

Maternal characteristics and causes associated with refractory postpartum haemorrhage after vaginal birth: a secondary analysis of the WHO CHAMPION trial data

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Objective To assess the maternal characteristics and causes associated with refractory postpartum haemorrhage (PPH).

Design Secondary analysis of the WHO CHAMPION trial data.

Setting Twenty-three hospitals in ten countries.

Population Women from the CHAMPION trial who received uterotonics as first-line treatment of PPH.

Methods We assessed the association between sociodemographic, pregnancy and childbirth factors and refractory PPH, and compared the causes of PPH between women with refractory PPH and women responsive to first-line PPH treatment.

Main outcome measures Maternal characteristics; causes of PPH.

Results Women with labour induced or augmented with uterotonics (adjusted odds ratio [aOR] 1.35; 95% CI 1.07–1.72), with episiotomy or tears requiring suturing (aOR 1.82; 95% CI 1.34–2.48) and who had babies with birthweights ≥ 3500 g (aOR 1.33; 95% CI 1.04–1.69) showed significantly higher odds of refractory PPH compared with the reference categories in the

multivariate analysis adjusted by centre and trial arm. While atony was the sole PPH cause in 53.2% (116/218) of the women in the responsive PPH group, it accounted for only 31.5% (45/143) of the causes in the refractory PPH group. Conversely, tears were the sole cause in 12.8% (28/218) and 28% (40/143) of the responsive PPH and refractory PPH groups, respectively. Placental problems were the sole cause in 11 and 5.6% in the responsive and refractory PPH groups, respectively.

Conclusion Women with refractory PPH showed a different pattern of maternal characteristics and PPH causes compared with those with first-line treatment responsive PPH.

Keywords Postpartum haemorrhage, refractory, uterotonics.

Tweetable abstract Women with refractory postpartum haemorrhage are different from those with first-line treatment responsive PPH.

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Introduction

Postpartum haemorrhage (PPH) occurs in approximately 6% of all live births and despite multiple efforts it remains a leading cause of maternal morbidity and mortality in low- and middle-income countries (LMIC).¹ The World Health Organization (WHO) recommends a set of interventions as first-line treatment for women who start to bleed. These include administration of uterotonic drugs and tranexamic acid, and uterine massage.^{2,3} For women who continue to bleed despite the implementation of the first-line treatment (a condition denoted as 'refractory PPH'), and before proceeding to invasive surgical procedures, the WHO recommends the administration of additional uterotonics, a second dose of tranexamic acid and the use of an intrauterine balloon tamponade (UBT).^{2,3} However, there is limited information about the causes of PPH in women with refractory bleeding, to allow targeted use of interventions. Uterine atony, or failure of the uterus to contract after delivery, is the most common cause of PPH.² However, in an analysis of routinely collected data, Mousa et al. reported that in women with PPH who did not respond to first-line treatment, the main cause of PPH was trauma, accounting for 50% of the cases in either vaginal or caesarean births.⁴

If uterine atony was not the main cause of refractory PPH, then the currently recommended treatment interventions would have limited impact to treat this complication, as they mainly target PPH caused by uterine atony. The results of a stepped-wedge cluster randomised trial of a condom catheter UBT as an option for treatment of unresponsive postpartum bleeding in Egypt, Senegal and Uganda showed that this intervention was ineffective to reduce PPH-related morbidity and mortality, and raised safety concerns.⁵ One of the possible reasons for this negative finding may be that the primary cause of poor outcomes in the study patients was not atony (which is what the UBT was intended to treat) but other causes.

A better understanding of the association of maternal characteristics with refractory PPH and of the causes of the PPH in women who experience refractory PPH is relevant to guide the approaches to management of PPH cases that do not respond to first-line treatment. We, therefore, conducted a secondary analysis of the WHO CHAMPION trial data. The WHO CHAMPION trial was a large study ($n = 29\,645$) comparing heat-stable (HS) carbetocin with oxytocin for PPH prevention.⁶

Methods

Study aims, design and participants

This is a secondary analysis of the WHO CHAMPION trial data (Trial registration number: ACTRN12614000870651).

The aims were to assess the maternal characteristics associated with refractory PPH, and to assess the causes of PPH by comparing women with PPH unresponsive to first-line treatment with uterotonics (refractory PPH), and women with PPH who responded to first-line treatment. Additionally, we describe the treatment interventions received by women with refractory PPH.

The WHO CHAMPION trial was a randomised, double-blind, non-inferiority trial comparing the effectiveness of an intramuscular injection of HS carbetocin with oxytocin administered immediately after vaginal birth. The trial methods and results are described in detail elsewhere.⁷ Briefly, the study randomly assigned almost 30 000 women across 23 sites in 10 countries, to a prophylactic HS carbetocin arm or a prophylactic oxytocin arm. The primary outcomes were the proportion of women with blood loss of ≥ 500 ml or the use of additional uterotonic agents, and the proportion of women with blood loss of ≥ 1000 ml. Secondary outcomes included the proportion of women having additional surgical interventions to control bleeding. Results of this trial were published in June 2018.⁶

Analysis population

As the main interest was to analyse the women with PPH according to their response to first-line treatment, the population for the comparison of maternal characteristics included the women enrolled in the trial who received uterotonics as first-line treatment of PPH. However, for the comparison of causes of PPH, we had to use the sub-population of women who received uterotonics as first-line treatment of PPH and who had blood loss of ≥ 1000 ml (severe PPH), because in the CHAMPION trial the causes of PPH were collected only for women with severe PPH.

Definition of refractory PPH

For this analysis, refractory PPH was defined as PPH in which women received interventions considered as second-line treatment: three or more uterotonics for treatment, or treatment procedures (at least one of suturing cervical or high vaginal tear, bimanual uterine compression, UBT use, exploration of the uterine cavity, uterine or hypogastric artery ligation, uterine compressive sutures (e.g. B-Lynch), or hysterectomy). The cut-off point of three uterotonics or more was adopted because, in the CHAMPION trial, 60% of the women receiving two additional uterotonics for PPH treatment received them within a 5-minute time frame, implying that two uterotonics were often used as first-line treatment. Based on this assumption, we preferred to be conservative, and selected a more demanding threshold of three uterotonics or more ($n = 344$, 11.2% of women receiving additional uterotonics in the CHAMPION trial).

Maternal and childbirth characteristics, and causes of PPH in women with severe PPH

The variables collected in the CHAMPION trial that were selected for the analysis were: maternal age, parity, previous caesarean section, previous PPH, gestational age, uterotonics for labour induction, uterotonics for labour augmentation, instrumental vaginal birth, perineal trauma leading to suture, newborn status at birth and birthweight.

The causes of PPH collected in the trial and used in the analysis were: uterine atony, vaginal/perineal/cervical tear, retained placenta and coagulopathy as clinically defined by the investigators at each of the hospitals. More than one cause could be assigned to each woman with severe PPH.

Statistical analysis

For the analysis of maternal characteristics, counts and percentages of women with refractory PPH in each category of the maternal variables were reported. We conducted logistic regressions with refractory PPH as dependent variable and each exposure variable as independent variable, adding in the model study centre and trial arm, as these were design variables. From these models, odds ratios were obtained for each exposure variable, adjusted only for centre and trial arm, with 95% CIs.

Multivariate logistic regression was used to obtain odds ratios (with 95% CIs) adjusted for centre and arm and for all the other characteristics to separate the effects of each characteristic from other confounding characteristics. The use of logistic regression is appropriate given our aim of studying the association between maternal characteristics and refractory PPH, as it gives the output of odds ratios with confidence intervals, conveniently measuring this association. We performed the selection of independent variables to be included in the model based on scientific knowledge and clinical experience, without performing any stepwise procedure. For the continuous variables (age of the woman and gestational age at birth), we made three categories based on biological knowledge, so that a non-linear gradient could be assessed. We used Wald confidence intervals for the odds ratios, and the *P*-values were obtained from the likelihood ratio chi-square statistic. We assessed the goodness of fit using residual plots and used the log-likelihood as a measure of goodness of fit, but we did not compare different models (see Supplementary material, Table S1). In the tables, we report the relevance and significance of each variable in the model. We did not assess the interaction between independent variables in the model.⁸

For the analysis of causes of severe PPH, counts and percentages were calculated for the refractory PPH and the responsive PPH groups. We did not make any statistical inferences for this comparison because of the small numbers and consequent lack of power. All the analyses were performed with SAS software version 9.4.

The original research that generated the data for this secondary analysis and the conduct of the secondary analysis were supported by MSD, through the MSD for Mothers Program, an initiative of Merck, and HRP.

Results

Of the 29 539 women randomised in the CHAMPION trial who had a vaginal birth and satisfied consent requirements, 3061 (10.4%) received additional uterotonics.⁶ Of these, 497 (16.2%) were unresponsive to PPH first-line treatment and constituted the 'refractory PPH' group. The 2564 (83.8%) women who responded to first-line treatment constituted the 'responsive PPH' group. Of the 497 women with refractory PPH, 143 (28.8%) had blood loss of ≥ 1000 ml (Figure 1). There were three maternal deaths among women who received additional uterotonics; all three in the group of women with refractory PPH. The three maternal deaths were PPH related: one associated with placental abruption, another with placental retention and the third with uterine atony.

Table 1 shows the association of refractory PPH with maternal and delivery characteristics. Nulliparous women, women whose labour was induced or augmented with uterotonics, who delivered beyond 41 weeks of gestational age, had babies with birthweights ≥ 3500 g, or had an episiotomy or tear requiring suturing, showed significantly higher odds of refractory PPH compared with the reference categories in the analysis adjusted only by centre and trial arm. After adjustment for the other maternal characteristics, induced or augmented labour with uterotonics, episiotomy or tears requiring suturing, and having babies weighing ≥ 3500 g remained statistically associated with refractory PPH.

For the subgroup of women receiving additional uterotonics and having blood loss of ≥ 1000 ml ($n = 361$), Figure 2 shows the percentages of women with different causes of severe PPH as the sole cause, by the refractory PPH group ($n = 143$) and the responsive PPH group ($n = 218$). Although atony was the sole PPH cause in 53.2% ($n = 116$) of the women in the responsive PPH group, it only accounted for 31.2% ($n = 45$) of the sole causes in the group of women with refractory PPH. Conversely, although tears were the sole cause in 12.8% ($n = 28$) of the women in the responsive PPH group, it was the sole cause in 28% ($n = 40$) of those in the refractory PPH group. Placental problems were the sole cause in 11% ($n = 24$) and 5.6% ($n = 8$) of the women in the responsive and refractory PPH groups, respectively. Combinations of the above causes were observed in 22.5% ($n = 49$) of women in the responsive PPH group and in 35.0% ($n = 50$) of those in the refractory PPH group. Most of the combinations in either group included atony as one of the causes (data not shown). A sensitivity analysis

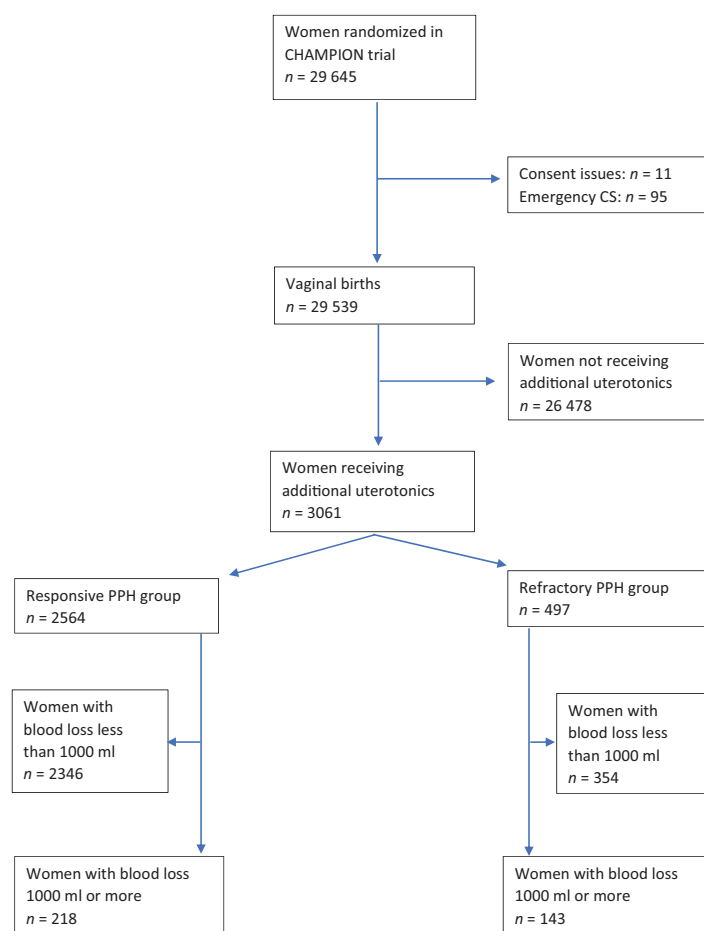


Figure 1. Study diagram. Refractory Group: three or more additional uterotonics ($n = 344$); exploration of the uterine cavity ($n = 27$); bimanual uterine compression ($n = 58$); UBT ($n = 31$); suturing cervical or high vaginal tears ($n = 149$); uterine compression sutures ($n = 0$); artery ligation ($n = 1$); hysterectomy ($n = 7$).

broadening the definition of refractory PPH to also include the use of two additional uterotonics administered separately by more than 5 minutes showed similar results (data not shown).

Of the 143 women in the refractory PPH group with severe PPH, 68.5% received second-line treatment procedures. Suturing of cervical or high vaginal tears was the most frequently used intervention ($n = 59$, 41.3%), followed by bimanual uterine compression ($n = 32$, 22.4%), UBT ($n = 22$, 15.4%) and hysterectomies ($n = 5$, 3.5%). There was only one artery ligation, and no use of compressive uterine sutures (e.g. B-Lynch).

Discussion

Main findings

In this secondary analysis of a large PPH prevention trial in vaginal births, we have shown that 16.2% of the women receiving uterotonics as first-line PPH treatment did not

respond to such treatment and received additional interventions. These women with refractory PPH were more likely to have been induced or augmented with uterotonics, have had episiotomies or tears requiring suturing, and have babies weighing ≥ 3500 g. The causes of severe PPH in women with refractory PPH showed a different pattern to those in women with responsive PPH. While for women with responsive PPH atony was the sole cause in 53% of the cases and traumatic causes were not more than 13%, in refractory PPH both atony and trauma showed similar rates between 28 and 31%. In the same direction, the second-line treatment received by women with refractory PPH showed similar frequencies for interventions to treat cervical or vaginal tears (41.3%) and to treat uterine atony (compressive manoeuvres or UBT 36.4%).

Strengths and limitations

This analysis has several strengths. The WHO CHAMPION trial is the largest PPH prevention trial conducted so far,

Table 1. Refractory PPH according to maternal and delivery characteristics

	All PPH <i>n</i> = 3061	Refractory PPH <i>n</i> (%)	OR* (95% CI)	Lower CL	Upper CL	<i>P</i> -value	OR** (95% CI)	Lower CL	Upper CL	<i>P</i> -value
Age (years)										
<20	170	29 (17.1)	1.44	0.89	2.31	0.1475	1.34	0.82	2.19	0.2463
20–34	2471	405 (16.4)	Ref				Ref			
>34	420	63 (15.0)	0.98	0.71	1.32	0.8367	1.05	0.76	1.45	0.7810
Parity										
Parous	1678	245 (14.6)	Ref				Ref			
Nulliparous	1383	252 (18.2)	1.31	1.06	1.62	0.0123	1.06	0.83	1.36	0.6433
Gestational age (completed weeks)										
<37	211	31 (14.7)	0.82	0.53	1.26	0.3547	1.09	0.68	1.75	0.7070
37–41	2795	445 (15.9)	Ref			–	Ref			
>41	55	21 (38.2)	1.91	1.04	3.54	0.0416	1.71	0.92	3.20	0.0971
Uterotonic for labour induction or augmentation										
No	958	146 (15.2)	Ref			–	Ref			
Yes	2103	351 (16.7)	1.42	1.12	1.79	0.0029	1.35	1.07	1.72	0.0127
Pre-eclampsia during labour or childbirth										
No	2950	473 (16.0)	Ref			–	Ref			
Yes	111	24 (21.6)	0.96	0.58	1.59	0.8719	1.00	0.60	1.67	0.9972
Instrument-assisted vaginal birth										
No	2710	444 (16.4)	Ref			–	Ref			
Yes	351	53 (15.1)	1.11	0.75	1.64	0.6115	0.90	0.60	1.35	0.6172
Perineum										
Intact or tear without suturing	919	94 (10.2)	Ref			–	Ref			
Episiotomy or tear with suturing	2142	403 (18.8)	1.89	1.44	2.48	<.0001	1.82	1.34	2.48	<.0001
Birthweight (grams)										
<2500	150	24 (16.0)	0.67	0.41	1.09	0.0977	0.72	0.43	1.21	0.2077
2500–3499	1920	301 (15.7)	Ref			–	Ref			
≥3500	991	172 (17.4)	1.36	1.08	1.73	0.0101	1.33	1.04	1.69	0.0225
Vital status at birth										
Alive	3031	489 (16.1)	Ref			–	Ref			
Stillbirth	30	8 (26.7)	0.84	0.36	2.00	0.6944	0.87	0.35	2.18	0.7724
Caesarean section in previous deliveries										
Nulliparous	1383	252 (18.2)								
No	1551	233 (15.0)	Ref			–	Ref			
Yes	127	12 (9.4)	0.66	0.34	1.27	0.2005	0.65	0.34	1.24	0.1740
PPH in previous deliveries										
Nulliparous	1383	252 (18.2)								
No	1583	221 (14.0)	Ref			–	Ref			
Yes	95	24 (25.3)	1.33	0.77	2.32	0.3156	1.52	0.88	2.64	0.1415

*Adjusted by study centre and trial arm.

**Adjusted by center, trial arm and all the variables shown in the table.

has a wide representation as women are enrolled from different regions, and collected high-quality data. The fact that it collected detailed information on the use of additional uterotonics, surgical procedures to treat PPH and postpartum blood loss measurement in each woman, allowed us to conduct a thorough analysis on women with PPH.

However, the analysis has several limitations. First, it is an observational secondary analysis of a trial with different aims, which did not collect data on whether women with

PPH responded or not to first-line treatment. Second, in the absence of a formal refractory PPH definition, we constructed our own definition based on the additional treatment received by a woman with PPH. Although a similar approach was used by Mousa et al. in another observational analysis, it has limitations.⁴ On one hand, it assumes that every woman with unresponsive PPH received an additional treatment intervention among those pre-defined in the study. This is likely to have been the case as all

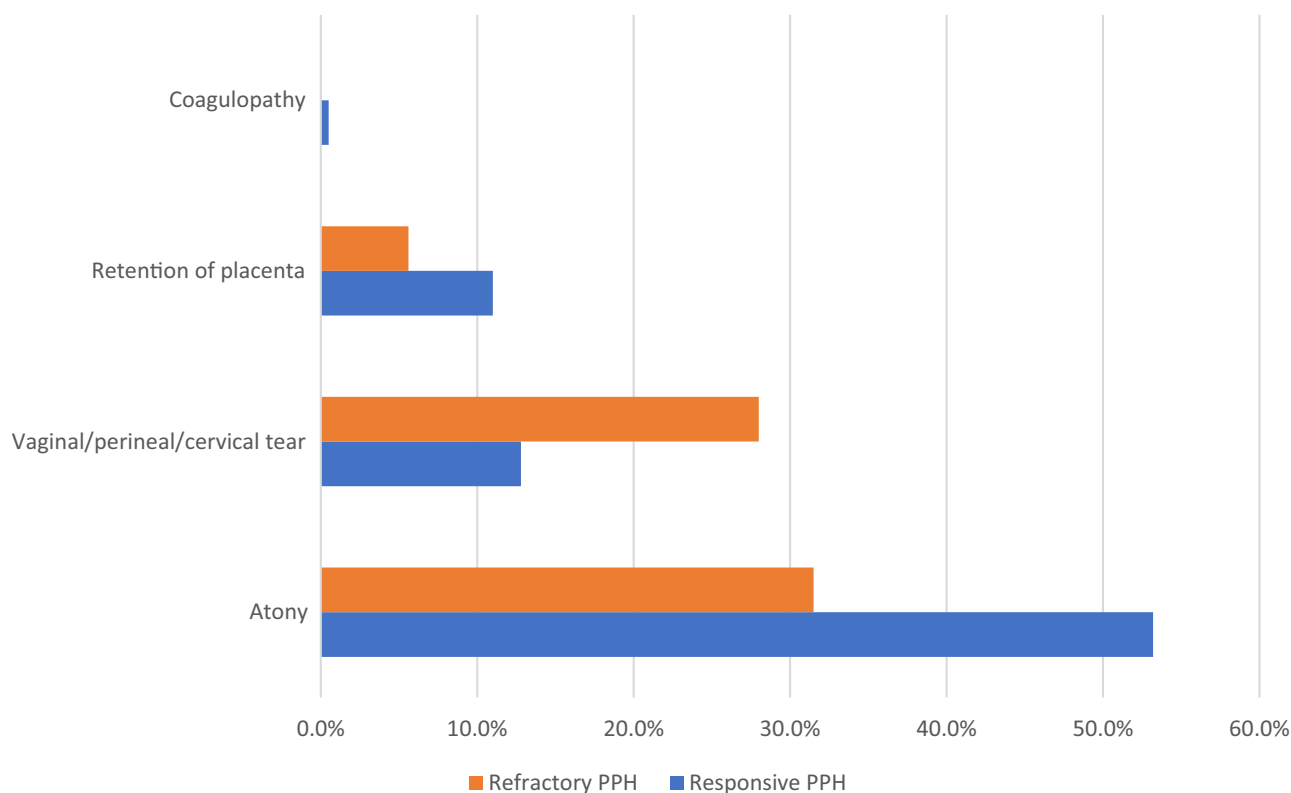


Figure 2. Percentages of women with different causes of severe PPH as the sole cause, for women with refractory PPH and for women who responded to first-line treatment (in women with blood loss ≥ 1000 ml).

participating hospitals are referral facilities with surgical capacities to treat emergency obstetrical complications. In fact, the three maternal deaths in the women included in this analysis were all in the refractory PPH group, meaning that all received additional surgical procedures. However, we cannot exclude that substandard quality of care could have resulted in misclassifying some refractory PPH cases as responsive PPH cases. On the other hand, our definition of refractory PPH did not include those women who received two additional uterotonics for treatment, assuming that most of these cases were first-response treatment of PPH, which might not be the case. However, expanding the definition to also include those who received two additional uterotonics – but not within a 5-minute time-frame – did not change the results. Finally, as the trial collected the causes of bleeding only in those women who bled ≥ 1000 ml, the comparison of causes of bleeding can only be applicable to women with refractory and severe PPH. Similarly, these results are only applicable to women with PPH after single vaginal births at facility level.

Interpretations

Women with refractory PPH were more likely to have been induced with uterotonics, have had episiotomies or tears requiring suturing, and have had large babies. These factors

have already been identified as risk factors of PPH, so it is not surprising that they are also associated with refractory PPH.⁹ This finding suggests that the timely administration of a proven effective treatment with a different mechanism of action, like a different uterotonic from the one used for induction or tranexamic acid, may be important as part of the first-line treatment.^{3,10} When we compare the causes of PPH, the relative contribution of uterine atony decreased from around half of the causes in responsive PPH to one-third in refractory PPH. Conversely, trauma doubled its contribution. This different pattern is very plausible. Uterotonics are known to be very effective first-line treatments for PPH caused by atony. However, high vaginal or cervical tears are not usually identified as the source of bleeding until exploration under anaesthesia, which is often performed only as a second-line intervention.²

Both the rate of refractory PPH and the observed different pattern of causes are consistent with what Mousa et al. reported in another observational analysis. The authors reported that in vaginal births, 21% of women with blood loss of ≥ 1500 ml failed to respond to first-line treatment. Considering that our analysis reported refractory PPH in women with PPH overall, our 16% seems consistent with their 21% figure. Regarding causes, uterine atony was shown to contribute to 52 and 36% of responsive and

refractory PPH cases, respectively, while trauma was 15% in responsive PPH and 50% in refractory PPH. Other studies also reported that the contribution of trauma among the causes of PPH increases with the severity of the PPH.^{11,12}

Conclusion

Women with refractory PPH represent a small, but important group where the majority of the burden related to PPH can be found. The causes of severe PPH showed a rather different pattern in women with refractory PPH compared with those women with responsive PPH. It is important to identify whether trauma is the main cause of refractory PPH, because it might have implications for clinical practice. Women with refractory PPH may benefit from being transferred without delay to a setting in which upper vaginal or cervical trauma could be effectively treated early. Studies to address this issue are a priority.

Disclosure of interests

The authors declare no conflicts of interests. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

MW, GP, GJH, GC, AC, IG, SG, SLL, PL, KM, OO, ZQ and AMG participated in the CHAMPION trial. FA and MW conceived this secondary analysis, GP conducted the statistical analysis, and all authors contributed to the drafting of the manuscript, and to review and approval of the final article.

Details of ethics approval

Ethical approval for the CHAMPION trial was obtained from the WHO Research Ethics Review Committee (WHO ERC) as well as from the ethics review committee of each participating hospital before commencement of the trial. The protocol was first approved by WHO ERC on 2 June 2014.

Funding

The original research that generated the data for this secondary analysis and the conduct of the secondary analysis were supported by MSD, through the MSD for Mothers Programme, an initiative of Merck, and HRP.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Criteria for assessing goodness of fit. ■

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