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Maternal hemodynamics and neonatal birth weight in pregnancies complicated by gestational diabetes: new insights from novel causal inference analysis modeling

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Contribution

What are the novel findings of this work?

In a graphical causal inference model, maternal body mass index (BMI), cardiac output and pulse wave velocity positively influence neonatal birthweight. Among women with gestational diabetes the relationship between hemodynamics and birthweight is similar, although only the relationship between BMI and birthweight reaches statistical significance.

What are the clinical implications of this work?

Fetal growth restriction occurring in pregnancies complicated by gestational diabetes may indicate underlying maternal cardiovascular dysfunction.

Abstract:

Objectives

Normal pregnancy is characterised by significant changes in maternal hemodynamics which correlate with fetal growth. Pregnancies complicated by gestational diabetes (GDM) are associated with large for gestational age (LGA) and macrosomia, but the relationship between maternal hemodynamic parameters and birthweight among women with GDM is yet to be established. Our objective was to investigate the influence of maternal hemodynamics on neonatal birthweight in healthy pregnancies and those complicated by GDM.

Methods

We conducted a prospective cross-sectional case controlled study. GDM was defined as a fasting glucose ≥5.3mmol/L, and/or serum glucose of ≥7.8mmol/L 2 hours following a 75g oral glucose load. Data were collected on maternal characteristics and pregnancy outcomes, including body mass index (BMI) and birth weight centile, adjusted for gestation at delivery. Maternal hemodynamics were assessed using the Arteriograph® and bioreactance techniques at 34-42 weeks gestation. Graphical causal inference methodology was used to identify causational effects of the measured variables on neonatal birthweight centile.

Results

141 women with GDM and 136 normotensive non-diabetic controls were included in the analysis. 62% of the women with GDM were managed pharmacologically, with metformin and/or insulin. Variables included in the final model were cardiac output (CO), mean arterial pressure (MAP), total peripheral resistance (TPR), aortic augmentation index (AIx), pulse wave velocity (PWV) and BMI. Among controls, maternal BMI, CO and aortic PWV were significantly associated with neonatal birthweight. Each standard deviation increase in BMI, CO and PWV produced an increase of 8.4 (p=0.002), 9.4 (p=0.008) and 7.1 (p=0.017) birth weight centiles, respectively. We found no significant relationship between MAP, TPR or aortic AIx and neonatal birthweight.

Among the women with GDM, maternal hemodynamics influenced neonatal birth weight in a similar manner to the control group. Only the relationship between maternal BMI and neonatal birthweight reached statistical significance, with a 1 standard deviation increase in BMI producing a 6.1 centile increase in the birthweight (p=0.019).

Conclusions

Maternal BMI, CO and PWV were determinants of birthweight in our control group. The relationship between maternal hemodynamics and neonatal birthweight is similar between women with GDM and healthy controls. Our findings demonstrate that FGR in pregnancies complicated by GDM may indicate maternal cardiovascular dysfunction. The differences between our findings and that of previous work could be reconciled by a non-linear relationship between MAP and neonatal birthweight, which warrants further investigation.

INTRODUCTION

Normal pregnancy is characterised by an increase in maternal cardiac output (CO)[1, 2], and a decrease in mean arterial pressure (MAP)[2], total peripheral resistance (TPR)[1, 2] and central arterial stiffness (AS)[3, 4]. These changes to the maternal cardiovascular system sustain the increasing utero-placental perfusion and are closely related to fetal growth.

The majority of research in this area has focused on the difference in cardiovascular adaptation between changes in healthy pregnancies, compared to those with restricted fetal growth. Pregnancies complicated by fetal growth restriction (FGR) or small for gestational age (SGA) are characterised by a lower maternal CO[5, 6], and a higher TPR[5-7], aortic augmentation index (AIx)[5, 8, 9] and pulse wave velocity (PWV)[5,10], compared to those with normal neonatal birthweight. Pregnancies complicated by hypertensive disorders are also well known to be associated with FGR[11, 12].

In comparison, the volume of work which has studied maternal hemodynamics across the full spectrum of fetal growth, including pregnancies delivering large for gestational age (LGA), as well as SGA infants, is much smaller. One study has shown neonatal birthweight to have a positive relationship with maternal CO, and a negative linear correlation with TPR and MAP[13]. Two smaller studies, each with 50 subjects, have reported a negative association between birthweight and aortic AIx[14] and PWV[15].

In contrast to hypertensive disorders, pregnancies complicated by gestational diabetes mellitus (GDM) are associated with increased fetal growth, and GDM is considered an independent risk factor for macrosomia[16]. However, the relationship between maternal hemodynamics and neonatal birthweight in pregnancies complicated by GDM is yet to be explored.

Finally, whilst there is some evidence in the literature to describe the relationships between fetal growth and maternal cardiovascular parameters in non-diabetic populations, the study designs and statistical methods employed can only conclude association, but not causality. Causal inference is a statistical technique which utilises domain expertise, often in the form of direct acyclic graphs (DAGs), in order to draw causal rather than associational conclusions.

This method is increasingly being used to handle observational data, for studies attempting to prove hypotheses for which a randomised controlled trial is not feasible[17].

The aim of this pilot study therefore was to investigate the influence of maternal hemodynamics on neonatal birthweight in healthy pregnancies, compared to those complicated by GDM, using a graphical causal inference methodology. The null hypothesis was that maternal hemodynamic variables would not significantly impact neonatal birthweight.

METHODS

We conducted a prospective cross sectional case controlled study of maternal hemodynamics in the late third trimester amongst women attending the antenatal clinic, and subsequently delivering, at the Leicester Royal Infirmary. Participants were identified from women recruited to a larger study of longitudinal maternal haemodynamics between January 2016 and February 2021. Ethical approval was obtained from the East Midlands Research Ethics Committee (15/EM/0469, IRAS 182250), and all women provided written consent to participate. The study was conducted in accordance with STROBE guidelines[18].

We included women aged ≥16 years with a singleton viable pregnancy. Women with pre-existing hypertension or diabetes, cardiovascular disease, or taking medication known to affect cardiovascular function were excluded. Multiple pregnancies, and pregnancies complicated by aneuploidy or fetal abnormality were also excluded. Women who developed pre-eclampsia (PET) or pregnancy induced hypertension (PIH), as defined by the National Institute for Health and Care Excellence (NICE) [19], were excluded from the control group. We also excluded women who did not speak English as funding for translation services for the study was not available. GDM was defined as a fasting glucose ≥5.3mmol/L, and/or a serum glucose of ≥7.8mmol/L 2 hours following a 75g oral glucose load[20].

Data regarding baseline characteristics and pregnancy outcomes were obtained from the electronic maternity records. Maternal age and body mass index (BMI) were recorded at booking; that is, at initial contact with their midwife in the first trimester. Gestational age was calculated from the crown-rump length measured at ultrasound performed between 11+0 to 13+6 weeks gestation. Birth weight centiles were calculated using the Fetal Medicine Foundation Birth Weight Calculator[21]. LGA was defined as birth weight >90th centile, and SGA as birth weight <10th centile.

Haemodynamic Assessment

We included haemodynamic assessments performed between 34+0 to 42+0 weeks' gestation were in the analysis, since cardiovascular adaptations to pregnancy have already reached their peak, and change only minimally during this period[1, 2]. If a participant had more than one assessment during this gestational window, the assessment performed at the later

gestation was included in the analysis. Assessments were performed in a temperature controlled room, free from noise or any other distractions. Patients were positioned in the semi-recumbent position, and were asked not to move or talk during the assessment. All measurements were performed by a researcher who had received appropriate training. The assessments were performed at scheduled appointments between 0900 and 1700. Previous studies have shown that stroke volume (SV), MAP, heart rate (HR), TPR, PWV and AIx are not significantly affected by the time of the day at which they are measured[22].

Maternal hemodynamic parameters were measured using the Arteriograph® (TensioMed Ltd, Budapest, Hungary), which measures AS oscillometrically, through a single, non-invasive BP cuff, and a non-invasive bioreactance method (NICOM®, Cheetah Medical, Portland, Oregon, USA). The Arteriograph® has been validated against invasive assessment of AS in a non-pregnant population undergoing cardiac angiography[23], and shown to have good to excellent repeatability amongst healthy pregnant subjects in the third trimester[22]. Recruits had a minimum of two Arteriograph® readings taken at each visit. Measurements with a standard deviation of ≥1.0 were excluded, as recommended by the Arteriograph® user manual[24], and an average taken of the remaining readings. The NICOM® has significant correlation with CO assessment by transthoracic echocardiography, and good intra-observer reproducibility[25, 26].

Statistical and causal analysis

Statistical analysis was performed using Stata (Version 15.0, StataCorp LLC, College Station, TX, USA). Only cases with a complete data set were included. Continuous data were confirmed as normally distributed using the Kolmogorov-Smirnov analysis, and compared using the mean, standard deviation and t-test. Numerical outliers, defined as those with a value that was >4 standard deviations above or below the mean, were removed from the analysis. Categorical data were compared using the Chi squared test. Results were considered statistically significant if $p<0.05$.

Causal analysis was performed using a graphical causal inference approach in which a causal DAG[17], based on known relationships, was used to systematically identify a set of adjustment variables to eliminate confounding and for use in regression analysis. The R package, Dagitty[27], was used to identify a suitable adjustment set for each relationship of interest. We

selected the smallest set of variables sufficient to mitigate all sources of confounding bias according to the causal DAG, and before estimating the effect of each variable, computed a correlation matrix to identify and remove any highly collinear variables. Data for each variable were standardised (by subtracting the mean and dividing by the standard deviation for all continuous prediction variables). We then used linear regression models[28] to predict the effect of increasing each variable by one standard deviation above its mean on the mean birth weight centile. Insulin and metformin have been shown to reduce endothelial dysfunction and inflammation[29 - 31], however evidence regarding the effect of hypoglycaemic treatment on central haemodynamics in GDM is limited to a single pilot study[32]. We therefore did not include hypoglycaemic treatment as a node on the DAG, but did perform a sub-analysis of the diabetic cohort, using only the women treated with diet therapy to investigate any potential confounding effect from hypoglycaemic agents. A variable was considered to have a statistically significant effect on birth weight centile if the effect estimate 95% confidence intervals did not contain zero.

RESULTS

A total of 141 women with GDM, and 136 non-diabetic, normotensive controls underwent hemodynamic assessment within the inclusion window and were included in the analysis. All participants had a complete data set.

Baseline characteristics, birth outcomes and haemodynamic profiles of the two groups are shown in Table 1. Compared to the controls, women with GDM were significantly older (32 ± 5.2 vs. 29 ± 5.3 years, p<0.001), had a higher BMI at booking (30 ± 6.5 vs. 26 ± 5.6 kg/m^2, p<0.001), and were less likely to be of white ethnic origin (49% vs. 81%, p<0.0001). Gestation at assessment was later in the controls (38+2 ± 2.1 vs. 37+0 ± 1.5 weeks, p<0.001). At the time of assessment, 38% of the GDM group were treated with dietary management, 40% with metformin, 4% with insulin alone and 18% with metformin and insulin in combination. Women with GDM delivered earlier than those in the control group (38^{+6} ± 1.0 vs. 39^{+4} ± 1.3 weeks, p<0.001). The neonatal birth weight for women with GDM was less than that of controls, but after accounting for the earlier gestation at delivery, there was no difference in the birth weight centiles (56 ± 31.3 vs. 53 ± 29.6, p=0.322), or the rates of LGA (15.6% vs 14.7%, p=0.387).

Maternal PWV was significantly higher (8.7 ± 1.4 vs. 8.2 ± 1.2, p=0.003) amongst women with GDM, but there was no difference in maternal CO (p=0.266), TPR (p=0.808), HR (p=0.366), SBP (p=0.965), DBP (p=0.784), MAP (p=0.854) or AIx (p=0.098) between the two groups.

Variables included in the model

The initial graphical model (DAG), showing the variables (nodes) of interest and the relationships between them (edges), is shown in Figure S1, and the final DAG in Figure S2. After removal of variables showing a high degree of collinearity (demonstrated in Figure S3), variables retained in the model were CO, MAP, TPR, aortic AIx, PWV and BMI at booking. Our initial DAG did not include an edge between gestational age and CO, PWV or AIx, since the change in these variables with late gestation is less than at earlier stages of pregnancy[1]. Incorporating an adjustment of these variables for gestation did not significantly change the results, supporting our initial decision not to include this association.

Determinants of neonatal birthweight

Figure 1 shows the relationships between the included variables and birthweight centile in the GDM and control groups. Figure 2 shows the mean overall effects of each variable on birthweight centile and 95% confidence interval in the control and GDM groups, and Figure 3 shows the relative effect of each variable to the birth weight centile.

Among the non-diabetic, normotensive controls, maternal BMI, CO and aortic PWV were significantly associated with neonatal birthweight. Each standard deviation increase in BMI, CO and PWV produced an increase of 8.4 ($p=0.002$), 9.4 ($p=0.008$) and 7.1 ($p=0.017$) birth weight centiles, respectively. We found no significant relationship between MAP, TPR or aortic AIx and neonatal birthweight.

Among the women with GDM, maternal hemodynamics influenced neonatal birth weight in a similar manner to the control group. Only the relationship between maternal BMI and neonatal birthweight reached statistical significance, with a 1 standard deviation increase in BMI producing a 6.1 centile increase in the birthweight ($p=0.019$).

With the exception of MAP, the direction of association between all variables and neonatal birthweight centile remained the same in subgroup analysis of the dietary controlled GDM patients, although none of the associations reached statistical significance (Figure 4).

DISCUSSION

Summary of main findings

We have conducted a prospective case-controlled study using graphical causal inference modelling. Amongst the controls, maternal BMI, CO and PWV showed a significant positive relationship with birthweight. In the GDM group, maternal hemodynamics influenced neonatal birthweight in a similar manner, although only the relationship between maternal BMI and birthweight reached statistical significance.

Interpretation of main findings and comparison with the literature

Previous work in non-diabetic women has also demonstrated a positive relationship between maternal CO, BMI and neonatal birthweight, with neonatal birthweight positively correlating with $\log_{10}$ multiples of the median (MoM) CO ($r=0.117$, $p<0.001$)[13], and increasing by 14.7g for every unit increase in maternal BMI[33].

Our findings of a positive relationship between aortic PWV and neonatal birthweight in our control group contrast with a smaller study, which reported each 1m/s increased in PWV was associated with a 17.6% decrease in birthweight centile[15]. We also did not find a significant relationship between MAP or TPR and birthweight centile in either group, whereas Guy et al[13] reported a negative associations between neonatal birthweight and both MAP ($r= -0.067$, $p<0.0001$) and TPR ($r= -0.133$, $p<0.0001$).

This contrast might be explained by the differences between our population, and that examined by Guy et al[13]. Whilst women who developed PET or PIH were excluded, Guy's population did include women with other conditions known to affect maternal hemodynamics, including chronic hypertension, diabetes, systemic lupus erythematosus and antiphospholipid syndrome. MAP for Guy's study population as a whole is not reported, but data presented for subgroups of cohort show that the lowest observed median and interquartile range for MAP occurred in the appropriate for gestational age (AGA) group, not the LGA group. The data also suggest that our cohort had a lower BP, since the median MAP in our cohort was equal with the 25th centile of Guy's AGA group (84.0mmHg), and the 75th

centile in our cohort (89.5mmHg) overlaps with the median MAP in the AGA group (89.7mmHg)

DBP has an inverted U-shaped relationship with birthweight, which increases as DBP increases up to 70mmHg, plateaus until a DBP of 90mmHg, and then falls as DBP increases further[34]. Maternal chronic hypotension has also been associated with low neonatal birthweight[35, 36]. Since DBP is a function of MAP, we propose that MAP could also be related to birthweight in a non-linear manner. An inverted U-shaped relationship would explain why the Guy's population[13] with higher MAPs showed a negative relationship with birthweight, and our cohort, with a lower distribution of MAP demonstrated both positive and negative relationships producing an overall indeterminate effect.

The relationships between neonatal birthweight and maternal hemodynamics in pregnancies complicated by GDM were highly similar to those seen in normotensive non-diabetic controls. However there was no difference between the two groups in most of the haemodynamic measurements, the birthweight centile, and the rate of LGA. This homogeneity of the two groups may therefore explain the similarity in behaviour of their hemodynamics in relation to neonatal birthweight.

There was no significant interaction between maternal hemodynamic variables and neonatal birthweight amongst women with GDM controlled with diet alone, due to larger confidence intervals for the effect estimates, most likely explained by the smaller sample size of patients in this sub-analysis. With the exception of the MAP, the directions of the associations did not change with the removal of patients controlled by pharmacological management. We have therefore not demonstrated an effect of pharmacological treatment of GDM on the relationship between maternal hemodynamics and birthweight in this cohort.

Strengths and limitations

Causal inference has previously been used to investigate relationships between neonatal birthweight, smoking and perinatal morbidity[37, 38], but to our knowledge, the present study is the first to employ a graphical causal inference methodology to investigate the effect of hemodynamics on birthweight. A strength of this analysis is significant results can be

interpreted not just as associations between the variables, but as causative relationships in which the change in the haemodynamic variable produces the change in birthweight.

Gestational age at hemodynamic assessment was earlier in the GDM, compared to the control group, but since the change in maternal hemodynamics change in the late third trimester is relatively small[1, 2], this is unlikely to have impacted the final results.

Our study is limited by the inclusion of only English speaking women, which had an impact on the number of subjects included in the study and sample size, and by the similarity in hemodynamics and birthweight between the control and study groups.

Clinical and research implications

Our results demonstrate the significant contribution of maternal BMI to neonatal birthweight, and highlight the importance of pre-pregnancy lifestyle interventions, which improve weight loss among overweight and obese women[39].

Since the influence of hemodynamics on neonatal birthweight was similar between both groups, our findings suggest that FGR in pregnancies complicated by GDM could indicate maladaptation of the maternal cardiovascular system. GDM is associated with cardiovascular dysfunction[40, 41], which predates the onset of clinical disease[42, 43], and our results demonstrate the potential impact of this on neonatal birthweight.

Finally, we propose that the contrasting findings regarding MAP and birthweight between the current and previous studies[13] may be explained by a non-linear relationship between these variables. Larger studies involving women with MAP at both the upper and lower extremes are required to test this hypothesis, which has significant implications for BP targets during pregnancy. The Control of Hypertension in Pregnancy Study[44] demonstrated that among women with chronic hypertension and PIH, tight BP control was not associated with any increase in SGA. However, the mean DBP in the tight and 'less tight' groups, were 85.3 and 89.9mmHg respectively – both of which would sit on the plateaued portion of the DBP/birthweight curve proposed by Steer et al[34]. NICE guidelines propose a BP of <135/85mmHg as a goal in the management of gestational hypertensive disorders, but also

acknowledge that there is 'no evidence on target BP levels for PET'[19]. An inverse U-shaped relationship between MAP and neonatal birthweight would therefore identify optimal 'windows' for target BP in pregnancy, in which lower, as well as upper, boundaries of ideal values are defined.

Conclusion

Using a graphical causal inference methodology, we have demonstrated that among women with GDM, maternal hemodynamics influence neonatal birthweight in a similar manner to non-diabetic, normotensive controls. Differences between our findings and those of previous work could be reconciled by a non-linear relationship between MAP and birthweight, which warrants further investigation.

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REFERENCES

1. Mulder EG, de Haas S, Mohseni Z, Schartmann N, Hasson A, Alsadah F, van Kuijk SMJ, van Drongelen J, Spaanderman MEA, Ghossein-Doha C. Cardiac output and peripheral vascular resistance during normotensive and hypertensive pregnancy – a systematic review and mata-analysis. BJOG 2021; https://doi.org/10.1111/1471-0528.16678

2. Meah VL, Cockroft JR, Backx K, Shave R, Stöhr. Cardiac output and related haemdynamics during pregnancy: a series of meta-analyses. Heart 2016; 102: 518-526.

3. Robb AO, Mills NL, Din JN, Smith IBJ, Paterson F, Newby DE, Denison F. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. Hypertension 2009; 53(6): 952–8.

4. Osman MW, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA. Longitudinal study to assess changes in arterial stiffness and cardiac output parameters among low-risk pregnant women. Pregnancy Hypertens 2017; 10: 256–61.

5. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, Lees CC. Early and late preeclampsia are characterized by high cardiac output, but in presence of fetal growth restriction, cardiac output is low: insights from a prospective study. Am J Obstet Gynecol 2018; 218(5): 517.e1-517.e12.

6. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Longitudinal maternal hemodynamics in preganncies affected by fetal grwoth restriction. Ultrasound Obstet Gynecol 2017; 49(6): 761-768.

7. Roberts LA, Ling HZ, Poon LC, Nicolaides KH, Kametas NA. Maternal haemodynamics, fetal biometry and Doppler indices in pregnancies follwed up for suspected fetal grwoth restriction. Ultrasound Obstet Gynecol 2018; 52: 507-514.

8. Perry H, Gutierrez J, Binder J, Thilaganathan B, Khalil A. Maternal arterial stiffness in

hypertensive pregnancies with and without small-for-gestational-age neonate. Ultrasound Obstet Gynecol 2020; 56(1): 44-50.

9. Osman MW, Nath M, Breslin E, Khalil A, Webb DR, Robinson TG, Mousa HA. Association between arterial stiffness and wave reflection with subsequent development of placental-mediated diseases during pregnancy: Findings of a systematic review and meta-analysis. J Hypertens. 2018;36(5):1005–14.

10. Webster LM, Myers JE, Nelson-Piercy C, Mills C, Watt-Coote I, Khalil A, Seed PT, Cruickshank JK, Chappell LC. Longitudinal changes in vascular function parameter in pregnant women with chronic hypertension and association with adverse outcome: a cohort study. Ultrasound Obstet Gynecol 2019; 53(5): 638-648.

11. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 2014; 348: g2301.

12. Odegård RA, Vatten LJ, Nilseon ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstet Gynecol 2000; 96(6): 950-5.

13. Guy GP, Ling HZ, Machuca M, Poon LC, Nicolaides KH. Maternal cardiac function at 35-37 weeks' gestation: relationship with birth weight. Ultrasound Obstet Gynecol 2017; 49: 67-72.

14. Khan F, Mires G, Macleod M, Belch JJF. Relationship between maternal arterial wave reflection, microvascular function and fetal growth in normal pregnancy. Microcirculation 2010; 17(8): 608-14.

15. Elvan-Taspinar A, Franx A, Bots ML, Koomans HA, Bruinse HW. Arterial stiffness and fetal growth in normotensive pregnancy. Am J Hypertens 2005; 18(3): 337-41.

16. He XJ, Qin FY, Hu CL, Zhu M, Tian CQ, Li L. Is gestational diabeted mellitus an independent risk factor for macrosomia: a meta-analysis? Arch Gynecol Obstet 2015; 291(4): 729-35.

17. Tennant PWG, Murray EJ, Arnold KF, Berrie L, Fox MP, Gadd SC, Harrison WJ, Keeble C, Ranker LR, Textor J, Tomova GD, Gilthorpe MS, Ellison GTH. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. Int J Epidemiol 2021; 50(2): 620-632.

18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61(4): 344-9. PMID: 18313558

19. National Institute for Health and Care Excellence (NICE). Hypertension in pregnancy: diagnosis and management [NICE Guideline NG 133]. 2019. https://www.nice.org.uk/guidance/ng133

20. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period [NICE Guideline NG3]. 2015. https://www.nice.org.uk/guidance/ng3

21. Fetal Medicine Foundation: Birth Weight assessment. https://fetalmedicine.org/research/assess/bw [Last accessed 28th February 2021]

22. Osman MW, Leone F, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA. Diurnal variation and repeatability of arterial stiffness and cardiac output measurements in the third trimester of uncomplicated pregnancy. J Hypertens. 2017; 35(12): 2436–42.

23. Horváth IG, Németh Á, Lenkey Z, Alessandri N, Tufano F, Kis P, Gaszner B, Cziráki A. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. J Hypertens 2010; 28(10): 2068–75.

24. Tensiomed: Arteriograph Users Manual. Available from: https://www.tensiomed.com/assets/images/download-pdf/Tensiomed_arteriograph-02v4-00.pdf

25. Vinayagam D, Patey O, Thilaganathan B, Khalil A. Cardiac output assessment in pregnancy: comparison of two automated monitors with echocardiography. Ultrasound Obstet Gynecol 2017; 49(1): 32–8.

26. Doherty A, El-Khuffash A, Monteith C, McSweeney L, Breatnach C, Kent E, Tully E, Malone F, Thornton P. Comparison of bioreactance and echocardiographic non-invasive cardiac output monitoring and myocardial function assessment in primigravida women. Br J Anaesth 2017; 118(4): 527-532.

27. Textor J, ven der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol 2016; 45(6): 1887-1894.

28. Sharma A, Kiciman E. DoWhy: An end-to-end library for causal inference. https://arxiv.org/abs/2011.04216

29. Ding Y, Zhou Y, Ling P, Feng X, Luo S, Zheng X, Little PJ, Xu S, Weng J. Metformin in cardiovascular diabetology: a focused review of its impact on endothelial function. Theranostics 2021; 11(19): 9376 – 9396.

30. Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for endothelial dysfunction. Am J Physiol Endocrinol Metab 2009; 297(3): E568 – 77.

31. Anness AR, Baldo A, Webb DR, Khalil A, Robinson TG, Mousa HA. Effect of metformin on biomarkers of placental – mediated disease: A systematic review and meta- analysis. Placenta 2021; 107: 51- 8.

32. Osman MW, Nath M, Khalil A, Webb DR, Robinson TG, Mousa HA. The effects of metformin on maternal haemodynamics in gestational diabetes: A pilot study. Diabetes Res Clin Pract 2018; 139: 170- 178.

33. Strøm-Roum EM, Tanbo TG, Eskild A. The associations of maternal body mass index with birthweight and placental weight. Does maternal diabetes matter? A population study of 106 191 pregnancies. Acta Obstet Gynecol Scand 2016; 95: 1162–1170.

34. Steer PJ, Little MP, Kold-Jensen T, Chapple J, Elliot P. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: prospective study. BMJ 2004. Doi: 10.1136/bmj.38258.566262.7C

35. Ng PH, Walters WAW. The effects of chronic maternal hypotension during pregnancy. Aus NZ J Obstet Gynaecol 1992; 32(1): 14-6.

36. Grünberger W, Leodolter S, Parschalk O. Maternal hypotension: fetal outcome in treated and untreated cases. Gynecologic Obstetric Invest 1979; 10: 32-8.

37. Hernández-Diaz S, Schisterman EF, Hernán MA. The Birth Weight “Paradox” Uncovered? Am J Epidemiol 2006; 164(11): 1115-1120.

38. Brand JS, Gaillard R, West J, McEachan RRC, Wright J, Voerman E, Felix JF, Tilling K, Lawlor DA. Associations of maternal quitting, reducing, and continuing smoking during pregnancy with longitudinal fetal growth: Findings from Mendelian randomization and parental negative control studies. PLoS Med 2019; 16(11): e1002972.

39. Lan L, Harrison CL, Misso M, Hill B, Teede HJ, Mol BW, Moran LJ. Systematic review and meta-analysis of the impact of preconception lifestyle interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women. Hum Reprod 2017; 32(9): 1925-1940.

40. Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B. Impact of gestational diabetes mellitus on maternal cardiac adaptation to pregnancy. Ultrasound Obstet Gynecol 2020; 56: 240-6.

41. Aguilera J, Sanchez Sierra A, Abdel Azim S, Georgiopoulos G, Nicolaides KH, Charakida M. Maternal cardiac function in gestational diabetes mellitus at 35-36 weeks' gestation and 6 months postpartum. Ultrasound Obstet Gynecol 2020; 56: 247-54.

42. Khalil A, Garcia-Mandujano R, Chiriac R, Akolekar R, Nicolaides KH. Maternal hemodynamics at 11-13 weeks' gestation in gestational diabetes mellitus. Fetal Diagn Ther 2012; 31 (4): 216-20.

43. Gibbone E, Wright A, Vallenas Campos R, Anzoategui S, Nicolaides KH, Charakida M. Maternal cardiac function at 19-23 weeks' gestation in prediction of gestational diabetes mellitus. Ultrasound Obstet Gynecol 2021; 58 (1): 77-82.

44. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, Gruslin A, Helewa M, Hutton E, Lee SK, Lee T, Logan AG, Ganzevoort W, Welch R, Thornton JG, Moutquin J-M. Less-tight versus tight control of hypertension in pregnancy. N Eng J Med 2015; 372: 407-17.

Figures

Figure 1: Relationship between maternal hemodynamic variables and birth weight centile, amongst A) controls, and B) women with GDM. CO = cardiac output, TPR = total peripheral resistance, ao_AIx = aortic augmentation index, MAP = mean arterial pressure.

Figure 2A: Effects of maternal hemodynamic variables on birth weight centile, amongst healthy controls. Plots represent mean and 95% confidence interval. Results are significant if the 95% CI does not include 0. P values for significance are provided adjacent to each plot. Figure 2B: Effects of maternal hemodynamic variables on birth weight centile, amongst women with GDM. Plots represent mean and 95% confidence interval. Results are significant if the 95% CI does not include 0. P values for significance are provided adjacent to each plot. CO = cardiac output, TPR = total peripheral resistance, ao_AIx = aortic augmentation index, MAP = mean arterial pressure.

Figure 3A: Quantitative effects of maternal hemodynamic variables on birth weight centile, amongst controls. Numbers represent change in birth weight centile for an increase of 1 standard deviation in the corresponding variable. Figure 3B: Quantitative effects of maternal hemodynamic variables on birth weight centile, amongst women with GDM. Numbers represent change in birth weight centile for an increase of 1 standard deviation in the corresponding variable. CO = cardiac output, TPR = total peripheral resistance, ao_AIx = aortic augmentation index, MAP = mean arterial pressure.

Figure 4: Effects of maternal hemodynamic variables on birth weight centile, amongst women with GDM controlled by dietary management. Plots represent mean and 95% confidence interval. Results are significant if the 95% CI does not include 0. P values for significance are provided adjacent to each plot. CO = cardiac output, TPR = total peripheral resistance, ao_AIx = aortic augmentation index, MAP = mean arterial pressure.

Figure S1: Initial direct acyclic graph (DAG). A directed acyclic graph (DAG) representing the causal relationships amongst various haemodynamic variables, baseline characteristics, and birthweight. In this DAG, boxes represent variables of interest (nodes) and arrows (edges) represent the direction of known relationships between these variables. The outcome of interest is birthweight, and the other nodes represent the haemodynamics (blue boxes) and

baseline characteristics (black boxes). BMI = body mass index, HR = heart rate, SV = stroke volume, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, TPR = total peripheral resistance, Ao AIx = aortic augmentation pressure, PWV = pulse wave velocity

Figure S2: Final direct acyclic graph (DAG). The final DAG, following the removal of highly collinear variables from the initial DAG. Based on the structure of this DAG, the statistical package, Daggity27, was used to identify a suitable adjustment set for each of the relationships of interest to mitigate confounding bias from the estimates. bmi = body mass index, hr = heart rate, mapr = mean arterial pressure, pp = pulse pressure, tpr = total peripheral resistance, co = cardiac output, ao_aix = aortic augmentation pressure, ao_pwv = pulse wave velocity, bw = birthweight, gest_days = gestational age in days at assessment

Figure S3: Heat map of collinearity. White areas on the map identify variables with a high degree of collinearity. bmi = body mass index, gest_days = gestational age in days at assessment, del_gest_days = gestational age in days at delivery, sbp = systolic blood pressure, dbp = diastolic blood pressure, map = mean arterial pressure, pp = pulse pressure, hr = heart rate, ao_aix = aortic augmentation pressure, ao_pwv = pulse wave velocity, ao_sbp = aortic systolic blood pressure, co= cardiac output, ci = cardiac index, tpr = total peripheral resistance, sv = stroke volume, svv = stroke volume variation

TABLES

Table 1: Comparison of maternal baseline characteristics, haemodynamic assessment and pregnancy outcomes between pregnancies complicated by GDM and controls.

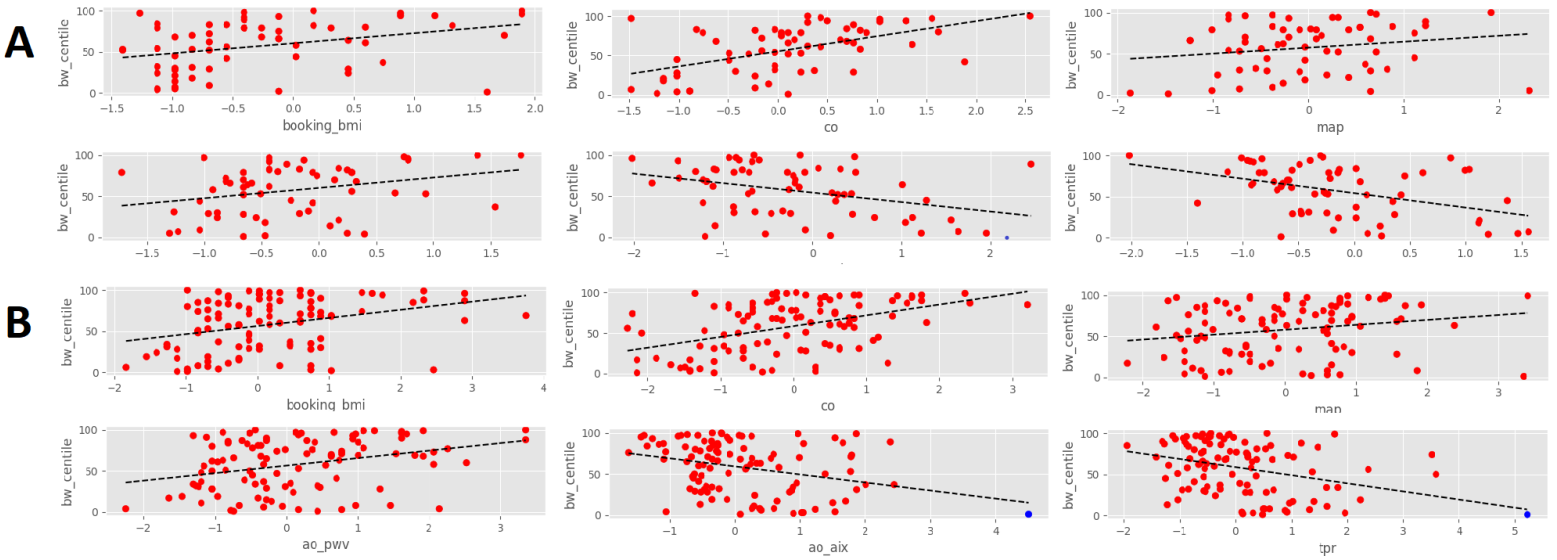
Baseline characteristics	**Control Group (n=136)**	**GDM Group (n=141)**	**P Value**
Maternal age (years)	29 ± 5.3	32 ± 5.2	**<0.001**
Maternal height (cm)	164 ± 7.1	163 ± 7.0	0.252
Maternal weight (kg)	69 ± 17.0	79 ± 21.1	**<0.001***
Maternal body mass index at booking (kg/m^2)	26 ± 5.6	30 ± 6.5	**<0.001***
Parity (n)			0.225
0	61 (44.9)	55 (39.0)	
1	43 (31.6)	50 (35.4)	
2	23 (16.9)	18 (12.8)	
≥3	9 (6.6)	18 (12.8)	
Maternal ethnicity (n)			**<0.001**
African/ Afro-Caribbean	7 (5.1)	16 (11.3)	
South Asian	15 (11.0)	42 (29.8)	
White British/ European	110 (81.0)	69 (48.9)	
Other	4 (2.9)	14 (9.9)	
Current Smoker (n)	4 (2.9)	7 (5.0)	0.389
Maternal haemodynamic assessment			
Gestational age at assessment (weeks)	38^{+2} ± 2.1	37^{+0} ± 1.5	**<0.001**
Cardiac Output (L/min)	7.0 ± 1.37	7.2 ± 1.54	0.266
Stroke Volume (mls)	77 ± 15.3	79 ± 18.4	0.473
Heart Rate (bpm)	92 ± 12.9	93 ± 13.5	0.366
Total Peripheral Resistance (dynes x s/cm^2)	1085 ± 230.6	1078 ± 238.4	0.808
Systolic blood pressure (mmHg)	117 ± 10.2	118 ± 12.4	0.965
Diastolic blood pressure (mmHg)	68 ± 7.9	68 ± 9.9	0.784
Mean arterial blood pressure (mmHg)	84 ± 8.0	85 ± 10.2	0.854

Aortic Augmentation Index (%)	9.5 ± 9.25	11.3 ± 9.42	0.098
Aortic Pulse Wave Velocity (m/s)	8.2 ± 1.21	8.7 ± 1.44	**0.003**
Pregnancy outcomes			
Gestational age at delivery (weeks)	39^{+4} ± 1.3	38^{+6} ± 1.0	**<0.001***
Birth weight (g)	3442 ± 518	3372 ± 461	0.238
Birth weight centile	53 ± 29.6	56 ± 31.3	0.322*
Birthweight categories: (n)			0.387
Small for gestational age	10 (7.4)	17 (12.1)	
Appropriate for gestational age	106 (77.9)	102 (72.3)	
Large for gestational age	20 (14.7)	22 (15.6)	

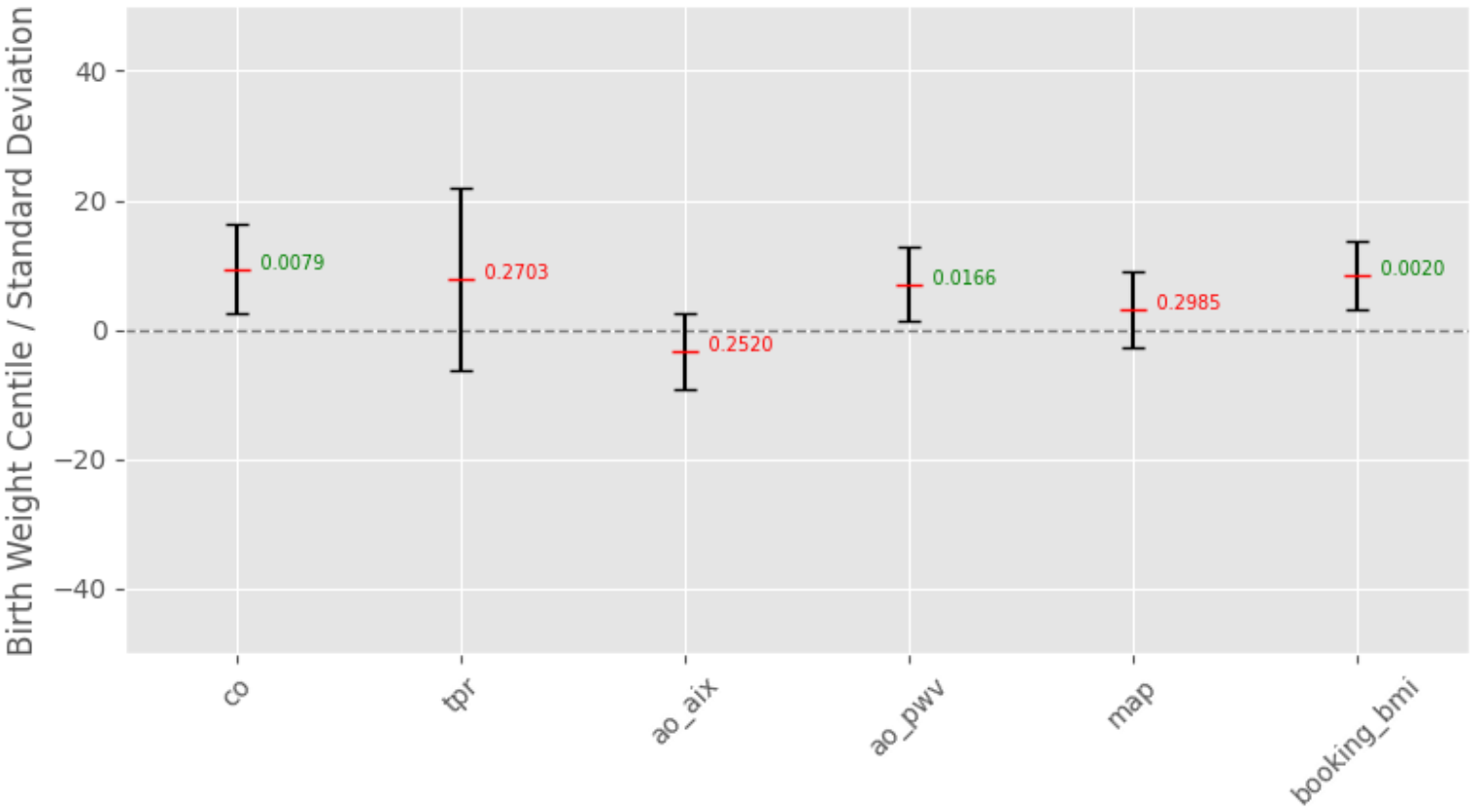
*Indicates Mann-Whitney U test. All other data were analysed by t test for continuous data and Chi-squared test for categorical data.

Data presented as mean ± standard deviation or number (percentage).

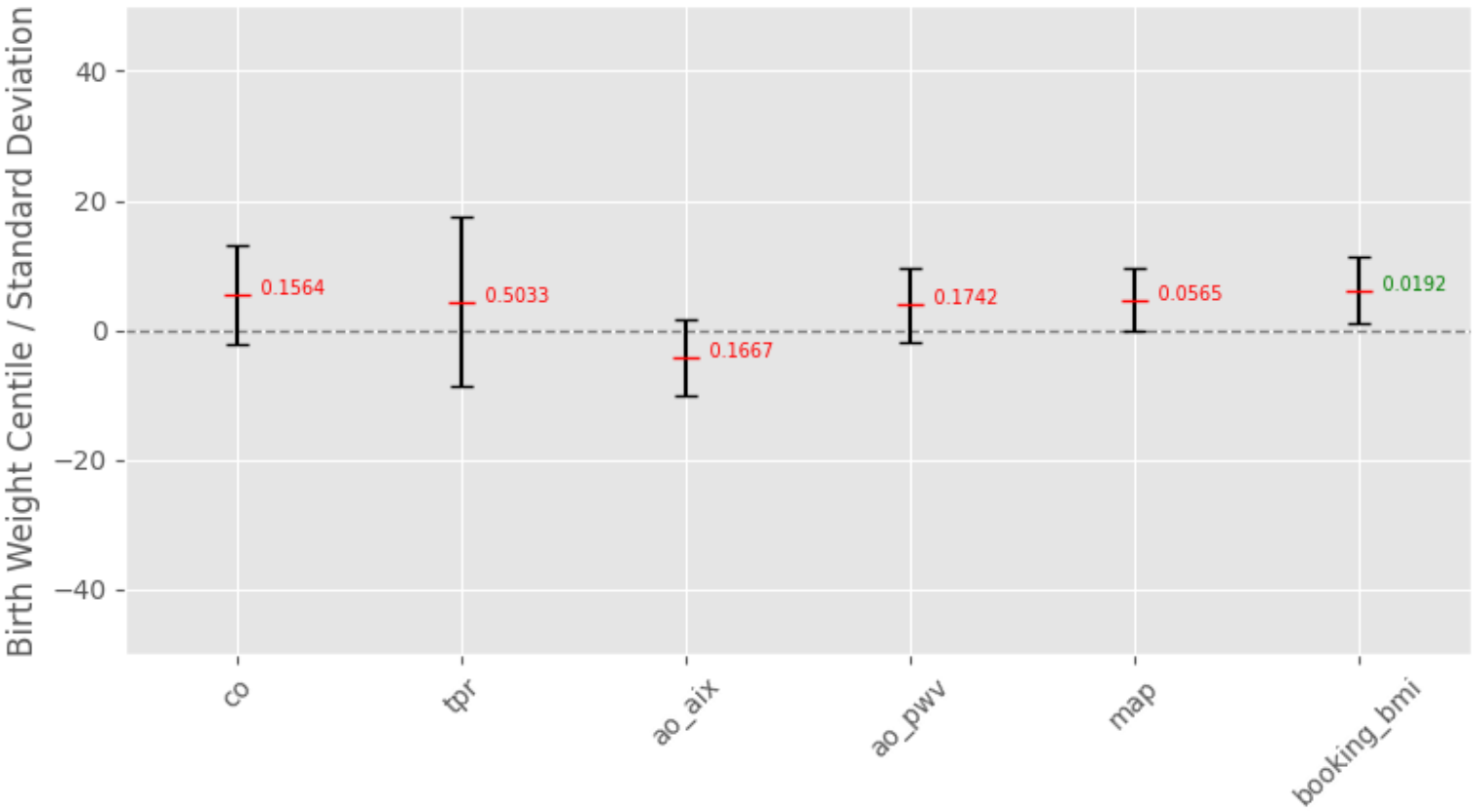
Significant findings are presented in bold.



UOG_24864_Figure 1 Relationship between haemodynamic variables and BW.png



UOG_24864_Figure 2A Effect on BW (Control group).png



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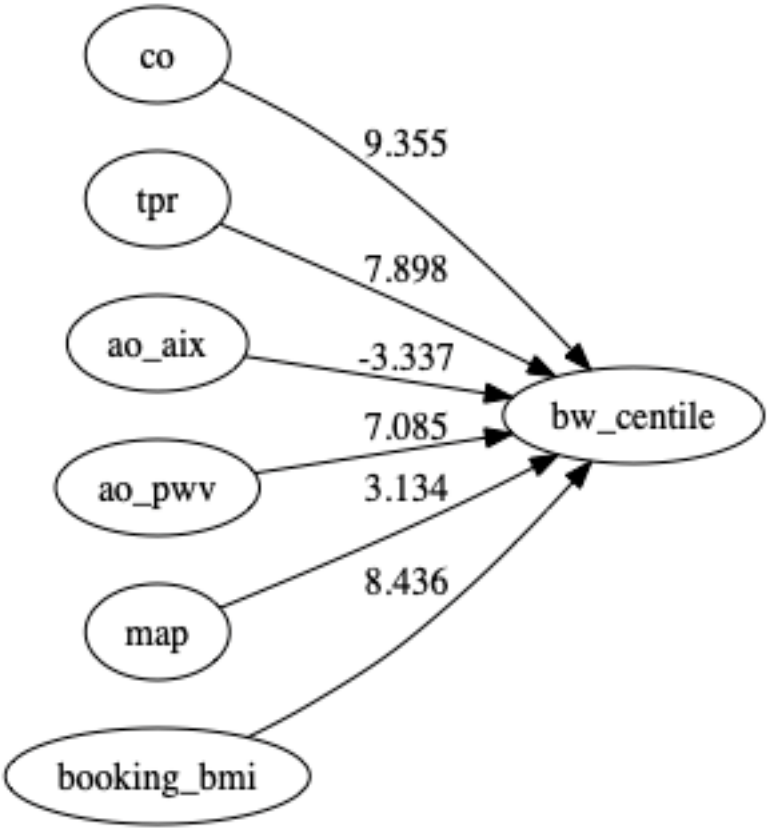
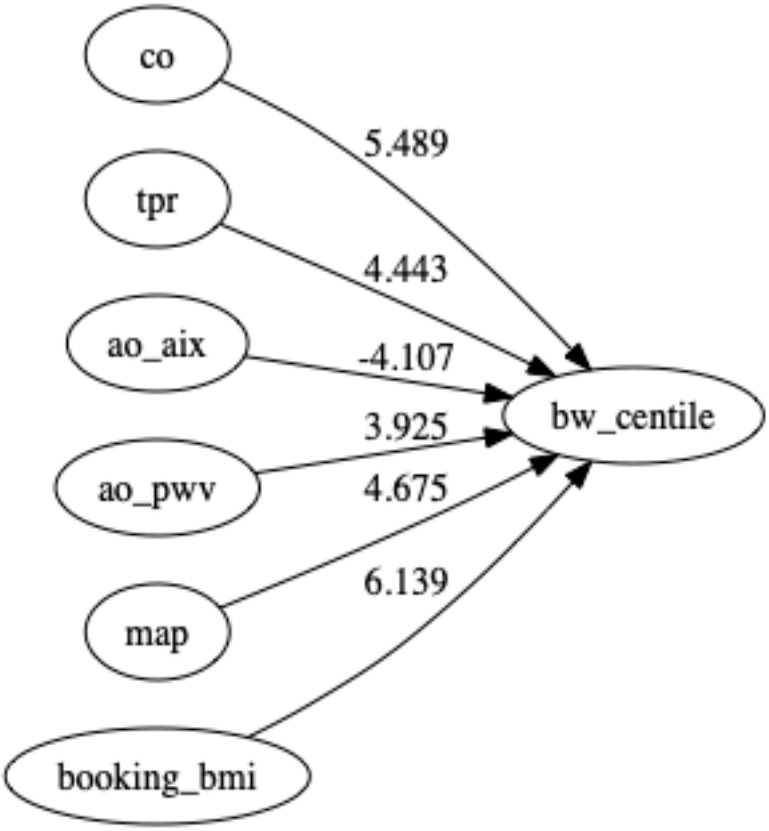


UOG_24864_Figure 3A Quantitative effect on BW (Control group).png



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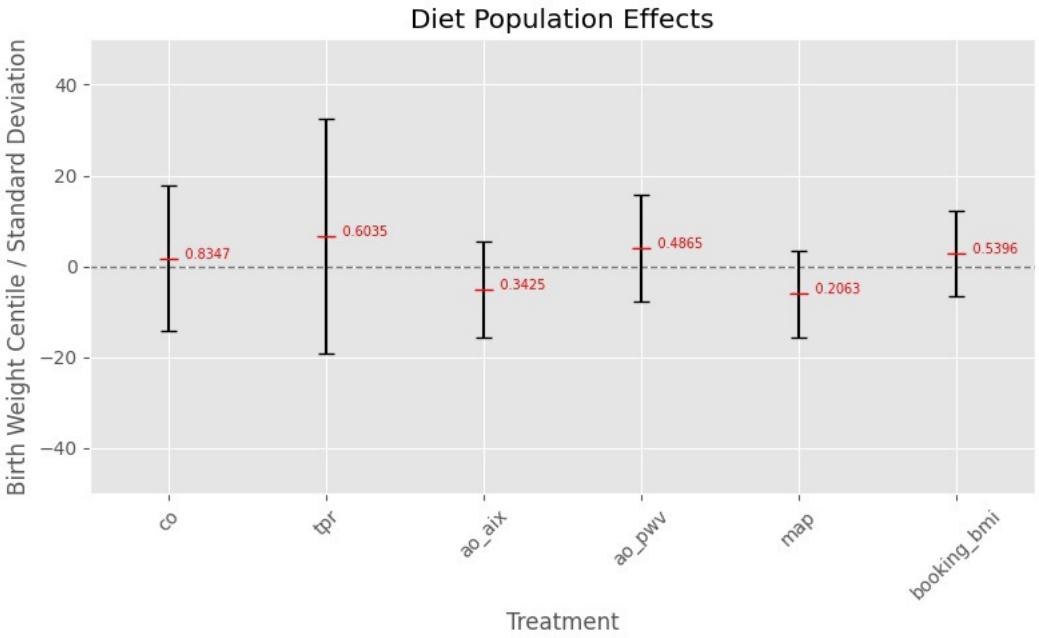

UOG_24864_Figure 4 Effect on BW (Diet subanalysis) JPEG.jpg