	Probability of gain in CBCW						
	>0%		>5%		>10%		
Prior belief	Prior	Posterior	Prior	Posterior	Prior	Posterior	95% CrI of treatment effect
SE	0.99	1.00	0.85	0.91	0.40	0.37	3.0–15.0
ME	0.92	0.99	0.66	0.82	0.27	0.29	1.3–14.8
NI	0.50	0.96	0.31	0.70	0.16	0.27	7.4–15.7
MS	0.50	0.88	0.10	0.33	0.01	0.02	−2.4–9.5
SS	0.50	0.81	0.025	0.09	0.00	0.00	−2.4–6.4

Cells are colour-coded according to the previously defined probability perception scale. Red indicates unlikely. Orange indicates probable. Yellow indicates highly probable. Green indicates almost certain.
CBWC, customised birth weight centile; CrI, credible interval; ME, moderately enthusiastic; MS, moderately skeptical;; NI, non-informative; SE, strongly enthusiastic; SS, strongly skeptical.

adjusted for the six main non-pathological affecting birth weight.

Bayesian reanalysis of customised birth weight centile

For the Bayesian reanalysis of the GPT data, the effect of PT (in comparison to sham-PT) on CBWC per the GROW standard (V.8.0.6.2) was computed under varying levels of enthusiasm and scepticism (see table 2). In table 2, for three levels of gain in CBWC (>0%, >5% and>10%), each prior probability for each predefined level of prior belief (SE, ME, NI, MS and SS) from online supplemental file 2 can be compared with its corresponding posterior probability so one can appreciate how the prior belief and GPT data influence the posterior probability. For example, considering the SE prior, when its prior probabilities of achieving a >0%, >5% and >10% gain in CBWC (0.99 (almost certain), 0.85 (highly probable) and 0.40 (unlikely), respectively, see online supplemental file 2) are combined with the GPT data, the posterior probabilities are 1.00 (almost certain), 0.91 (almost certain) and 0.37 (unlikely), respectively. The estimated 95% credible interval of the treatment effect of PT on CBWC under the posterior probability resulting from combining the GPT data with the SE prior was a gain of 3%–15% in CBWC. In summary, with maternal nightly PT from 28 weeks' gestation to birth, there is a highly probable (from the sceptics) to almost certain (from the NI and enthusiasts) benefit of >0% gain in CBCW; an unlikely (from the sceptics) to highly probable (from the enthusiasts) benefit of >5% gain in CBWC and an unlikely (from everyone) benefit of >10% in CBWC. That is, maternal nightly PT from 28 weeks' gestation to birth is likely to benefit CBWC, but the effect size is considered to be reasonably modest.

The results in table 2 are represented graphically in figure 2. While table 2 presents the posterior probabilities at three discrete thresholds of gain in CBCW with PT (>0%, >5% and >10%), figure 2 shows the distributions of the prior probabilities (darker shade) and posterior probabilities (lighter shade) for all thresholds. For ease of reference, the 0%, 5% and 10% thresholds are indicated by blue, purple and pink vertical dashed lines, respectively. The probability of PT conferring a gain in CBWC more than a given threshold is the area to the right of the threshold and under the posterior probability distribution curve. Furthermore, basic probability rules can be used to work out the probability of PT not attaining any given threshold for gain in CBWC, which is also just the area to the left of the threshold and under the posterior probability distribution curve. Note that after combining the prior probabilities with the GPT data, regardless of the level of enthusiasm or scepticism regarding the plausible range of the treatment effect of PT, all the posterior probability distributions became taller, narrower and moved to the right in comparison with their corresponding prior probability distribution. For all of the resulting posterior probability distributions, the bulk of the areas under the curve lie to the right of the zero percentile line, which indicates that PT, when used during sleep nightly from 28 weeks gestation through birth, benefits (results in a gain) the CBWC in comparison to sham-PT under the levels of enthusiasm and scepticism that we specified. Even with the SS prior, PT is more likely to result in a gain in CBWC (probability=0.81; see table 2) than a loss (probability=1.0–0.81 = 0.19). For an SE, ME and NI prior, it can also be stated that the probability of PT resulting in more than a five percentile gain in CBWC (probability 0.91, 0.82 and 0.70, respectively; see table 2) is greater than the probability of it not doing so (0.09, 0.18 and 0.30, respectively) since the majority of the areas under the curve for these posterior probability distributions lie to the right of the fifth percentile line.

DISCUSSION

On a frequentist analysis, using the latest GROW calculator (V.8.0.6.2) to calculate the CBWC in the GPT, we failed to reject the null hypothesis (p-value 0.06) that nightly maternal PT to minimise supine sleeping time from 28 weeks through birth does not have an effect on CBWC compared with sham-PT. See online supplemental

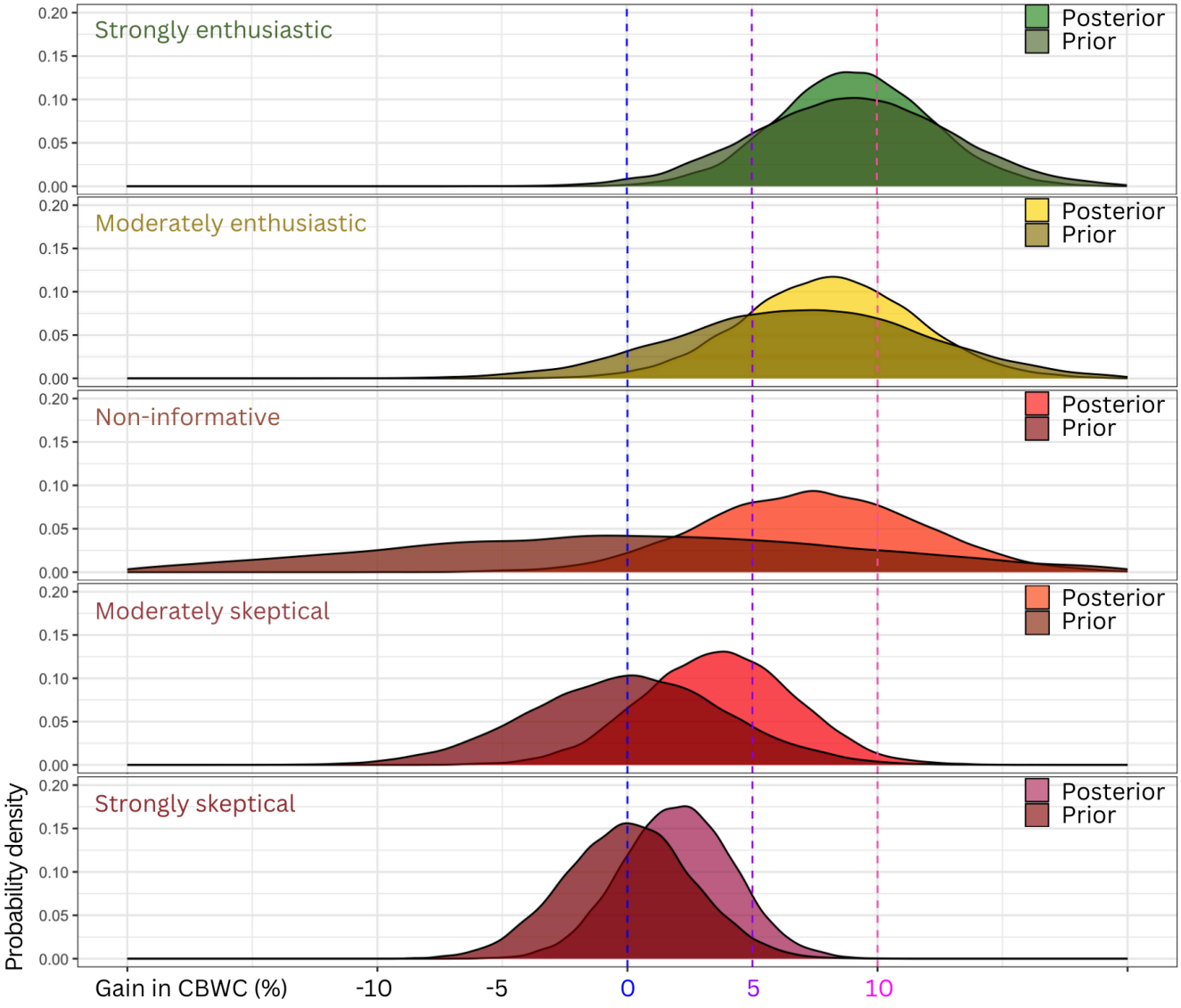

Figure 2 Probability density curves for prior and posterior probabilities for five levels of enthusiasm and scepticism regarding the plausible range of values for the treatment effect of positional therapy on customised birth weight centile compared with sham-positional therapy when used nightly across the third-trimester of pregnancy. Blue, purple and pink vertical dashed lines show the 0%, 5% and 10% thresholds for gain in customised birth weight centile.

file 3 for additional discussion. In summary, within the frequentist framework, we are unable to draw definitive conclusions, including disproving our null hypothesis, about the treatment effect of PT on CBWC based on the GPT results because the 95% CI of the mean difference in treatment effect includes clinically important values, which implies a lack of sensitivity (underpowered).

Approaching the data from a different analytical paradigm (Bayesian), however, indicates that there is a high probability that nightly maternal PT, compared with sham-PT, during sleep throughout the third-trimester confers a significant benefit to fetal growth, even for the sceptic. Bayesian analyses make more efficient use of the available data and present results in more clinically relevant format, telling clinicians the information that they want to know when making clinical decisions, namely, the direct probability of clinically important benefits. A clinician who is strongly sceptical about PT may be interested to know that PT is more likely to result in a gain in CBWC than to result in a loss—a probability of 0.81 (highly probable) to be exact. A more enthusiastic clinician, such as one with knowledge of Anderson *et al*'s IPD meta-analysis of sleeping position and fetal growth (the only such study to date),[22] may wish to update their knowledge with new information from the GPT via our Bayesian analysis. Combination of Anderson *et al*'s data with data from the GPT did not attenuate the treatment effect but, rather, confirmed a beneficial effect with less uncertainty (see taller and narrower posterior probability curve in figure 2). Such a clinician may be interested to know that there is a 95% probability that PT will benefit CBWC between 3% and 15% (95% credible interval).

They may also be interested in knowing that the probability of PT effecting at least a 5% and 10% gain in CBWC is 0.91 (highly probable) and 0.37 (unlikely), respectively. Similarly, a clinician without any prior knowledge in this domain (NI) may be interested to know that the probability of PT effecting any gain and at least a 5% gain in CBWC is 0.96 (almost certain) and 0.70 (probable), respectively. Given the relatively low probability of harm from PT, evidence of benefit for the CBWC may justify its use in clinical practice.

Limitations

First, it must be stated that limitations of this analysis include those inherent in the original GPT.[28] This includes lack of video-confirmation of sleeping position; lack of objective measurements of sleep architecture; reliance on participants' self-reported adherence to device (PT or sham-PT) use; informing participants' of the link between supine sleeping position, stillbirth and low birth weight as part of the informed consent process; the possibility that some participants may have become unblinded if they came into contact with a participant in the alternative and sought to compare their devices and limited generalisability to healthy pregnancies in Ghana. Furthermore, the average self-reported nightly adherence to device use, 56%, was lower than expected, which may have diluted the treatment effect.

Given that the present analysis was unplanned and post-hoc, the results must be interpreted with caution.[55] The original GPT publication had two primary outcomes: birth weight and CBWC. One factor that provides some protection against erroneous conclusions is that the present analysis tested the same hypothesis and the same primary endpoint (CBWC) as the original trial; however, we did not analyse the raw birth weight, so conclusions regarding the effect of PT on raw birth weight cannot be made. The reason the CBWC was chosen for reanalysis is two-fold. First, CBWC is more reflective of fetal growth than birth weight alone because it accounts for the six main non-pathological factors affecting growth,[29] which raw birth weight alone does not account for. For example, a 2500 g infant born at 35 weeks gestation may be normally grown, whereas a 2500 g infant born at 39 weeks gestation would be severely underweight. Second, the original analysis of birth weight from the GPT under the frequentist paradigm is unchanged because raw birth weight is not affected by the updated ethnicity coefficients in the GROW CBWC calculator.

To demonstrate how inferences from a Bayesian analysis of a trial can combine information from the trial with information external to the trial, we reanalysed the GPT data using a prior probability distribution of the estimated treatment effect of PT on CBWC derived from an earlier IPD meta-analysis of sleeping position by Anderson *et al* (see 'SE prior' in 'Methods' section).[22] One limitation is that the data composing the meta-analysis are from case–control studies, not interventional trials of PT. Another limitation is that the participant samples of the four studies included in the meta-analysis are different from the participant sample in the GPT. See online supplemental file 3 for more details.

CONCLUSIONS

A frequentist analysis of CBWCs (updated per the latest version of the GROW calculator) from the GPT does not show a statistically significant treatment effect (p=0.06) of nightly PT compared with sham-PT from 28 weeks gestation through birth. A Bayesian reanalysis of the GPT data enabled a more flexible and clinically relevant interpretation of the trial data. Using the data at hand, including a previous meta-analysis and the GPT data, we were able to report the probabilities of a range of beneficial treatment effects of PT on CBWC across a menu of prior beliefs, from enthusiasm to scepticism, reflecting the current range of controversy around the importance of sleeping position in pregnancy. Using Bayesian inference, we showed that nightly PT from 28 weeks gestation through birth is highly probable or almost certain to benefit CBWC compared with sham-PT.

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Contributors JC, AJK and JW conceived the Bayesian reanalysis of the GPT. AJK and SG recomputed the customised birth weight centiles using the GROW V.8.0.6.2 calculator with updated ethnicity coefficients. AJK wrote the R code to analyse the study data under the frequentist and Bayesian paradigms under the supervision of KL. AJK drafted and revised this manuscript and is guarantor. JC, SG, JW, SRH and KL made intellectual contributions to this manuscript.

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069/14-15) and the IWK Health Centre Research Ethics Board (Halifax, Canada; Project No. 1019318). Participants gave informed consent to participate in the study before taking part.

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Supplementary File 1: Additional Background Information

EVIDENCE OF MECHANISM

In recent years, evidence of mechanism between maternal supine sleeping position after 28 weeks gestation, foetal growth restriction, and late stillbirth has been mounting.(1–13) For example, Couper et al., using advanced magnetic resonance imaging techniques, demonstrated that in healthy pregnancies, the maternal supine position results in a 23.7% reduction in total internal iliac artery blood flow, a 6.2% reduction in oxygen delivery to the foetus, and an 11% reduction in foetal umbilical venous blood flow compared to the lateral position.(3) Based on the first of these three findings, a simple calculation can be performed to demonstrate that, from 28 through 40 weeks' gestation, if two hours per day were spent supine,(14–22) assuming an average of 500 ml/min of maternal blood going to the uterus and 80% of this going to the placenta,(23) the intervillous space (maternal side) of the placenta would experience a cumulative 1,000 litre deficit.

Furthermore, in the supine position, maternal respiratory parameters are affected. Because of increased abdominal pressure when supine, the functional residual capacity of the lungs decreases, the alveolar-arterial oxygen difference increases, and lung compliance decreases.(24–26) Studies have also shown deeper maternal oxygen desaturations, higher apnea-hypopnea index, higher 3% oxygen desaturation index, and higher respiratory disturbance index when sleeping supine in pregnancy.(14,21) Arterial partial pressure of oxygen is lower when supine in pregnancy.(24,27)

Taken together, it is intuitive that maternal supine sleep could affect foetal growth and, consequently, risk of stillbirth via decreased placental blood and oxygen supply.

GESTATION RELATED OPTIMAL WEIGHT STANDARD

The original Ghana PrenaBelt Trial (GPT)(28) selected the Gestation Related Optimal Weight (GROW) standard by Gardosi et al. (Perinatal Institute and Gestation Network, Birmingham, UK) as one of its primary outcomes.(29,30) The reason for using the GROW standard in the original GPT and in this study is because the GROW standard accounts for the main six non-pathological factors affecting birth weight, including gestational age, maternal height, maternal weight at booking, parity, ethnicity and sex of the neonate. As such, the customised birthweight centile (CBWC) computed using the GROW standard enables delineation between constitutional and pathological smallness and more accurate detection of pregnancies at increased risk for adverse outcomes.(31,32)

Changes in the GROW Standard Calculators Between Original and Current Analyses

The GROW standard calculators are continually being updated, according to availability of new databases from different populations from which additional ethnic coefficients can be derived.(33) This enables improvement on predicting normal variation, which reflect on the coefficient of variation of the curve. The extent of the data have enabled derivation of ethnic-specific sets of coefficients.(33) That is, GROW calculators adjust for maternal height and weight, parity, and sex of the neonate for each ethnicity or

country of origin.(33) As such, because we used the ”Ghanaian” ethnicity coefficient with the new (v.8.0.6.2) calculator, all the other coefficients in the model (maternal height and weight, parity, and sex of the neonate) were changed based on new datasets from Ghana because these coefficients are specific to the “Ghanaian” ethnicity. In the original GPT analysis with the old (v6.7.8.1) calculator, the authors used the “West African” ethnicity coefficient (based on West Africans giving birth at Queen’s Medical Centre, Nottingham, UK), which had its own set of coefficients for maternal height and weight, parity, and sex of the neonate.

Role of Maternal Ethnicity in Customised Foetal Growth Standards

We acknowledge that ethnicity can be poorly defined by both patients and clinicians and that assumptions about the impact of ethnicity on health has the potential to result in patient harm. However, several decades of epidemiological research along with several professional organisations (e.g., the Royal College of Obstetricians & Gynaecologists)(34) have established that the benefit outweighs the harm when assessing birth weight against individual growth potential calculated for each baby in each pregnancy (customised standards) rather than against the average of the population (population standards or norms).(35,36) Customised standards, adjusted for the main factors affecting foetal growth (including ethnicity), increase accurate detection of IUGR by improved distinction between physiological and pathological smallness.(35) In contrast, application of population standards fails to identify a significant proportion of pathological smallness (false negative) and erroneously identifies a significant proportion of physiological smallness as IUGR (false positive, risking unnecessary and

potentially harmful intervention).(37–39) In a study of over 130,000 births from 2009-2013, Gardosi et al. have demonstrated that maternal height, maternal weight, maternal ethnicity, parity, and sex of the newborn account for 76% (R-squared 0.759) of the normal variation in birth weight (excluding pathological factors).(36) Regarding the impact of ethnicity alone, it accounts for approximately 24% of the normal variation in birth weight,(36) which highlights the clinical importance of taking maternal ethnicity into account. Finally, there is now a substantial evidence base that supports that differences in foetal growth potential between ethnic groups are physiologic and that customization (which accounts for ethnicity) improves delineation between pathological and physiological smallness.(40–44)

COMPARISON OF FREQUENTIST AND BAYESIAN PARADIGMS

In the frequentist paradigm, the study hypothesis is evaluated indirectly by estimating an objective probability, a relative long-run frequency (also known as the p-value), of observing a treatment effect of the same or larger magnitude than the treatment effect observed in a given study if the same study were repeated indefinitely and assuming the null hypothesis (no effect) is true.(45) According to Royall, the frequentist approach can only guide our decision to either accept or reject the null hypothesis – in light of data, frequentist statistics tells us what to *do*.(46) If we want to know, in light of data, what we should *believe* or how strongly we should believe in different hypotheses, frequentist methods cannot answer that question and, rather, Bayesian methods are required.(46)

In the Bayesian paradigm, the study hypothesis is evaluated directly, that is, Bayesian methods tell us the probability of the study hypothesis being true given the available data.(47,48) Bayes' theorem enables the estimation of a plausible range of values of a treatment effect ("posterior probability") by formally combining data collected in a study with information available prior to the study about the plausible values of a treatment effect ("prior probability").(45) In other words, a unique feature of a Bayesian analysis is that it enables the use of clinically relevant priors probabilities in combination with trial data to provide updated and robust estimates that allow for a more comprehensive interpretation of the existing evidence. As such, one can appreciate the utility of Bayesian methods in clinical practice as clinical decisions can be directly informed by study results and, at the same time, incorporate the influence of clinical judgement and prior beliefs about the treatment effect.(47,49,50)

For readers who may be sceptical of Bayesian methodology, we direct them to a thorough discussion of the rationale, process, and interpretation of Bayesian analyses in a recent, open-access, systematic review in the Lancet, "Clinical trials in critical care: can a Bayesian approach enhance clinical and scientific decision making?" by Yarnell, Abrams, Baldwin, et al.(51)

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Supplementary File 2: Additional Methodological Details

BAYESIAN PRIORS

Rationale for Choosing a Variety of Priors

In a Bayesian analysis, the prior belief (prior probability) about the treatment effect must be specified. In the absence of existing evidence (e.g., meta-analysis and literature) to inform the priors, the priors must be derived from expert consensus and beliefs, which may be subjective because such beliefs are influenced by and specific to a given investigator and may not be accepted by anyone else.(1) Historically, this was a point of major criticism against Bayesianism, but it no longer needs to be because this can be overcome by choosing a variety of prior probabilities in an attempt to approximate the posterior distribution held by all types of readers. In fact, regulators have accepted this approach, and this is no longer a stumbling block to using Bayesian methods.(1)

Probability of Achieving Various Treatment Effects

To aid in understanding the strength of the enthusiasm or scepticism represented by each of our predefined priors, we computed the probability that a person holding this level of belief (about the treatment effect) would observe positional therapy (PT) achieving an average gain in customised birthweight centile (CBWC) greater than 0%, 5%, and 10% compared to sham-PT on the probability scale.

Furthermore, to aid the interpretation of prior and posterior probabilistic summaries of treatment efficacies, we provided the following probability perception scale: “unlikely” indicates a probability ranging between 0 and 0.5; “probable” indicates a probability

ranging between 0.5 and 0.8; “highly probable” indicates a probability ranging between 0.8 and 0.95; and “almost certain” indicates a probability ranging between 0.95 and 1.00.(2)

Strongly Enthusiastic Prior

For our strongly enthusiastic (SE) prior (μ=9.0; σ=3.9; N(9,3.9)), the probability that a person holding this level of belief (about the treatment effect) would observe PT achieving an average gain in CBWC of greater than 0%, 5%, and 10% compared to sham-PT was almost certain (P(treatment effect>0%) = 0.9894919), highly probable (P(treatment effect>5%) = 0.8474696), and unlikely (P(treatment effect>10%) = 0.398817), respectively, on the probability scale. Assuming the minimum clinically important difference (MCID) was selected as a 5% gain in CBWC, note that other investigators typically use a more enthusiastic prior than we selected and typically aim for a 95% probability of observing a treatment effect as large or larger than the selected MCID,(3) whereas the prior probability of observing PT achieving that MCID with our SE prior is 0.85.

Moderately Enthusiastic Prior

For our moderately enthusiastic (ME) prior (μ=7.0; σ=4.9; N(7,4.9)), the probability that a person holding this level of belief (about the treatment effect) would observe PT achieving an average gain in CBWC of greater than 0%, 5%, and 10% compared to sham-PT was highly probable (P(treatment effect>0%) = 0.9234363), probable (P(treatment effect>5%) = 0.6584231), and unlikely (P(treatment effect>10%) = 0.2701879), respectively, on the probability scale.

45 Non-Informative Prior

46 For our non-informative (NI) prior (μ=0; σ=10; N(0,10)), the probability that a person
47 holding this level of belief (about the treatment effect) would observe PT achieving an
48 average gain in CBWC of greater than 0%, 5%, and 10% compared to sham-PT was
49 unlikely (P(treatment effect>0%) = 0.5), unlikely (P(treatment effect>5%) = 0.3085375),
50 and unlikely (P(treatment effect>10%) = 0.1586553), respectively, on the probability
51 scale.

52 Moderately Sceptical Prior

53 For our moderately sceptical (MS) prior, (μ=0; σ=3.9; N(0,3.9)), the probability that a
54 person holding this level of belief (about the treatment effect) would observe PT
55 achieving an average gain in CBWC of greater than 0%, 5%, and 10% compared to
56 sham-PT was unlikely (P(treatment effect>0%) = 0.5), unlikely (P(treatment effect>5%)
57 = 0.09991233), and unlikely (P(treatment effect>10%) = 0.005172149), respectively, on
58 the probability scale.

59 Strongly Sceptical Prior

60 For our strongly sceptical (SS) prior, (μ=0; σ=2.55; N(0,2.55)), the probability that a
61 person holding this level of belief (about the treatment effect) would observe PT
62 achieving an average gain in CBWC of greater than 0%, 5%, and 10% compared to
63 sham-PT was unlikely (P(treatment effect>0%) = 0.5), unlikely (P(treatment effect>5%)
64 = 0.02495209), and unlikely (P(treatment effect>10%) = 0.00004398719), respectively,
65 on the probability scale. Note that if the MCID was selected as a 5% gain in CBWC, the
66 prior probability of observing a treatment effect as large or larger than this MCID is

0.025 (or 2.5%) on the probability scale, which somewhat matches with the level of confidence utilized in p-value metrics for hypothesis testing. In other words, with our SS prior, there is a 97.5% chance of not observing an MCID of a 5% or greater gain in CBWC. (PT or sham-PT).

BAYESIAN MODEL

We completed a Bayesian simple linear regression using a two-sample model:

$$\mu_i = \beta_0 + \beta_1 x_i$$

Where μ is the mean GROW v.8.0.6.2 calculator CBWC, xi = 0 for the PT group, and xi=1 for the sham-PT group. Therefore, for the PT group, μi = β0 (the intercept), and for the sham-PT group, μi = β0+β1.

The CBWC (GROW v.8.0.6.2 calculator) was regressed on the intervention (PT or sham-PT). Our Bayesian regression model is specified as:

$$y_i \mid \mu_i, \sigma^2, \sim \mathrm{N}(\mu_i, \sigma^2) \text{ where } \mu_i = \beta_0 + \beta_1 x_i.$$

N() is used to denote the normal density function. The prior distributions of these regression parameters, β_0 , β_1 and σ^2, are specified as follows,

$\beta_0 \sim N(\mu = 0, \sigma^2 = 100)$, $\beta_1 \sim N(\mu = 0, \sigma^2 = 10)$, and $\sigma \sim StudentT(\nu = 3, \mu = 0, \sigma = 10)$.

MINIMUM CLINICALLY IMPORTANT DIFFERENCE

We used a range of thresholds for the minimum clinically important difference (MCID) for two reasons. First, we included an MCID of a >0% increase in CBWC with PT compared to sham-PT because this is analogous to the GPT investigators' original frequentist analysis where the null hypothesis was that the mean CBWC of the PT and sham-PT groups were equal and no MCID was specified. Second, we included two additional arbitrary MCID's (>5%, and >10%) because professional societies have not yet agreed upon an MCID in this context as it is difficult to quantify due to the complex interplay between foetal size, growth velocity, and gestational age.

That said, Agarwal, Hugh, and Gardosi have shown that the closer a foetus is to the lower extreme of growth, the more consequential even small changes in CBWC are vis-a-vis stillbirth risk.(4) For example, at 37 weeks' gestation, they demonstrated that a foetus with a CBWC <3rd centile has a two fold risk of stillbirth compared to one with a CBWC in the 3rd to <10th centile range and a five-fold risk of stillbirth compared to one with a CBWC in the normal (10th to 90th centile) range. That said, we acknowledge that arguments could be made to support MCID's in addition to those we chose.

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Supplementary File 3: Additional Discussion

LEFT SHIFT IN CBWC BETWEEN V6.7.8.1 AND V8.0.6.2 GROW CALCULATORS

We acknowledge that the median CBWC dropped (left shift) from 43% (v6.7.8.1 calculator) to 42% (v8.0.6.2 calculator) in the treatment group and from 31% (v6.7.8.1 calculator) to 28% (v8.0.6.2 calculator) in the sham group. The “Ghanaian” ethnicity coefficient was not yet available in the v6.7.8.1 calculator, so the authors used the regional “West African” coefficient for the original GPT analysis, as did we when we replicated it (see Table 1 in our main text). The “West African” coefficient in the v6.7.8.1 calculator was derived from a 10 year database of routine, scan-dated, pregnancies booked and delivered at a single unit (Queen’s Medical Centre, Nottingham, UK).(1) While these data represent West Africans living in the UK, analyses have shown that differences between 1st and 2nd generation migrants are negligible.(1) However, the new centile calculators,(2) including the v8.0.6.2 calculator,(3) allow calculation of CBWC and use an ultrasound-derived estimated fetal weight, for 120 ethnic, country of origin, and region coefficients.(4) The v8.0.6.2 calculator is based on data from over 4 million pregnancies submitted from 33 countries.(4) The “Ghanaian” ethnicity coefficient in the v8.0.6.2 calculator is, therefore, directly based on datasets from Ghana, not West Africans living in the UK as with the v6.7.8.1 calculator. We submit that this key difference between the old (v6.7.8.1) and new (v8.0.6.2) calculators likely accounts for the left shift in the CBWC results. Furthermore, as GROW (Gestation-Related Optimal Weight) sets an “optimal” standard, overall one would expect the CBWC distribution to be left shifted and have more SGA than LGA cases, as it is more common for the growth potential to be not reached than to be exceeded. For reasons cited above, we

also submit that our results with the new (v8.0.6.2) calculator are more representative of the true population.

COMPARISON OF FREQUENTIST AND BAYESIAN PARADIGMS

Null Findings and Sensitivity in the Frequentist Framework

Note that in the course of experimentation, the null hypothesis is never proved or established but is possibly disproved.(5) A type I statistical error, also known as a false positive, occurs when investigators state that a treatment effect exists when it, in fact, does not.(6) A type II statistical error, also known as a false negative, occurs when investigators state that a treatment effect does not exist when, in fact, it does. When a treatment is relatively safe, as is the case with positional therapy (PT), the consequences of committing a type I error are minimal. In contrast, however, the consequences of committing a type II error can be substantial because it may result in patients being denied a treatment with beneficial effects, and may also suggest that further research is not required.(7) Tragically, there are several examples of the latter case occurring in the literature, including fibrinolytics.(8,9)

Whenever null findings are reported, it is important to complete a sensitivity analysis. The 95% confidence interval (95% CI) of the sample mean difference, which was -0.3% to 18.2% in our study, tells us the sensitivity of the experiment directly: if it includes both the value of the null hypothesis (0%) and other interesting effect sizes, e.g., the alternate hypothesis, then the experiment was not sensitive enough to draw definitive conclusions.(10) This is inherent in the true meaning of the 95% CI, which is often misinterpreted by readers of scientific literature as a de facto significance test by

examining whether its endpoints overlap the null value.(11) The 95% CI is computed by finding the set of all values of the dependent variable (customised birthweight centile [CBWC] in our study) that are non-significantly different from the sample mean difference (8.4% in our study) at the 5% level. That is, all the points in our 95% CI (-0.3% to 18.2%) are non-significantly different from the sample mean difference (8.4%), which tells us that the GPT data are consistent with PT both having no effect (0%) and with PT having an effect as large as an 18.2% gain in CBWC. Outside the interval of -0.3% to 18.2%, out to infinity in both directions, all the values are significantly different at the 5% level from the sample mean difference of 8.4% and can be ruled out as possible population values. However, all the points within the 95% CI of the mean difference in CBWC per the GROW standard (version 8.0.6.2) with PT versus sham-PT (-0.3% to 18.2%) cannot be ruled out as population values. As discussed in **Supplementary File 2**, while there is no consensus on the minimum clinically important difference (MCID) in CBWC, our 95% CI contains effect sizes that most clinicians would agree are important clinically such as 5%, 10%, and 15%. For example, a 5% gain in CBWC would boost a growth restricted foetus (<3rd centile by definition) into the 3rd to <10th centile range, halving its stillbirth risk, and a 10% gain in CBWC would boost it into the normal range (10th to 90th centile), reducing its stillbirth risk by five fold.(12)

Approach to Data and Hypotheses

Approaching the data from a different analytical paradigm (Bayesian), however, indicates that it is highly probably or almost certain that nightly maternal PT, compared to sham-PT, during sleep throughout the third trimester confers a significant benefit to foetal growth – even for the sceptic, benefit (>0% gain in CBWC) was highly probable

(0.81). This apparent discrepancy in the results under the frequentist paradigm compared to the Bayesian paradigm is not so much a discrepancy in the results as it is a discrepancy in the way that clinicians think and in the way these two paradigms approach data and hypotheses.

The frequentist asks, "*Does my data fit my hypothesis?*", whereas the Bayesian asks, "*Does my hypothesis fit my data?*". The p-value (frequentist paradigm) is the probability that if the experiment were repeated an indefinite number of times, we would observe results as extreme or more extreme than the results we observed assuming that the null hypothesis is true (i.e., "*Does my data fit my hypothesis?*").(10) As such, the p-value is a long-run frequency; however, clinicians think in terms of conditional probabilities (i.e., "*Does my hypothesis fit my data?*", or in other words, "*What is the probability of my hypothesis being true given my data?*"), not long-run frequencies.(13)

When a clinician encounters a patient, they perform a history and physical exam (data) and estimate a pre-test probability that the patient has a given disease (hypothesis). The clinician orders further investigations of the patient, and based on these results (new data), the post-test probability of disease (hypothesis) is revised, and so on. At no point in this process is the clinician thinking about the patient, the data, and the hypothesis in terms of long-run repeated experiments with a p-value.(6) Furthermore, when it comes to treating a disease with an intervention, clinicians are more interested in knowing the probability that the intervention is effective given the available data (Bayesian thinking) and less interested in the long-run frequency of observing data as extreme or more extreme than that observed previously assuming that the intervention is ineffective (frequentist thinking).

92 **Justification of Reanalysis of a "Negative Trial" with Bayesian Methods**

93 A Bayesian reanalysis of a "negative" trial under the frequentist paradigm does not
94 create positive results nor should it be employed as a statistical alternative in an effort to
95 demonstrate a treatment effect. To demonstrate, it is important to note that if PT had no
96 effect, the posterior probability of PT being better than sham-PT in a Bayesian analysis
97 would be 0.50 on average. That is, a truly futile intervention (not helpful nor harmful)
98 would result in 50% of the area under the posterior probability curve (lighter shade) in
99 **Figure 2** (see **Results** section in main text) being to the left of the 0% threshold and
100 50% being to the right of the 0% threshold. This was not the case seen in our analysis
101 where the bulk of the area under the posterior probability curve – for a menu of priors
102 reflecting varying levels of enthusiasm and scepticism – is located to the right of the 0%
103 threshold, which indicates a treatment benefit. As such, we made a deliberate choice to
104 use Bayesian methods to reanalyze the GPT data because frequentist methods had
105 previously provided an incomplete summary of the results.

106 **LIMITATIONS**

107 **Exclusion of Birth Weight From Bayesian Analysis**

108 The original GPT publication had two primary outcomes: birth weight and CBWC.(14)
109 We did not complete a Baysian analysis of the raw birth weight and, instead, chose the
110 CBWC for analysis for reasons described in the **Limitations** section of the main text.
111 That said, given the p-value (0.14), difference (gain of 110 grams), and 95% CI for the
112 treatment effect of PT on birth weight (−38 to 258 grams) in the original GPT

publication,(14) a Bayesian reanalysis of the GPT birth weights would likely show a beneficial treatment effect of PT on birth weight as we saw with CBWC, especially in light of the birth weight findings in Anderson et al.'s meta-analysis.(15) This meta-analysis reported that for n=57 participants whose going-to-sleep position in the third trimester (after 28 weeks) was supine, their infant's mean (standard deviation) birth weight centile was 3410 (112) grams, and for n=1703 participants whose going-to-sleep position in the third trimester was non-supine, their infant's mean (standard deviation) birth weight centile was 3554 (98) grams. Comparing these two groups, the adjusted mean difference in birth weight was a gain of 144 grams (95%CI: 36 to 253 grams; p-value 0.009) with non-supine going-to-sleep position.

Data-Derived Prior from Meta-analysis

We used data from a recent individual participant data meta-analysis of sleeping position in the third trimester (15) to inform our strongly enthusiastic (SE) prior (see the **Methods** section in main text) for the Bayesian analysis. Following our methodology, based on this meta-analysis, we would approach the GPT with a belief that nightly use of PT from 28 weeks to birth increases CBWC by 9% on average (probability 0.50) compared to sham-PT. This prior distribution corresponds to a probability of 0.99, 0.85, and 0.40 that PT improves CBWC by 0%, 5%, and 10% or more compared to sham-PT. This meta-analysis is a good source of information on which to base our prior belief vis-a-vis the impact of sleeping position on CBWC for at least two reasons: first, it analyses the CBWC using the customised growth standard that we used (GROW), and second, its inclusion criteria stipulated that participants must be at 28 weeks gestation or greater

at the time of interview about their sleeping position, which was the same eligibility criteria employed for participation in the GPT.

However, one major limitation is that the four studies included in the metaanalysis were observational (case-control) studies and, as such, did not use PT and, rather, analysed CBCW in light of the going-to-sleep position. While the going-to-sleep position does not tell the whole story about what happens to sleeping position after sleep onset, a recent study by Wilson et al. gives helpful and relevant insight: in the third trimester, the going-to-sleep position is the dominant sleeping position overnight in the majority (54%) of pregnancies, and the supine going-to-sleep position results in significantly more time spent sleeping supine overnight compared to a non-supine going-to sleep position (48% vs. 22.6%, $p<0.001$).(16) While these findings do not completely assuage this limitation of informing our SE prior from Anderson et al.'s meta-analysis, it may attenuate it until data are available from other interventional trials of PT in pregnancy. Note that as of the writing of the main text of this manuscript, the GPT is the only interventional trial of PT during sleep in pregnancy with foetal growth as an outcome.

Another limitation is that the participant samples of the four studies included in the meta-analysis were drawn from populations in New Zealand, Australia, and the United Kingdom, which are different from the participant sample in the GPT (Ghana). While the GROW CBCW, which the meta-analysis used, accounts for maternal ethnicity and other population-related factors (e.g., maternal height and weight), there may be other population-related factors that affect foetal growth (e.g., socioeconomic status). As such, sleeping position may not affect foetal growth in the same way in different populations; however, one study from the same setting and centre as the GPT,

158 indicates the contrary, at least in the Ghanaian population, and found that the newborns
159 of participants who reported supine sleep during pregnancy were at a five-fold
160 increased risk of low birth weight.(17)

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