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Progressive hematopoietic stem cell mobilization during human pregnancy is associated with cholesterol metabolism

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Running heads: HSC mobilization during human pregnancy

Data-sharing statement: For original data, please contact Hideyuki Oguro (oguro@uchc.edu).

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Contributions

Christine C. Nkemeh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Brandon L. Vu**: Data curation, Investigation, Resources, Writing – review & editing. **Itaevia M. Curry-Chisolm**: Data curation, Investigation, Project administration, Resources, Writing – review & editing. **Shontreal M. Cooper**: Conceptualization, Investigation, Methodology, Writing – review & editing. **Roshini Zachariah**: Data curation, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Wenqi Gan**: Formal analysis, Methodology, Resources, Visualization, Writing – review & editing. **Charissa J. Okang**: Data curation, Investigation, Resources, Writing – review & editing. **Makayla Murphy**: Data curation, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Kwong-Wai Choy**: Conceptualization, Methodology, Supervision, Writing – review & editing. **Winston A. Campbell**: Methodology, Project administration, Supervision, Writing – review & editing. **Andrea D. Shields**: Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Jeffrey G. McDonald**: Data curation, Investigation, Resources, Validation, Writing – review & editing. **Hideyuki Oguro**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Disclosures

No conflicts of interest to disclose.

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Blood cell production substantially increases during pregnancy to support expansion of maternal blood volume and the metabolic demands of the growing fetus. Insufficient erythropoiesis can result in severe anemia, which is associated with increased risks of preeclampsia, preterm delivery, low birth weight, and stillbirth.[1] Hematopoietic stem cells (HSCs) maintain lifelong hematopoiesis through self-renewal and multilineage differentiation.[2] Adult HSCs reside primarily in the bone marrow, and only a small fraction circulates in peripheral blood under steady-state conditions. Although physiological and pharmacologic stimuli can induce HSC mobilization into peripheral blood, whether increased erythropoietic demand during pregnancy alters HSC mobilization in humans remains unknown.

Using mouse models, our previous study showed that pregnancy induces HSC mobilization into the spleen via circulation, thereby expanding the capacity for red blood cell (RBC) production.[3] This process is mediated by 27-hydroxycholesterol (27HC),[4] the most abundant oxysterol in human plasma.[2] Mice deficient for *Cyp27a1*, which encodes the sterol hydroxylase required for conversion of cholesterol to 27HC,[2] display impaired HSC mobilization and reduced splenic erythropoiesis during pregnancy.[4] Consistent with these observations, spleen size increases during pregnancy in mice and correlates positively with litter size and splenic erythropoietic activity.[5] In humans, spleen size increases linearly with gestational age,[6] and splenectomy is an independent risk factor for preterm delivery.[7] These findings suggest that splenic hematopoiesis may contribute to fetal growth and pregnancy outcomes.

Cholesterol metabolism may play an important role in this process. Elevated cholesterol levels promote HSC mobilization in both mice[8] and humans,[9, 10] and plasma 27HC levels increase in parallel with total cholesterol.[11] We previously demonstrated that 27HC supplementation or pharmacological inhibition of the 27HC-metabolizing enzyme Cyp7b1 augments HSC mobilization in mice.[12] Both total cholesterol and 27HC levels increase during human pregnancy.[13]

Together, these observations suggest that pregnancy-associated changes in cholesterol metabolism may promote HSC mobilization to meet increased hematopoietic demand. However, whether HSC mobilization changes during human pregnancy and how it relates to cholesterol metabolism remain unknown.

To address these questions, we performed a longitudinal analysis of circulating HSCs, plasma total cholesterol, and oxysterol levels during pregnancy. This study was approved by the UConn Health Institutional Review Board. Peripheral blood samples were collected during the first (5-14 weeks), second (16-24 weeks), and third (28-32 weeks) trimesters, at delivery, and postpartum (4-6 weeks), and were compared with non-pregnant controls. Inclusion criteria for pregnant participants included female sex, age 18-40 years, and singleton pregnancy at <14 weeks of gestation. Inclusion criteria for non-pregnant controls included female sex, age 18-40 years, and negative pregnancy test. Exclusion criteria for pregnant and non-pregnant participants included hypercholesterolemia, a history of malignancy (unless disease-free for ≥5 years), congestive heart failure, recent (≤6 months) unstable cardiovascular disease, renal or hepatic dysfunction, diabetes, immunodeficiency, autoimmune disease, current use of prescribed medications more than three times per week for >2 weeks (excluding prenatal vitamins or supplements), recent (≤3 months) trauma or surgery, substance or alcohol abuse; and incarceration. Baseline characteristics and pregnancy outcomes are summarized in **Supplementary Table S1**. A total of 67 participants completed the study, including 41 pregnant participants with singleton pregnancies and 26 non-pregnant controls (**Supplementary Figure S1**).

Circulating $CD34^{+}CD38^{-}$ HSCs increased progressively from the first trimester through the third trimester and delivery (**Figure 1A**). HSC numbers during the second and third trimesters and at delivery were 2.1-, 2.6-, and 3.3-fold higher, respectively, than postpartum levels. Circulating HSC numbers in the third trimester and at delivery were also significantly higher than those in non-

pregnant controls (2.2- and 2.8-fold, respectively). Linear mixed-effect model analysis across all trimesters and delivery revealed a significant positive association between circulating HSC numbers and gestational age (**Figure 1B**). Given that maternal blood volume increases by approximately 30-50% during pregnancy,[14] the total number of circulating HSCs is likely even greater than indicated by the observed changes in frequency. These findings demonstrate a progressive increase in circulating HSCs during human pregnancy.

In contrast, mobilization of $CD34^+CD38^+$ hematopoietic progenitor cells (HPCs), which include lineage-committed progenitors but exclude multipotent progenitors and HSCs, peaked during the second trimester and declined significantly at delivery and postpartum (**Figure 1C**). Mobilized HPC numbers during the second trimester were significantly higher than those in non-pregnant controls. Notably, a modest but significant negative association was observed between mobilized HPC numbers and gestational age (**Figure 1D**). These findings suggest that HSCs and HPCs respond differently to pregnancy-associated mobilizing signals and that progenitor mobilization occurs earlier in pregnancy to rapidly support increased hematopoietic demand.

Complete blood counts showed the expected physiological changes, including decreased RBC counts and hemoglobin concentrations and increased white blood cell (WBC) counts during pregnancy (**Supplementary Figure S2A-C**). Platelet counts remained relatively stable in this cohort (**Supplementary Figure S2D**).

Total cholesterol levels increased significantly during the second and third trimesters and at delivery compared with the first trimester, postpartum, and non-pregnant controls (**Figure 2A**). Circulating HSC numbers were positively associated with total cholesterol levels (**Figure 2B**), whereas HPC numbers did not show a significant association (**Figure 2C**). Low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels increased during

pregnancy (**Supplementary Figure S2E-G**), as expected. Although mild increases in total bile acid levels during pregnancy have been reported,[15] no significant change was observed in this cohort (**Supplementary Figure S2H**).

Plasma 27HC levels, quantified by liquid chromatography-mass spectrometry, increased significantly during pregnancy compared with non-pregnant controls (**Figure 2E**), consistent with a previous report of modest increases during later trimesters.[13] As expected, 27HC levels strongly correlated with total cholesterol levels (**Figure 2D**).[11] Importantly, plasma 27HC levels were positively associated with mobilized HSC numbers but not HPC numbers (**Figure 2F-G**), similar to the relationship observed with total cholesterol.

We also measured two additional major oxysterols, 7α-hydroxycholesterol (7αHC) and 25-hydroxycholesterol (25HC). Plasma 7αHC levels, but not 25HC levels, increased significantly during pregnancy compared with non-pregnant controls (**Figure 3A-B**). However, neither oxysterol was associated with total cholesterol levels or circulating HSC or HPC numbers during pregnancy (**Figure 3C-H**).

Collectively, these results demonstrate that circulating HSCs progressively increase during human pregnancy and return to baseline postpartum. In contrast, HPC mobilization peaks earlier in pregnancy, suggesting that distinct hematopoietic populations respond differently to gestational physiological signals. This temporal pattern may reflect early mobilization of progenitors to rapidly support increased hematopoietic output, followed by progressive HSC mobilization to sustain long-term hematopoietic demand as maternal blood volume expands. Although HSCs and HPCs are regulated by shared mobilization pathways, including CXCL12-CXCR4 signaling, their distinct kinetics may reflect differences in niche retention, CXCR4 expression or downstream signaling, sensitivity to mobilizing cues, or responsiveness to pregnancy-associated metabolic, hormonal,

and inflammatory signals.

Our findings also suggest an association between cholesterol metabolism and HSC mobilization during pregnancy. Total cholesterol levels increased during pregnancy and positively correlated with circulating HSC numbers. Importantly, 27HC also correlated with HSC mobilization, whereas 7αHC and 25HC did not. These observations are consistent with our previous studies in mice demonstrating that 27HC promotes HSC mobilization and splenic erythropoiesis during pregnancy.[4] The selective association of 27HC with HSC mobilization may reflect metabolite-specific biological effects. Whereas 27HC is an abundant cholesterol-derived oxysterol that correlates with total cholesterol and promotes HSC mobilization in mice, 7αHC or 25HC arise through distinct metabolic pathways and may exert different biological activities. Although plasma 27HC levels increased modestly but significantly during pregnancy in this cohort, circulating concentrations may not fully reflect local production, intracellular transport, or bioavailability within hematopoietic niches. Thus, localized 27HC production or altered HSC sensitivity to 27HC may also contribute to pregnancy-associated mobilization.

These findings have broader implications for understanding physiological regulation of hematopoiesis. Pregnancy represents a unique systemic stress requiring coordinated metabolic and hematopoietic adaptation. The association between cholesterol metabolism and HSC mobilization suggests that lipid-derived signaling molecules may link systemic metabolic changes to HSC regulation. Our prior mouse studies showed that pregnancy promotes HSC mobilization to the spleen and enhances splenic erythropoiesis. These raise the possibility that increased circulating HSCs during human pregnancy may also reflect trafficking to extramedullary hematopoietic sites. Consistent with this possibility, human spleen size increases with gestational age,[6] suggesting that the spleen may contribute to hematopoietic adaptation during pregnancy.

This study has several limitations. The sample size is modest, with attrition at postpartum that may introduce bias despite the use of mixed-effects models. The observational design precludes causal inference. Future studies are needed to determine whether these findings extend to multifetal gestations and pregnancy-related complications and whether similar mechanisms regulate HSC trafficking in other hematologic or physiological conditions. In addition, circulating HSC measurements may not fully reflect functional hematopoietic activity, HSC homing, splenic hematopoiesis, or tissue-level dynamics. Direct assessment of extramedullary hematopoiesis was not feasible in this human cohort and remains an important area for future investigation.

In summary, we provide the first evidence that circulating HSC numbers increase during human pregnancy and identify an association between HSC mobilization and cholesterol metabolism. These findings reveal a previously unrecognized physiological adaptation of the human hematopoietic system and suggest a metabolic axis linking cholesterol-derived oxysterols to HSC trafficking.

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Figure Legends

Figure 1. Increased HSC and HPC mobilization during pregnancy.

(**A**,**C**) Absolute numbers of circulating $CD34^{+}CD38^{-}$ hematopoietic stem cells (HSCs) (**A**) and $CD34^{+}CD38^{+}$ hematopoietic progenitor cells (HPCs) (**C**) in peripheral blood from non-pregnant controls (Ctrl; n=26) and pregnant participants during the first (1st; n=41), second (2nd; n=38), and third (3rd; n=38) trimesters, at labor and delivery (L&D; n=38), and postpartum (Post; n=16). Absolute HSC and HPC numbers (cells/mL) were calculated by multiplying white blood cell counts obtained from complete blood counts by the corresponding flow cytometric frequencies within the $CD45^{+}$ viable singlet population. Data are presented as box-and-whisker plots showing the median, interquartile range, and minimum-to-maximum. Outcomes were analyzed using linear regression with visit as the main predictor, adjusted for age. Pairwise comparisons were performed using estimated marginal means with Tukey's method to adjust for multiple testing (*P<0.05, **P<0.01, ***P<0.001).

(**B**,**D**) Association between circulating HSC (**B**) or HPC (**D**) numbers and gestational age using combined data from all trimesters and delivery (n=155 samples from 41 participants). Associations were assessed using linear mixed-effects models with log-transformed cell counts, adjusted for age. Models account for within-individual correlation arising from repeated observations and accommodate unbalanced numbers of measurements across participants. Fixed effects were used to estimate the average association between predictors and outcomes, and a random intercept was included for each participant to account for between-subject variability. Regression coefficients (β) are shown with 95% confidence intervals (CI).

Figure 2. HSC mobilization correlates with cholesterol and 27HC during pregnancy.

(**A**,**E**) Plasma total cholesterol (**A**) and 27-hydroxycholesterol (27HC) (**E**) levels in non-pregnant controls (Ctrl, n=26) and pregnant participants (1st, n=41; 2nd, n=38; 3rd, n=38; L&D, n=38; Post,

n=16). Outcomes were analyzed by linear regression with visit as the main predictor, adjusted for age, followed by Tukey-adjusted pairwise comparisons (*P<0.05, **P<0.01, ***P<0.001).

(**B**-**D**,**F**,**G**) Associations between plasma total cholesterol and circulating hematopoietic stem cell (HSC) (**B**) or hematopoietic progenitor cell (HPC) (**C**) numbers, or 27HC levels (**D**), and between plasma 27HC and circulating HSC (**F**) or HPC (**G**) numbers, using combined data from all trimesters and delivery (n=155 samples from 41 participants). Associations were assessed using linear mixed-effects models with log-transformed cell counts.

Figure 3. Plasma 7αHC and 25HC levels during pregnancy.

(**A**,**B**) Plasma 7α-hydroxycholesterol (7αHC) (**A**) and 25-hydroxycholesterol (25HC) (**B**) levels in non-pregnant controls (Ctrl, n=26) and pregnant participants (1st, n=41; 2nd, n=38; 3rd, n=38; L&D, n=38; Post, n=16). Data were analyzed by linear regression with visit as the main predictor, adjusted for age, followed by Tukey-adjusted pairwise comparisons.

(**C**-**H**) Associations between plasma total cholesterol and 7αHC (**C**) or 25HC (**D**), and between 7αHC and circulating hematopoietic stem cell (HSC) (**E**) or hematopoietic progenitor cell (HPC) (**G**) numbers, as well as 25HC and circulating HSC (**F**) or HPC (**H**) numbers, using combined data from all trimesters and delivery (n=155 samples from 41 participants). Associations were assessed using linear mixed-effects models with log-transformed cell counts.

Figure 1

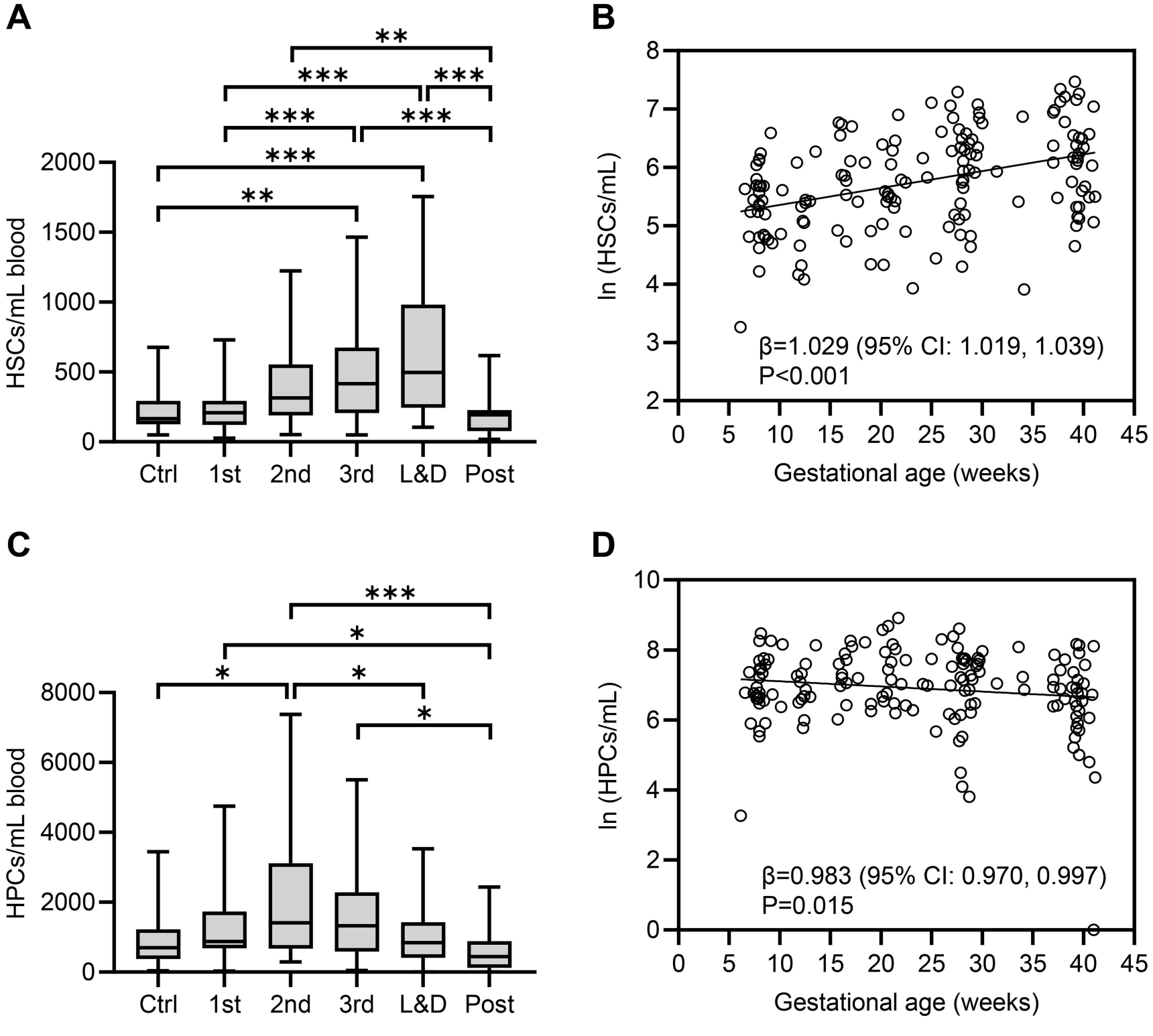

A
HSCs/mL blood
2000
1500
1000
500
0
Ctrl
1st
2nd
3rd
L&D
Post
**
***
***
***
***
**
B
ln (HSCs/mL)
β=1.029 (95% CI: 1.019, 1.039)
P<0.001
Gestational age (weeks)
C
HPCs/mL blood
8000
6000
4000
2000
0
***
*
*
*
*
D
ln (HPCs/mL)
β=0.983 (95% CI: 0.970, 0.997)
P=0.015
Gestational age (weeks)

Figure 2

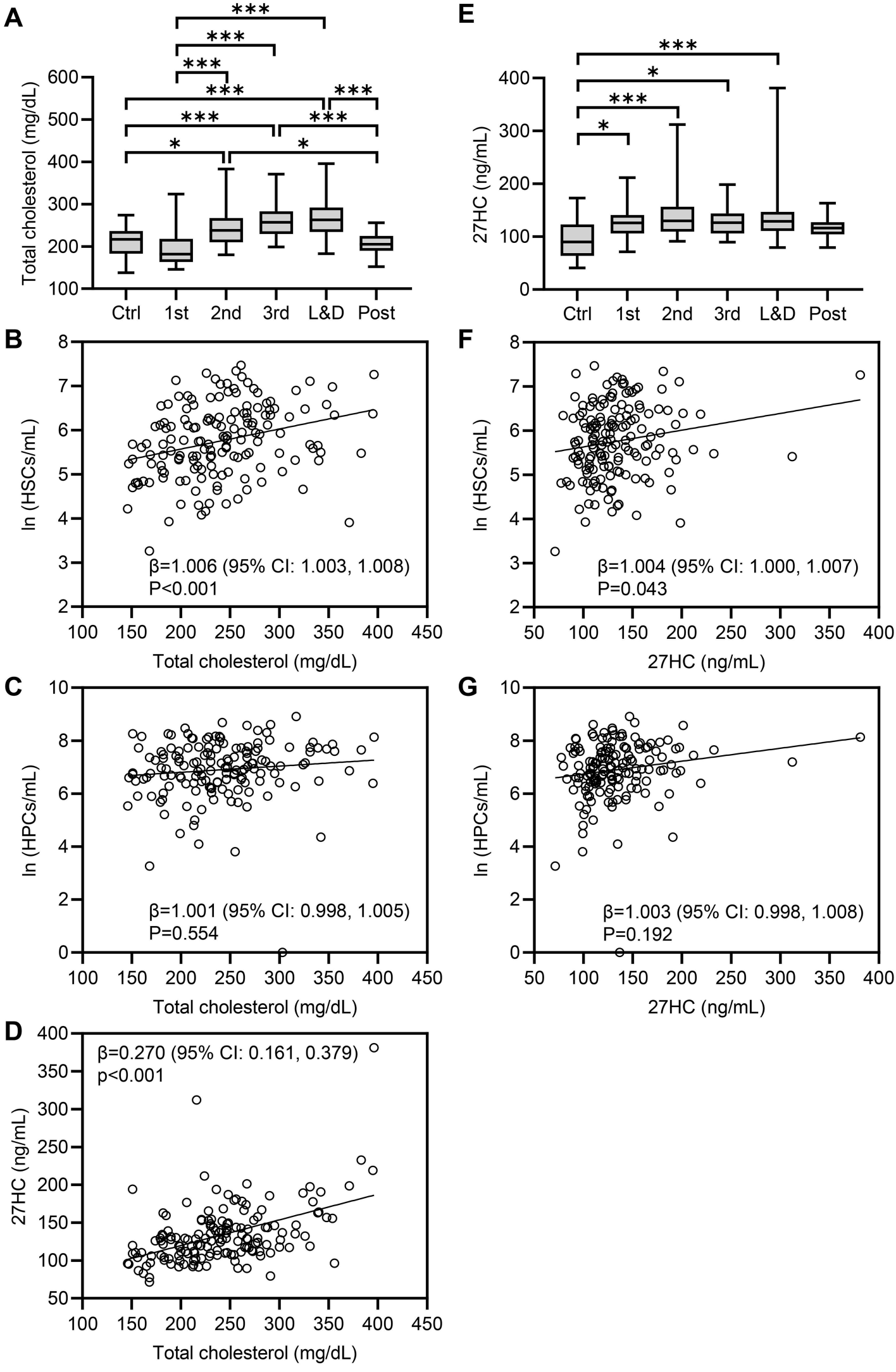
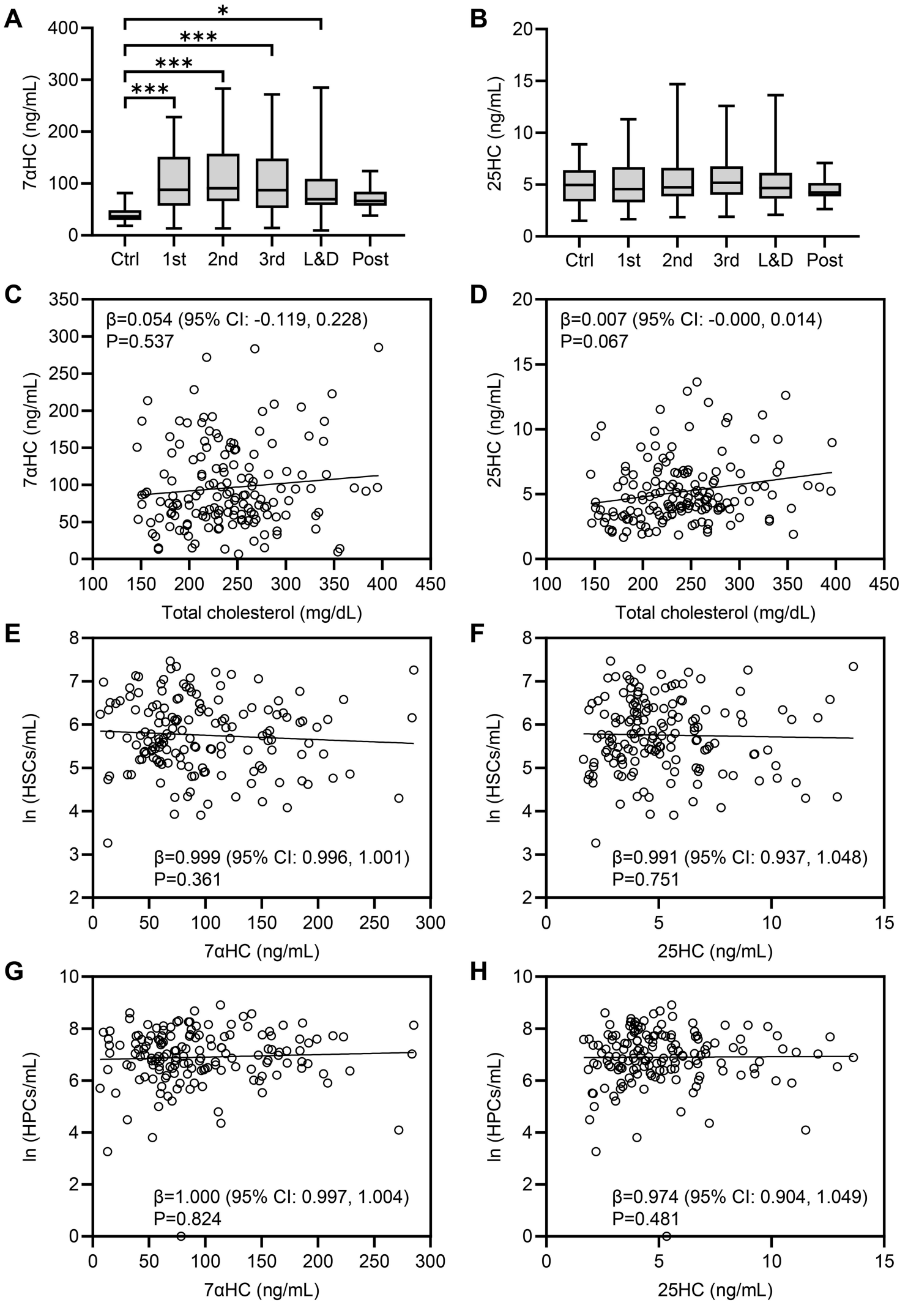

A
Total cholesterol (mg/dL)
Ctrl
1st
2nd
3rd
L&D
Post
E
27HC (ng/mL)
B
ln (HSCs/mL)
β=1.006 (95% CI: 1.003, 1.008)
P<0.001
Total cholesterol (mg/dL)
F
β=1.004 (95% CI: 1.000, 1.007)
P=0.043
27HC (ng/mL)
C
ln (HPCs/mL)
β=1.001 (95% CI: 0.998, 1.005)
P=0.554
G
β=1.003 (95% CI: 0.998, 1.008)
P=0.192
D
β=0.270 (95% CI: 0.161, 0.379)
p<0.001

Figure 3

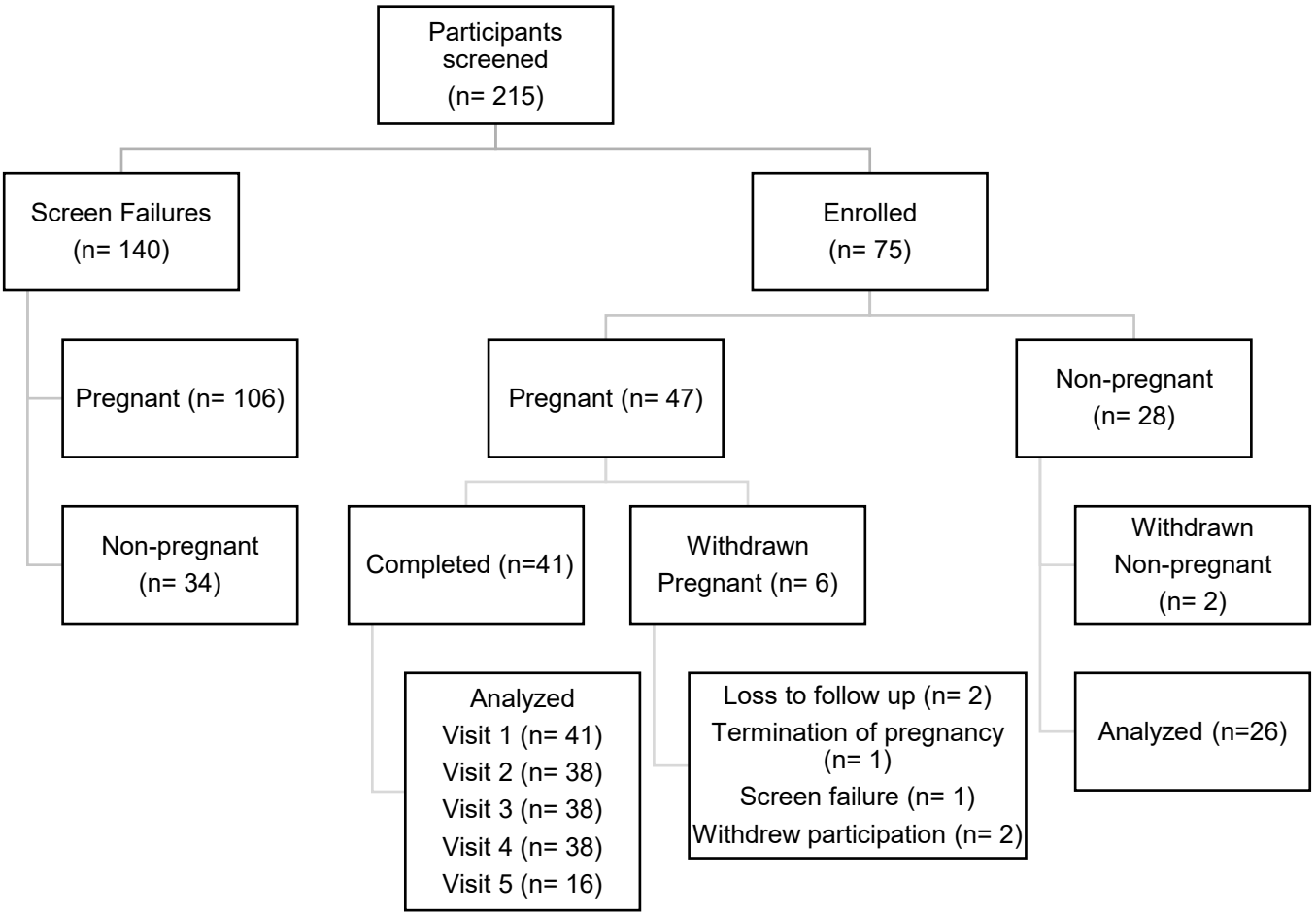

A
B
C
D
E
F
G
H
7αHC (ng/mL)
25HC (ng/mL)
Ctrl
1st
2nd
3rd
L&D
Post
*
***
***
***
β=0.054 (95% CI: -0.119, 0.228)
P=0.537
β=0.007 (95% CI: -0.000, 0.014)
P=0.067
Total cholesterol (mg/dL)
ln (HSCs/mL)
β=0.999 (95% CI: 0.996, 1.001)
P=0.361
β=0.991 (95% CI: 0.937, 1.048)
P=0.751
ln (HPCs/mL)
β=1.000 (95% CI: 0.997, 1.004)
P=0.824
β=0.974 (95% CI: 0.904, 1.049)
P=0.481

Supplemental Table S1. Participant baseline characteristics and pregnancy outcomes.

Characteristic	**Non-pregnant** (n = 26)	**Pregnant** (n = 41)	***P*-value**
Age (year), mean ± SD	29.6 ± 4.9	31.3 ± 4.8	0.160
Gravida, mean ± SD	0.8 ± 1.6	2.1 ± 1.6	0.001
Para, mean ± SD	0.3 ± 0.7	1.0 ± 1.5	0.056
Ethnicity			0.515
Hispanic	6 (23.1)	6 (14.6)	
Non-Hispanic	20 (76.9)	35 (85.4)	
Race			0.689
White	16 (61.5)	25 (61.0)	
Black	5 (19.2)	6 (14.6)	
Asian	4 (15.4)	5 (12.2)	
Other	1 (3.8)	5 (12.2)	
Weight (lbs), mean ± SD	171.6 ± 48.3	159.0 ± 28.6	0.182
BMI (kg/m²), mean ± SD	29.1 ± 8.1	27.7 ± 5.3	0.395
Preeclampsia/Hypertension			1.000
No	24 (92.3)	38 (92.7)	
Yes	2 (7.7)	3 (7.3)	
Anemia			1.000
No	25 (96.2)	40 (97.6)	
Yes	1 (3.8)	1 (2.4)	
Delivery outcome		**Pregnant** (n = 38)	
Weight (lbs), mean ± SD		188 ± 26	
BMI (Kg/m^2), mean ± SD		32 ± 5	
Gestational age at delivery (Weeks)		39.1 ± 1.4	
Preterm delivery		1 (2.6)	
Fetal growth restriction		1 (2.6)	
Birthweight (g)		3296 ± 498	
APGAR Score			
1 minute		7.8 ± 1.6	
5 minutes		8.8 ± 0.6	
NICU Admission		5 (13.2)	
Supplemental Iron		4 (10.5)	
Hypertensive disorders of pregnancy		5 (13.2)	
Anemia		3 (7.9)	

Data are presented as the number of participants (column proportion, %) for categorical variables, and mean ± SD for continuous variables. Baseline characteristics were compared between pregnant and non-pregnant cohorts using two-sample t-test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate.

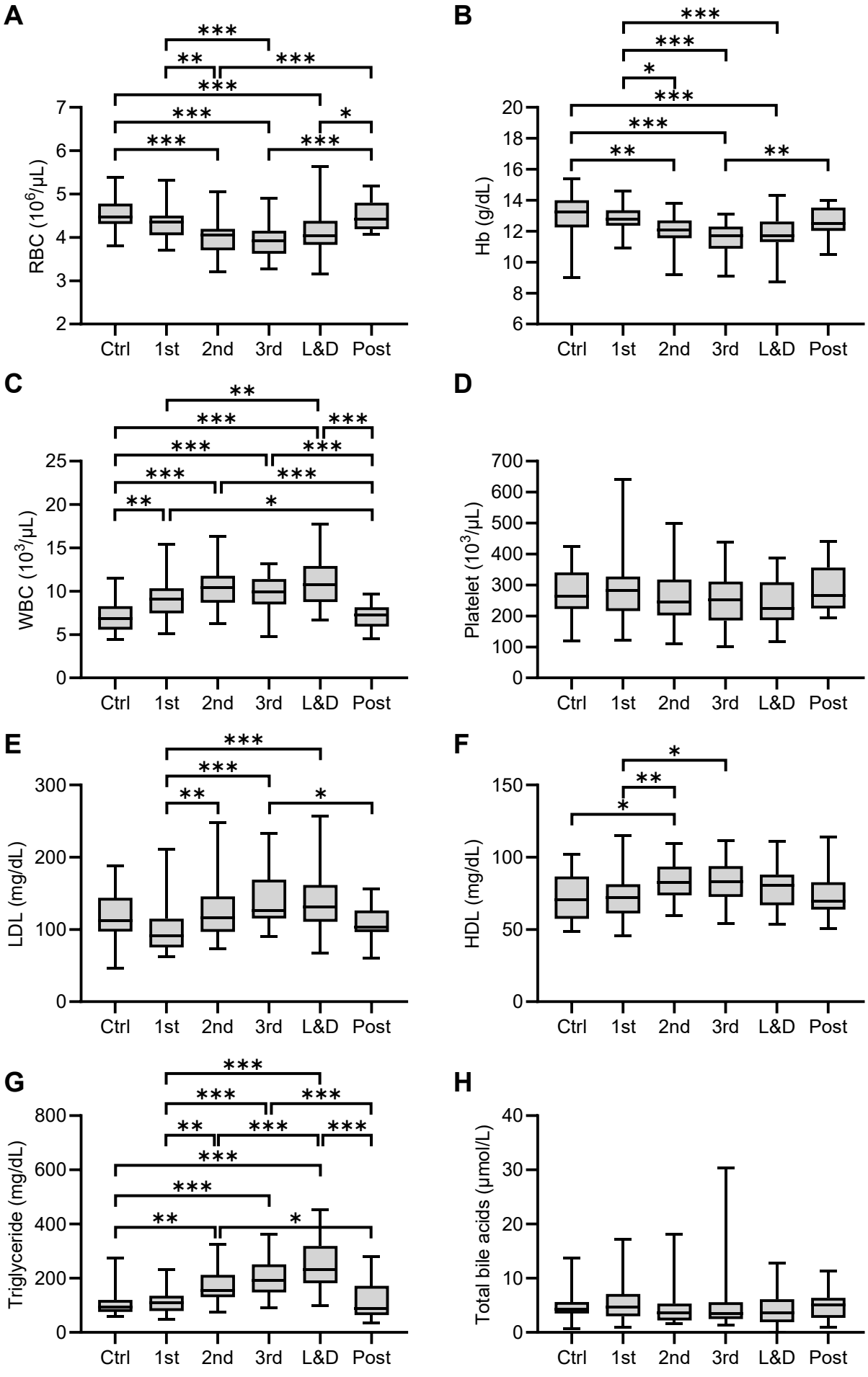
Supplemental Figure S1



Supplemental Figure S1. Study participant flow diagram.

Flowchart of participant screening, enrollment, and follow-up. This observational longitudinal study was approved by the UConn Health Institutional Review Board. All participants were females aged 18-40 years who provided written informed consent. Individuals who consented but did not meet eligibility criteria were classified as screen failures and excluded from analysis

Supplemental Figure S2



Supplemental Figure S2. Complete blood count and lipid parameters during pregnancy.

(**A**-**D**) Red blood cell (RBC) count (**A**), hemoglobin (Hb) (**B**), white blood cell (WBC) count (**C**), and platelet count (**D**) in peripheral blood from non-pregnant controls (Ctrl; n=26) and pregnant participants during the first (1st; n=41), second (2nd; n=38), and third (3rd; n=38) trimesters, at labor and delivery (L&D; n=38), and postpartum (Post; n=16).

(**E**-**H**) Low-density lipoprotein (LDL) (**E**), High-density lipoprotein (HDL) (**F**), triglycerides (**G**), and total bile acids (**H**) in non-pregnant controls (Ctrl, n=26) and pregnant participants (1st, n=41; 2nd, n=38; 3rd, n=38; L&D, n=38; Post, n=16).

Data were analyzed by linear regression with visit as the main predictor, adjusted for age, followed by Tukey-adjusted pairwise comparisons (*P<0.05, **P<0.01, ***P<0.001).