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Fetal genetic variants associated with angiogenesis cause altered umbilical blood flow and impacts placental perfusion in pregnancy

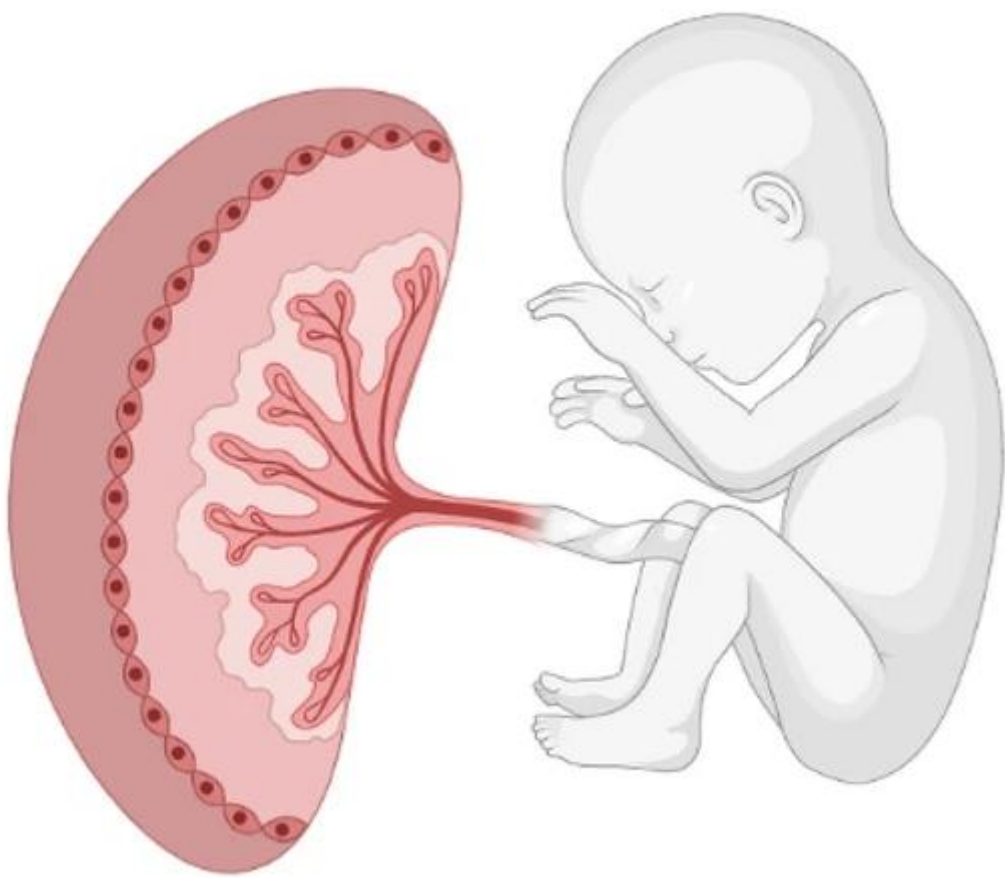
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Introduction:

Fetal growth is ensured by normal implantation, development and function of the placenta. During pregnancy, placenta undergoes extensive adaptations to meet the demands of the growing fetus, including vessel formation (angiogenesis), vessel dilatation, increase in vascular volume, density and permeability. Alterations in these adaptative mechanisms, leading to altered structure and function of the placenta can lead to fetal growth restriction, which is associated with both short- and long-term health consequences for the fetus. Similarly, placental dysfunction can have substantial maternal consequences leading to hypertensive disorders in pregnancy and preeclampsia. There is a body of evidence indicating that defective development of the placental villi and capillary network is associated with fetal growth restriction. Vascular endothelial growth factor (VEGFA) is considered to be one of the most important factors for angiogenesis in placenta. Previous studies have demonstrated that mice in which *VEGFA* have been knocked-out fail to initiate vasculogenesis and die in utero. In addition, mRNA expression of the VEGF family of angiogenic growth factor mRNA expression is reduced in gestational hypertensive disorders, SGA and in pre-term birth, supporting the hypothesis that gene expression of VEGFA variants may influence fetal growth. In a previous genome-wide association study (GWAS) 11 common variants have been identified to be associated with circulating levels of VEGFA, indicating that these variants may be involved in expression levels of VEGFA. The effect of these variants in angiogenesis in placenta is unknown.

In this study, we aimed to test the hypothesis that fetal VEGFA variants have substantial impact on intrauterine growth, blood flow and placental function during pregnancy.

Genetics of Angiogenesis



Fetal growth and blood flow

Methods:

We used data from a prospective pregnancy cohort, known as the Roskilde cohort in which we had genotypes from 665 children. The children were born of mothers who had been included in the Roskilde cohort at approximately 12-13 weeks of gestation and followed with ultrasound-based measurements of fetal weight and blood flow at week 20, 25, 32, as well as data on weight at birth. A total of 1179 singleton pregnant women fulfilling inclusion criteria were included in the study, and all gave oral and written informed consents prior to enrolment. Participants were invited for additional ultrasound examinations at gestational age (GA) 20, 25 and 32 to assess fetal malformations (GA 20), fetal growth and fetal blood flow. Birthweight and placental weight were registered at birth by trained hospital personal. Cord blood samples were collected at birth in 753 out of 1179 pregnancies. However, after exclusion of genotypes that did not pass genotyping quality control (n=52) and exclusion of cases with gestational diabetes, pre-eclampsia, incomplete number of ultrasound examinations, inclusion of pregnancy twice, or presence of an a-cardiac twin (n=36), a total of 665 genotypes from newborns were included in the analyses of this study.

Ultrasound scans were performed by trained sonographers or medical doctors on the following ultrasound equipment: Voluson E8, Voluson Expert 730, Voluson e, and Voluson Logic 7 (General Electric Company, Fairfield, CT, USA). Astraia software version 1.12.9 (Astraia software gmbh, München, Germany) was used. Gestational age was based on ultrasound measurements of the fetal crown-rump length (CRL) at the nuchal translucency scan (12 weeks). Fetal weight was assessed based on two-dimensional ultrasound scans which included measurements of abdominal circumference (AC) in millimeters (mm), bi-parietal diameter (BPD) in mm, occipito-frontal diameter (OFD) in mm and length of the femur bone (FL) in mm. Fetal weight in grams was calculated based on the Hadlock formula. Fetal growth trajectories were modeled using mixed linear regression. We tested the effect of a genetic variants associated with VEGF is a surrogate measure for angiogenesis. We calculated a genetic risk score (GRS) for angiogenesis based on prior GWAS-identified genetic variants associated with VEGF levels in adult populations. The tested the association between the GRS with fetal growth and flow measures.

Results:

In first trimester, the angiogenesis GRS was significantly associated impaired placentation represented by lower PAPP-A levels (p=0.03) and a higher occurrence of notch in the uterine artery in carriers of a high GRS compared to carriers of a low GRS (p=0.028).

The GRS was significantly associated increased pulsatility index (PI) in the umbilical artery (p= 0.032) and there was a trend towards a different slope of gestational decrease in PI in the umbilical artery in fetuses with a high GRS compared to a low GRS. Additionally, we found a significant association between the GRS and placental pulsatility ratio in second and third trimester (p=0.037). However, there was no association between the GRS and placental weight or occurrence of pre-eclampsia. The GRS was significantly associated with fetal growth in second trimester, but not with fetal growth throughout pregnancy.

Table 1: Demographic characteristics of pregnancies

Variable	Mean (SD)
Maternal age (years)	30.2 (4.7)
Maternal pre-pregnancy BMI	24.8 (4.8)
Birth weight (g)	3594 (464.7)
Gestational age at birth (weeks)	279.6 (9.1)
Placental weight at birth (g)	648 (138.7)

Variable	VEGF weighted β (95% CI)	P value
Weight (g) (week 20-32)	2.25e-07 (-4.92e-05; 4.97e-05)	0.843
Weight (g) including BW	2.09e-05 (-5.58e-05; 9.78e-05)	0.752
Weight week 20 (g)	6.07e-06 (-3.34e-05; 4.55e-05)	0.762
Weight week 25 (g)	1.70e-04 (-4.67e-06; 3.45e-04)	0.056
Weight week 32 (g)	-2.18e-04 (-5.41e-04; 1.04e-04)	0.185
Flow MCA (PI)	0.015 (-0.011; 0.041)	0.417
Flow Umbilical artery (PI)	0.003 (0.0004; 0.006)	0.032
Flow Uterine artery (PI)	0.002 (-0.001; 0.006)	0.107
Cerebroplacental ratio (MCA/UA)	0.0008 (-0.367; 0.034)	0.995
Placental pulsatility ratio (UA+UtA/2)	0.004 (0.0001; 0.007)	0.038
Placental weight (g)	1.010 (-2.842 ; 4.863)	0.607

Table 2: Associations between weighted genetic risk score (GRS) for angiogenesis and fetal growth and blood flow

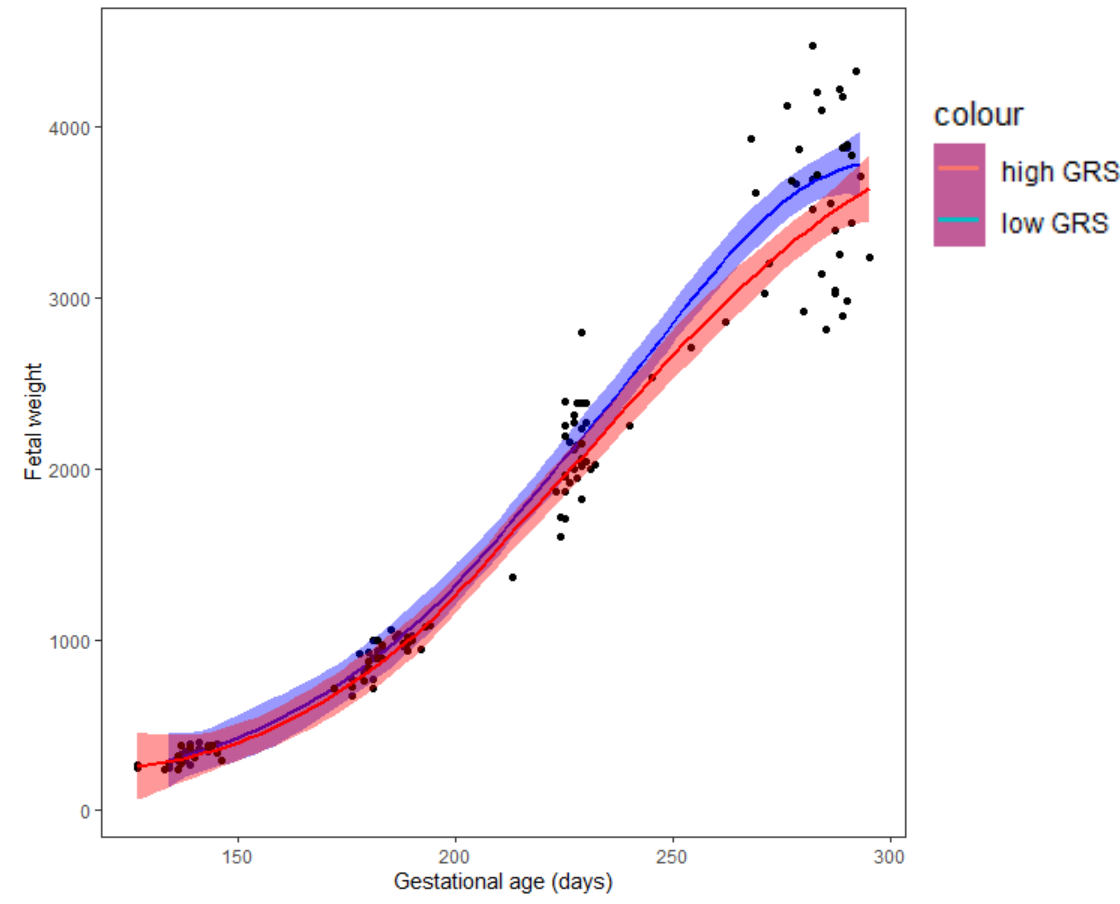


Figure 1: Fetal growth in fetuses with a high vs low GRS for angiogenesis

Conclusion:

We demonstrate that fetal genetic variants associated with angiogenesis have substantial impact on umbilical blood flow as well as on placental perfusion and function throughout pregnancy, which may unravel important physiologic insight into placental function.

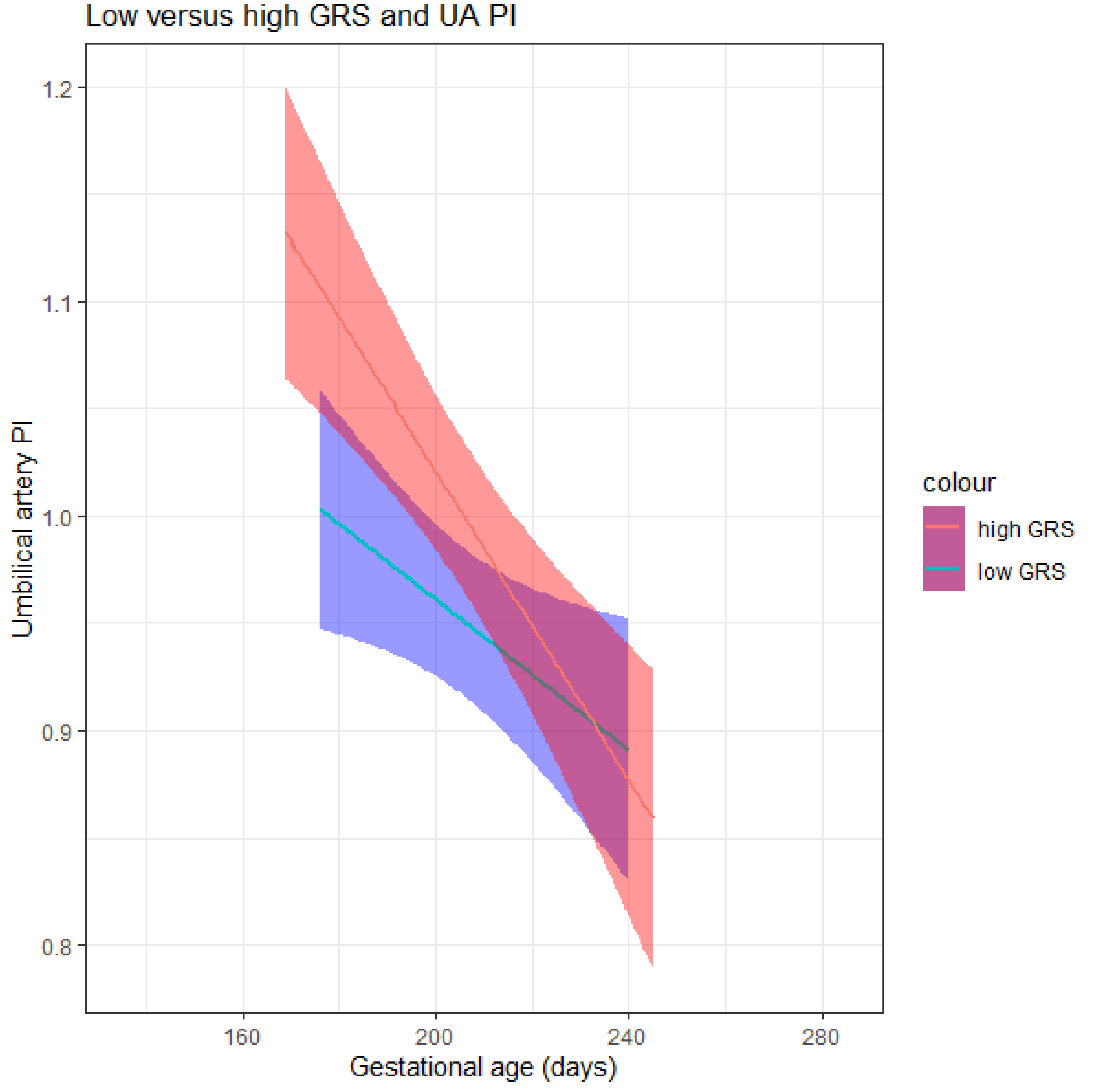


Figure 2. Comparison of a high vs low GRS for angiogenesis ans association with pulsatility index in the umbilical artery

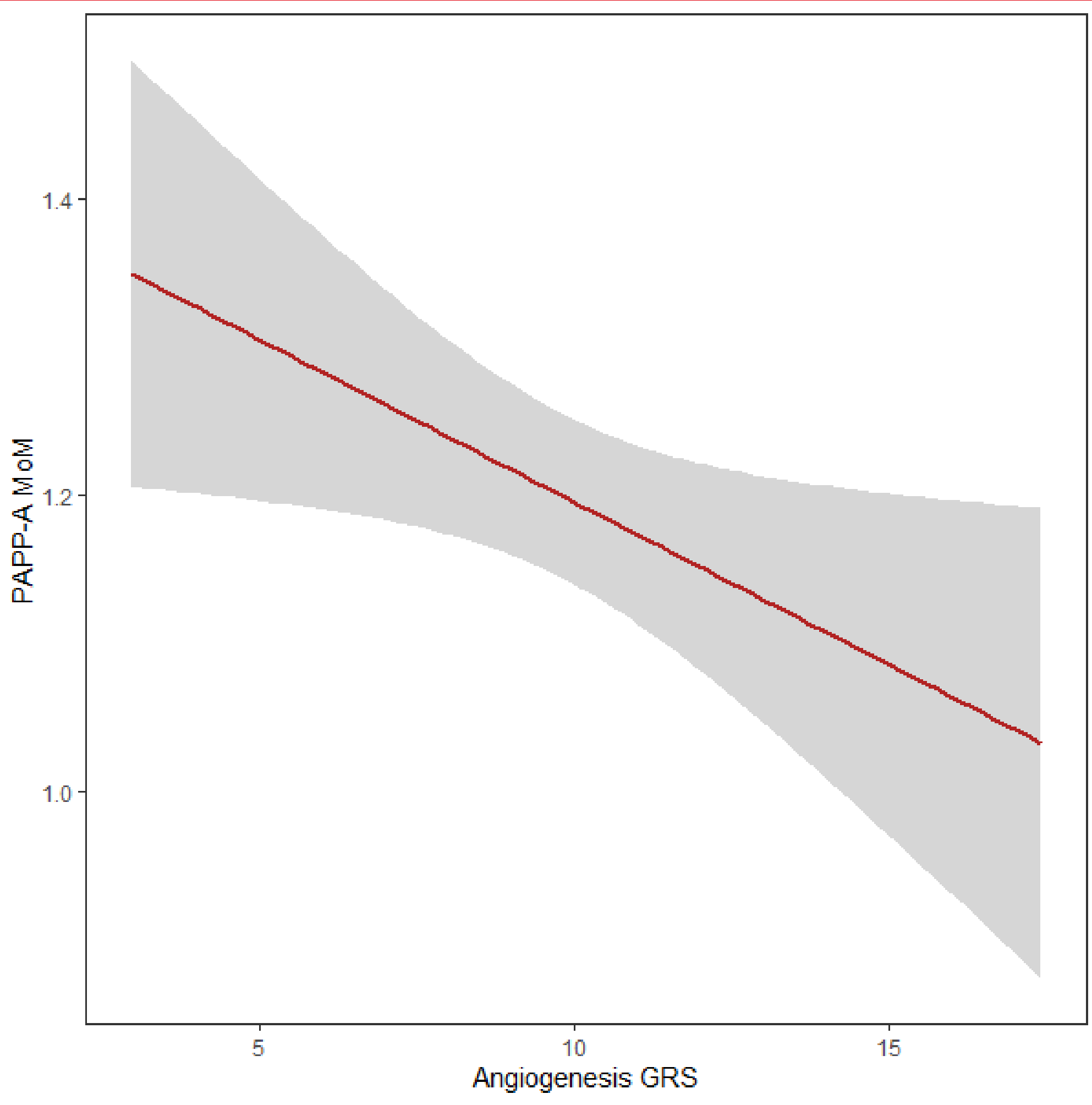


Figure 3. Association between angiogenesis GRS and PAPP-A MoM