North Clin Istanb 2026;13(5):568–576
doi: 10.14744/nci.2026.71419

Original Article PHYSIOLOGY

Periovulatory decline in circulating neutrophils coincides with a low-density lipoprotein-cholesterol rise in healthy young women: A paired within-subject study

Mustafa Sevim,[1] Tulin Altinoluk,[2] Merve Meric Kahraman,[3] Berrak Caglayan Yegen[1]

[1]Department of Physiology, Marmara University Faculty of Medicine, Istanbul, Turkiye
[2]Vocational School of Health Services, Izmir University of Economics, Izmir, Turkiye
[3]Department of Physiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkiye

ABSTRACT

OBJECTIVE: Prior experimental work indicated that neutropenia selectively elevates circulating low-density lipoprotein (LDL) cholesterol in male but not female mice, suggesting that estrogen may attenuate a neutrophil-associated mechanism of LDL regulation. Whether a comparable phase- and sex-dependent association between neutrophils and LDL is detectable in healthy humans has not been examined.

METHODS: Eleven healthy women (age 21.5 years, interquartile range 20.0–23.5) were sampled during menstruation and again at the luteinizing hormone-confirmed pre-ovulatory/ovulatory phase. Thirteen healthy men were sampled on matched dates. Serum LDL-cholesterol (LDL-C), a five-part leukocyte differential, and reproductive hormones were measured at each time point. Paired phase comparisons used the Wilcoxon signed-rank test, and within-subject deltas (Δ=Ovu − Mens) were analyzed by Spearman correlation.

RESULTS: In women, the neutrophil percentage fell from menstruation to ovulation (p=0.005), the absolute neutrophil count declined in parallel without reaching significance (p=0.183), and serum LDL-C rose (p=0.002). The lymphocyte count rose reciprocally (p=0.024). The within-subject decrease in neutrophils tended to accompany the LDL rise inversely, although this association did not reach statistical significance at the available sample size. Among abundant subsets, the inverse trend was neutrophil-selective. Δlymphocyte, Δmonocyte, and Δeosinophil counts showed no relation to ΔLDL. Δestradiol did not predict ΔLDL (ρ=-0.22, p=0.542), indicating the neutrophil–LDL trend is not an estradiol proxy. No phase-linked LDL or neutrophil change occurred in men, and the menstrual-phase sex difference in LDL-C (women lower; p=0.038) was no longer significant at ovulation (p=0.622).

CONCLUSION: In healthy young women, a periovulatory decline in circulating neutrophils coincides with a rise in LDL cholesterol, and the two within-subject changes tend to move in opposite directions, although this inverse association did not reach statistical significance in a sample of this size. The trend is neutrophil-selective among abundant leukocytes, is not explained by estradiol, and is absent in non-cycling men. These observational data are compatible with but do not establish a contribution of peripheral neutrophils to LDL turnover that is attenuated during the high-estradiol ovulatory window. Causal and mechanistic inferences require interventional and functional studies in larger cohorts.

Keywords: Estrogen; low-density lipoprotein cholesterol; neutrophils.

Cite this article as: *Sevim M, Altinoluk T, Kahraman MM, Caglayan Yegen B. Periovulatory decline in circulating neutrophils coincides with a low-density lipoprotein cholesterol rise in healthy young women: A paired within-subject study. North Clin Istanb 2026;13(5):568–576.*

Received: August 03, 2026 *Revised:* September 18, 2026 *Accepted:* September 23, 2026 *Online:* October 16, 2026

Correspondence: Mustafa SEVIM, MD. Istinye Universitesi Tip Fakultesi, Fizyoloji Anabilim Dali, Istanbul, Turkiye.
Tel: +90 505 548 51 38 e-mail: sevimmustafa@gmail.com

Istanbul Provincial Directorate of Health - Available online at www.northclinist.com

The bidirectional relationship between lipid metabolism and innate immune cell trafficking has attracted considerable interest [1, 2]. It is well established that dyslipidemia drives neutrophilia by expanding granulopoiesis through cholesterol-mediated modulation of CXCR4 surface expression on hematopoietic stem cells and by potentiating pro-inflammatory CXCR2 ligand signaling [3, 4]. This unidirectional model, in which altered cholesterol reshapes neutrophil kinetics, has been extensively validated. Far less explored is the reverse direction: whether changes in the circulating neutrophil pool are associated with plasma low-density lipoprotein (LDL) levels. The daily turnover of approximately 1–2×1011 neutrophils [5] represents a substantial lipid flux, and clinical observations suggest a neutrophil–cholesterol coupling. Fraunberger et al. [6] reported reduced serum cholesterol in neutropenic febrile patients. Our own pre-clinical investigation [7] extended this by experimentally manipulating neutrophil counts in C57BL/6 mice. In this study, anti-neutrophil-serum-induced neutropenia and filgrastim-induced neutrophilia both altered total blood cholesterol, with the LDL fraction implicated. Notably, while both manipulations elevated total cholesterol in males, in females only neutrophilia – not neutropenia – produced a significant rise, a sex dissociation that prompted the present question: what protects females from the neutropenia-associated LDL elevation seen in males?

Estrogen is a biologically plausible candidate. Premenopausal women exhibit systematically lower circulating LDL than age-matched men, a disparity that narrows after menopause [8, 9]. Estradiol exerts well-characterized, though context-dependent, effects on neutrophil biology. Estrogen can suppress bone-marrow leukocyte production and promote redistribution of neutrophils out of the circulating pool [10], and, via estrogen receptor alpha (ERα) signaling, it blocks neutrophil adhesion to the vascular endothelium [11]. These actions are not uniform. In tumor-bearing settings, estradiol has instead been reported to augment neutrophil production via ERα [12], so the net direction of estrogenic action on the circulating neutrophil pool is tissue- and context-specific. In parallel, estrogen enhances hepatic LDL-receptor expression, upregulates CYP7A1, and augments reverse cholesterol transport, which has effects tending to lower LDL and raise high-density lipoprotein (HDL) [13, 14].

The menstrual cycle provides a within-subject model in which estradiol rises physiologically from a menstrual low to a pre-ovulatory peak. Circulating neutrophil numbers are themselves under rhythmic (circadian) control [15], and leukocyte counts have been reported to vary across the menstrual cycle, though not consistently in direction [16].

We therefore tested whether the pre-ovulatory estradiol rise is accompanied by a within-subject change in circulating neutrophils that is associated with LDL, whether any such association is specific to neutrophils and independent of estradiol, and whether it diverges from the pattern in non-cycling men.

Highlight key points

- During the menstrual-to-ovulatory transition in healthy young women, the circulating neutrophil percentage significantly decreases, whereas serum LDL cholesterol levels rise, with a parallel decline in absolute neutrophil count.
- This decline shows a moderate within-subject inverse correlation with the rise in LDL cholesterol that is specific to neutrophils and absent in other abundant leukocyte subsets, though it does not reach statistical significance at this sample size.
- The concurrent estradiol rise does not itself predict the LDL change, indicating the neutrophil–LDL relationship is not simply a proxy for estradiol.
- These phase-linked changes are absent in non-cycling men, leading to a temporary convergence of male and female LDL cholesterol levels during the ovulatory window.

MATERIALS AND METHODS

Study Design and Participants

This observational paired repeated-measures study followed the Declaration of Helsinki and was approved by the Marmara University Clinical Research Ethics Committee (protocol 09.2020.1051). All participants gave written informed consent.

Eighteen healthy women aged 18–25 years with regular cycles (25–35 days), not using hormonal contraception, with no metabolic, cardiovascular, immunological, or gynecological disease were recruited. Seven were subsequently excluded because of pre-analytical or assay-related sample-quality problems that rendered one or both of their paired measurements unusable, leaving 11 women in the analyzed dataset. Thirteen healthy men of comparable age served as a non-cycling reference group; one man did not provide a usable second sample, so 12 men contributed paired data. Among women, 10 had paired LDL-cholesterol (LDL-C) measurements; among men, 11 had paired estradiol measurements, and 10 had paired follicle-stimulating hormone (FSH) measurements. Ex-

Table 1. Paired phase comparisons within sex (primary parameters)

Variable	Mens	Ovu	Δ	Test	p	dz
Women (n=11; n=10 for LDL-C)						
Estradiol (pg/mL)	32.3±15.6	88.1±77.4	+55.8	W=3	**0.005**	0.74
LH (IU/L)	6.4±5.3	11.3±9.2	+4.8	W=6	**0.014**	0.76
Neutrophil count (×10⁹/L)	4.37±1.00	3.61±1.16	-0.76	W=17.5	0.183	-0.48
Neutrophil %	63.0±8.4	54.6±8.8	-8.5	W=3	**0.005**	-1.29
LDL-C (mg/dL)	77.4±17.3	89.5±19.0	+12.1	W=0	**0.002**	1.81
CRP (mg/L)	1.86±2.92	0.39±0.26	-1.47	W=15	0.123	-0.50
WBC (×10⁹/L)	6.90±0.96	6.48±1.35	-0.42	W=25	0.504	-0.22
HDL-C (mg/dL)	65.3±14.1	68.5±10.8	+3.2	W=14	0.102	0.55
Men (n=12; n=11 for oestradiol; n=10 for FSH)						
Estradiol (pg/mL)	24.8±10.3	27.3±13.7	+2.5	W=26	0.577	0.21
FSH (IU/L)	5.60±4.67	5.44±4.05	-0.16	W=24	0.770	-0.16
Neutrophil count (×10⁹/L)	3.54±1.08	4.15±1.38	+0.61	W=19	0.129	0.58
Neutrophil %	56.0±6.9	57.7±9.1	+1.7	W=33	0.666	0.24
LDL-C (mg/dL)	99.2±26.6	96.8±25.0	-2.3	W=27	0.621	-0.17
WBC (×10⁹/L)	6.27±1.56	7.09±1.81	+0.83	W=13	**0.040**	0.62

Mean±SD; Wilcoxon signed-rank test; dz=within-subject Cohen's d; bold p<0.05. LDL-C: Low-density lipoprotein cholesterol; WBC: White blood cell; HDL-C: High-density lipoprotein cholesterol; CRP: C-reactive protein; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

clusion criteria (both sexes) were body mass index (BMI) >30 kg/m^2, current medication, acute/chronic inflammation, smoking, and blood donation within 3 months.

Sampling and Phase Confirmation

Women were sampled twice: (1) the menstrual phase (days 1–4, confirmed by onset of bleeding; "Mens"); and (2) the pre-ovulatory/ovulatory phase ("Ovu"). Men were sampled on matched dates approximately 14 days apart (Time-1/Time-2) to balance any time-related environmental factors. Adequacy of phase capture was verified post hoc by the significant within-subject estradiol and luteinizing hormone (LH) rise in women.

Measurements

Anthropometry and bioelectrical-impedance body composition were obtained by standard protocols. Fasting (≥10 h) venous blood was drawn at 08:00–10:00 h. A complete blood count with a five-part differential was performed on an automatic hematology analyzer, using a combination of physical, electrical, and optical methods. Total leukocyte count and the percentages and absolute counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils were recorded. LDL-C, HDL-cholesterol (HDL-C), total cholesterol, triglycerides, and C-reactive protein (CRP) were determined via colorimetric assay using a biochemistry autoanalyzer.

Estradiol, LH, and FSH were measured using a biochemistry autoanalyzer. Estradiol was reported in pg/mL, and LH and FSH in IU/L.

Statistical Analysis

All analyses were conducted in Python 3.10 (NumPy, SciPy, and pandas). Paired within-subject comparisons between the menstrual and ovulatory phases were analyzed with the Wilcoxon signed-rank test, reported as W with the p-value. Descriptive summaries are specified in each table or figure (mean±standard deviation [SD], median [interquartile range (IQR)], or median [range]), together with the mean paired change where reported. Table 1 uses complete pairs for each analyte. Effect sizes for paired tests were computed as Cohen's dz, defined as the mean of the Ovu-minus-Mens difference scores divided by their SD. Comparisons between sexes at a given phase used the Mann–Whitney U test with rank-biserial correlation (r_rb) as effect size, signed so that positive

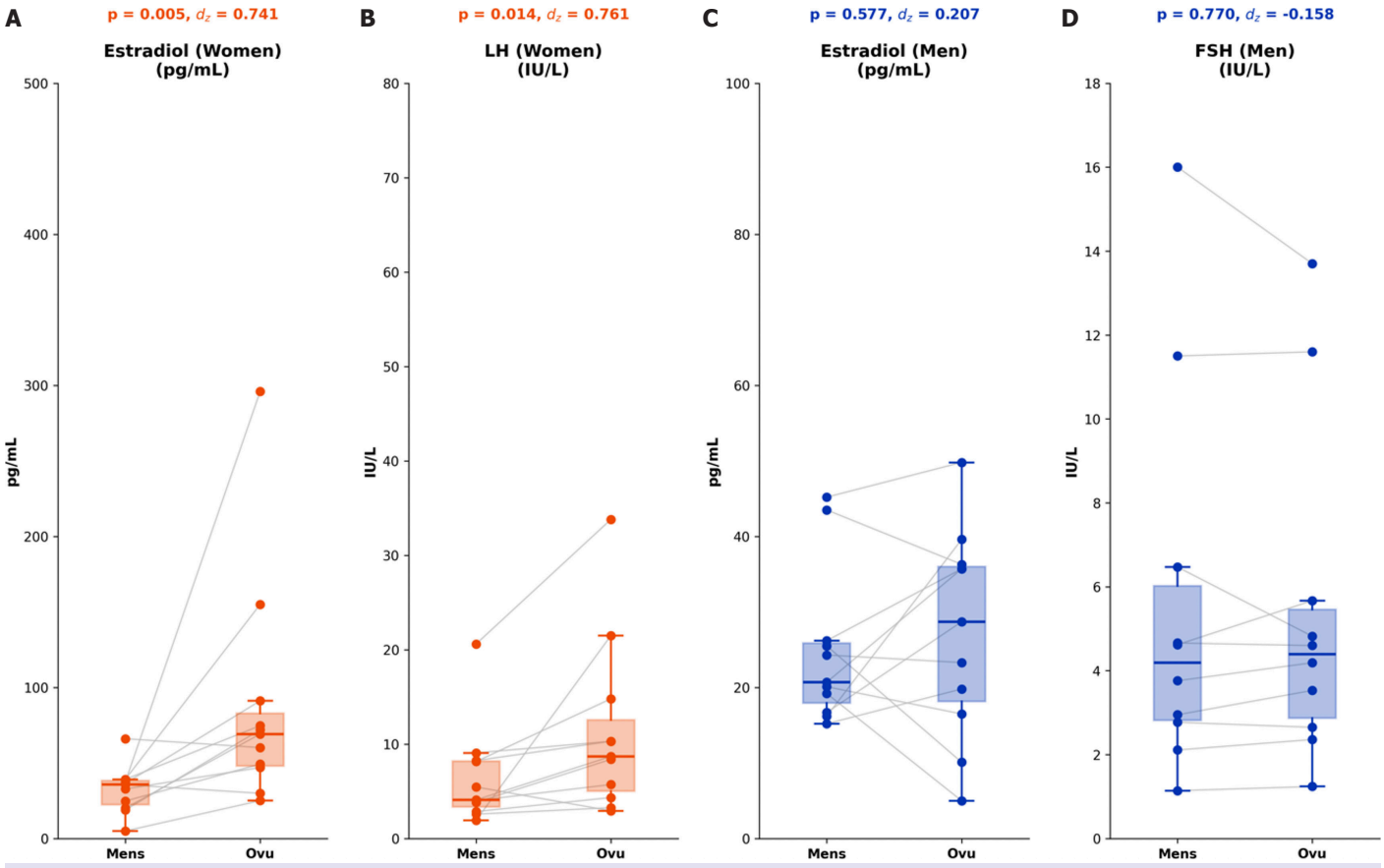

FIGURE 1. Phase-specific hormonal profiles. **(A)** Women's estradiol rose (Δ+55.8 pg/mL; p=0.005, dz=0.74). **(B)** Women's LH rose (Δ +4.8 IU/L; p=0.014, dz=0.76). **(C)** Men's estradiol unchanged (p=0.577). **(D)** Men: follicle-stimulating hormone unchanged (p=0.770). Paired individual trajectories over box plots (median, interquartile range, whiskers); Wilcoxon signed-rank test.

values indicate higher values in women. Spearman rank correlation was used for association analyses, including within-subject delta (Δ=Ovu−Mens) correlations. The pooled male plot in Figure 3C is descriptive: Its 25 observations arise from 13 participants, and no ordinary Spearman inferential p-value is reported because observations within participants are not independent. Each comparison was performed on all participants with complete data for the variables concerned, and the corresponding n is reported throughout. The significance threshold was set at p<0.05. All tests were two-sided.

RESULTS

Participant Characteristics

The study dataset comprised 24 participants (11 women and 13 men; Table 2). Paired analyses included up to 11 women and 12 men because one man did not provide a usable second sample. The available paired sample size varied by analyte: LDL-C analyses included 10 women, and male estradiol and FSH analyses included 11 and 10 men, respectively. Each analysis used participants with complete data for the variables concerned. Age was similar in women (21.5 [IQR 20.0–23.5]) and men (20.0 [IQR 19–23]; p=0.447). As expected, men had higher BMI (24.1 vs. 21.1 kg/m^2, p=0.003), lower body fat (16.5% vs. 24.1%, p=0.002), and greater waist circumference (85.5 vs. 71.0 cm, p<0.001).

Hormonal Validation of Phase

Phase capture was confirmed by within-subject hormonal change in women (Fig. 1A, B): estradiol rose from 32.3±15.6 to 88.1±77.4 pg/mL (Wilcoxon W=3, p=0.005, dz=0.74) and LH from 6.4±5.3 to 11.3±9.2 IU/L (W=6, p=0.014, dz=0.76). The wide ovulatory estradiol distribution (median 69.2 pg/mL) reflects interindividual variation in the precise sampling point relative to the surge. In men, estradiol did not change between matched visits (Fig. 1C, D; Table 1).

Table 2. Participant characteristics (menstrual/time-1 phase)

Variables	Women (n=11)	Men (n=13)	p
Age (years)	21.5 (19–24)	20.0 (18–24)	0.447
BMI (kg/m^2)	21.1 (18.9–23.5)	24.1 (19.5–29.9)	0.003
Body fat (%)	24.1 (15.9–33.4)	16.5 (9.2–24.6)	0.002
Waist (cm)	71.0 (62–77)	85.5 (75–98)	<0.001
LDL-C (mg/dL)	73.5 (58–104)	105.0 (60–137)	0.038
HDL-C (mg/dL)	61.8 (43–91)	51.1 (40–69)	0.049
Total cholesterol (mg/dL)	159.0 (123–208)	163.0 (111–229)	0.602
Triglycerides (mg/dL)	68.2 (28–124)	73.3 (26–128)	0.862
WBC (×10^9/L)	6.7 (5.7–9.2)	5.9 (4.1–9.4)	0.202
Neutrophil count (×10^9/L)	4.2 (3.1–6.6)	3.6 (2.0–5.5)	0.059
Neutrophil %	63.2 (45.5–75.3)	57.5 (42.3–65.2)	0.034
CRP (mg/L)	0.52 (0.17–9.77)	0.49 (0.13–3.10)	0.862

Median (range), Mann–Whitney U. Anthropometric variables were available for 10 of the 11 women, and waist circumference for 12 of the 13 men; menstrual-phase LDL-C was available for 10 of the 11 women. LDL-C: Low-density lipoprotein cholesterol; WBC: White blood cell; HDL-C: High-density lipoprotein cholesterol; BMI: Body mass index; CRP: C-reactive protein.

Phase-Dependent Changes in the Leukocyte Differential and LDL-C in Women

Across the menstrual-to-ovulatory transition (Fig. 2 and Table 1), the neutrophil percentage fell (63.0±8.4→54.6±8.8%; W=3, p=0.005, dz=-1.29), and the absolute neutrophil count declined in parallel, although this change did not reach significance (4.37±1.00→3.61±1.16×10^9/L; W=17.5, p=0.183, dz=-0.48). Reciprocally, the absolute lymphocyte count rose (1.85→2.22×10^9/L; W=8, p=0.024, dz=+0.80), whereas monocyte, eosinophil, and basophil counts were unchanged (Table 3). Serum LDL-C rose (median 73.5→90.0 mg/dL; W=0, p=0.002, mean Δ=+12.1 mg/dL), whereas the fall in CRP (1.86→0.39 mg/L; W=15, p=0.123) did not reach significance. Neither total white blood cell (WBC) nor HDL-C changed.

In men, neutrophil percentage, neutrophil count, and LDL-C were unchanged. Total WBC showed a nominal rise (p=0.040). No change was observed in estradiol levels (Fig. 2D, F, Table 1).

Table 3. Full leukocyte differential, women, paired phase change (absolute counts ×10^9/L; n=11)

Subsets	Mens	Ovu	Δ	p	dz
Neutrophil	4.37	3.61	-0.76	0.183	-0.48
Lymphocyte	1.85	2.22	+0.36	0.024	+0.80
Monocyte	0.48	0.46	-0.02	0.844	-0.17
Eosinophil	0.16	0.17	+0.01	0.922	+0.13
Basophil	0.04	0.05	+0.01	0.230	+0.36

Wilcoxon signed-rank test.

Sex Differences in LDL-C: Phase-Dependent Convergence

At the menstrual/time-1 phase, LDL-C was lower in women than men (median 73.5 vs. 105.0 mg/dL; U=31, p=0.038, r_rb=-0.52). By ovulation, the sex difference was no longer significant (91.0 vs. 95.0 mg/dL; U=57.5, p=0.622, r_rb=-0.13). This convergence was specific to LDL. HDL-C remained higher in women at both phases (p=0.049; p=0.006), and the menstrual-phase female excess in neutrophil percentage (p=0.034), with a comparable trend in neutrophil count (p=0.059), disappeared by ovulation (Table 4).

Within-Subject Neutrophil–LDL Association, Specificity, and Estradiol-Independence

The primary analysis (change in absolute neutrophil count vs. change in LDL-C in women) showed a moderate inverse association that did not reach statistical sig-

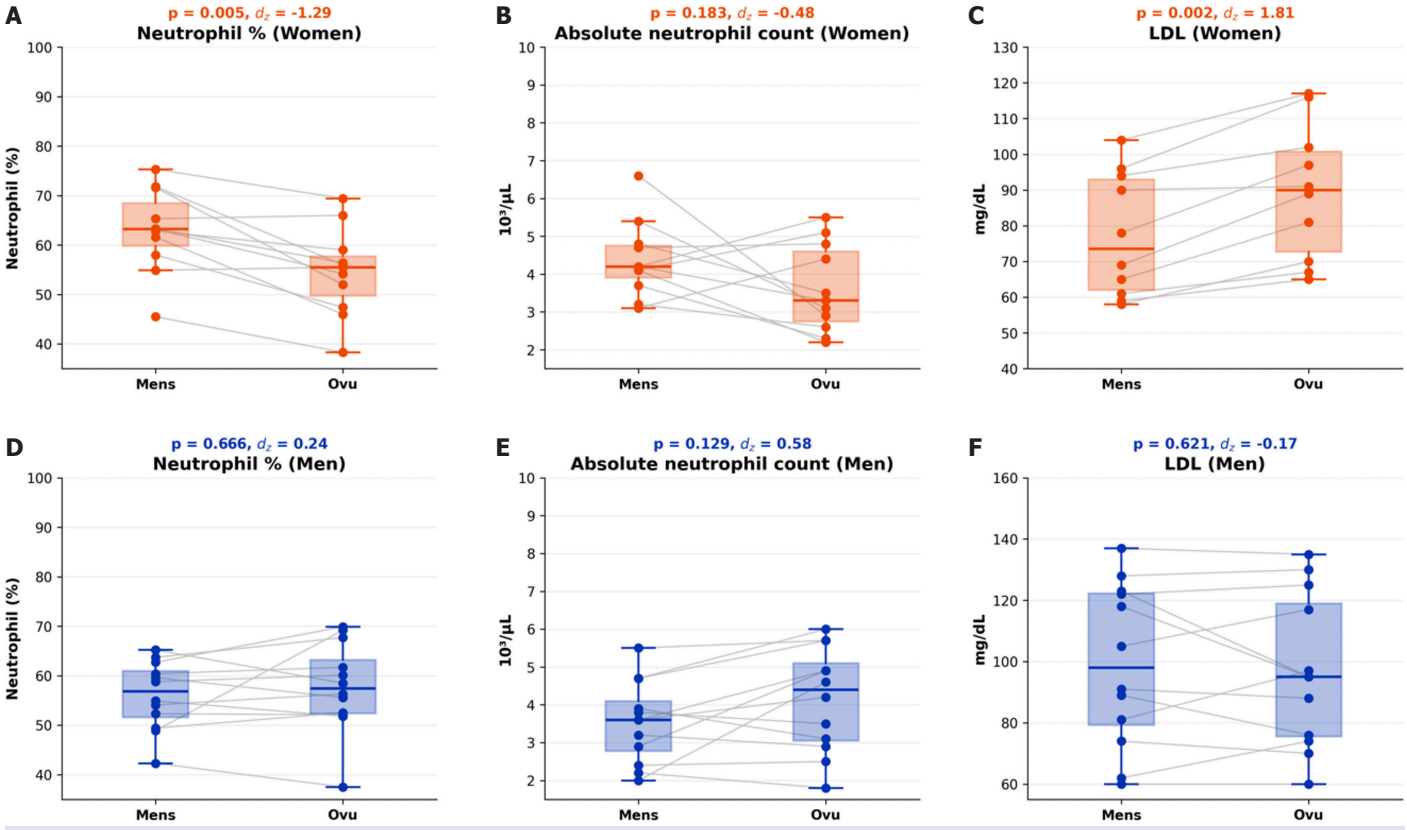

FIGURE 2. Phase-dependent changes in neutrophils and low-density lipoprotein cholesterol (LDL-C). Women **(A–C)**: neutrophil % (A, p=0.005), absolute neutrophil count (B, p=0.183), LDL-C (C, p=0.002). Men **(D–F)**: neutrophil % (D, p=0.666), neutrophil count (E, p=0.129), LDL-C (F, p=0.621). Connected lines=individual participants; boxes show median and interquartile range. Wilcoxon signed-rank test with Cohen's dz.

nificance (Spearman ρ=-0.40, p=0.249, n=10). The secondary neutrophil-percentage analysis was concordant and somewhat stronger (ρ=-0.52, p=0.120, n=10; Fig. 3D). Cross-sectional correlations between neutrophil count and LDL-C within each phase were likewise non-significant (Fig. 3A–C).

Among abundant leukocyte subsets, the inverse trend with ΔLDL was confined to neutrophils. Δlymphocyte count (ρ=+0.01, p=0.980), Δmonocyte count (ρ=-0.09, p=0.806), and Δeosinophil count (ρ=-0.16, p=0.667) showed no association with ΔLDL (Table 5). Δbasophil count showed a positive but non-significant association (ρ=+0.41, p=0.234); basophil counts in any case lie near the analyzer's lower precision limit (≈0.04–0.05×10^9/L).

Δestradiol itself did not predict ΔLDL (ρ=-0.22, p=0.542; Fig. 3E), so the ovulatory estradiol rise was not accompanied by a proportionate LDL change. The neutrophil–LDL trend is therefore unlikely to be a simple proxy for estradiol level.

In men, the Δneutrophil%–ΔLDL association was not significant and was directionally opposite (ρ=+0.51, p=0.089, n=12; Fig. 3F).

DISCUSSION

The principal observation is that a periovulatory decline in circulating neutrophils occurs alongside a concurrent rise in LDL-C in healthy young women, and that these two within-subject changes tend to move in opposite directions – an inverse trend that is specific to neutrophils among abundant leukocytes, is not explained by estradiol level, and is not reproduced in men.

These findings contextualize our experimental work [7], in which neutropenia elevated LDL-C in male but not in female mice. In that study, the absence of an LDL-elevating effect in females was speculated as one of the pieces of evidence that estrogen, either through direct hepatic LDLR upregulation or through buffering of neutrophil-dependent lipid clearance, maintains LDL homeostasis even when the

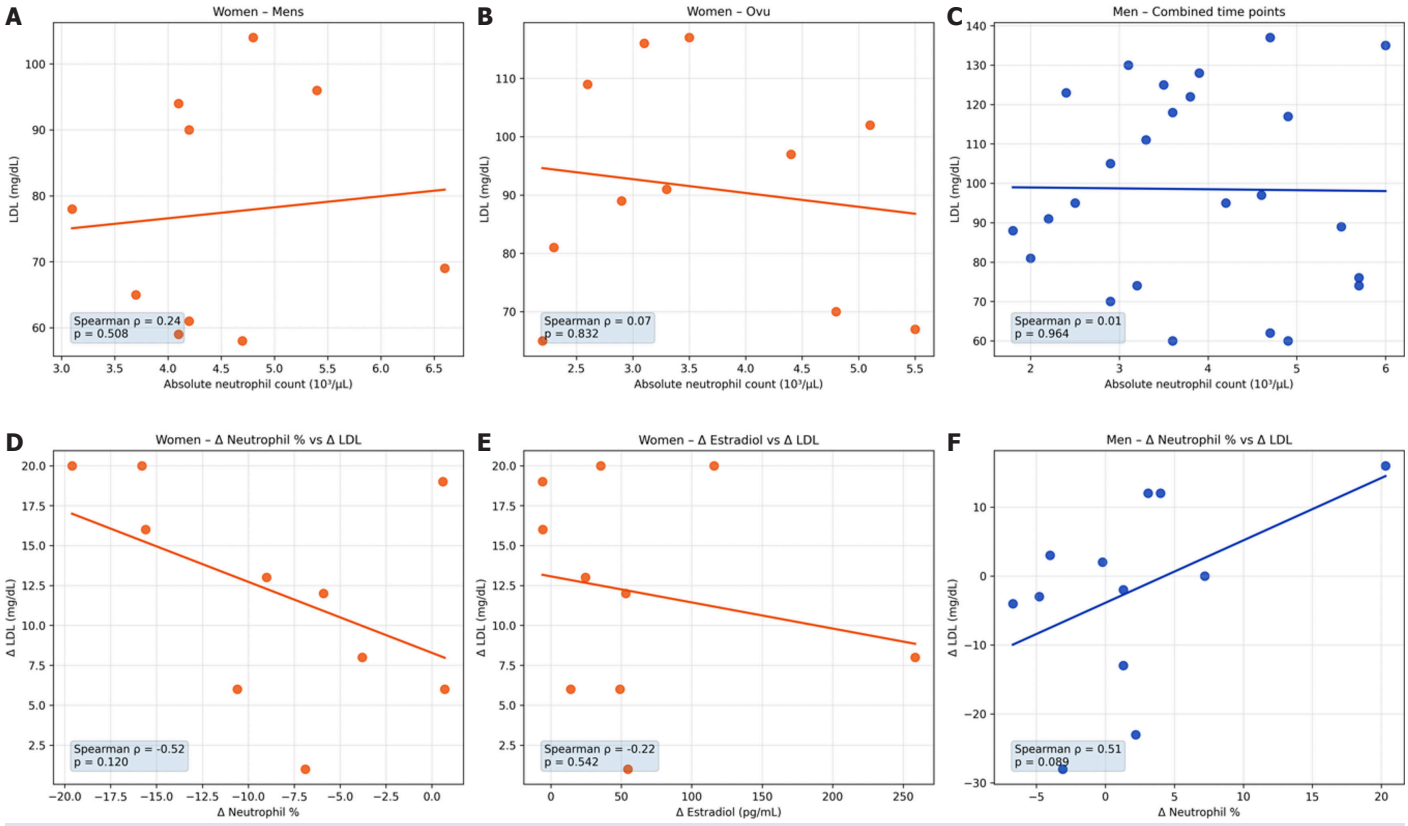

FIGURE 3. Within-subject neutrophil-low-density lipoprotein (LDL) associations. **(A–C)** Cross-sectional Spearman correlations between absolute neutrophil count and LDL-C: women at menstruation (a, ρ=+0.24, p=0.508, n=10), women at ovulation (b, ρ=+0.07, p=0.832, n=11), and men with both time points pooled (c, ρ=+0.01, p=0.964, n=25) – all non-significant. **(D)** Women: Δneutrophil % versus ΔLDL-C (ρ=-0.52, p=0.120, n=10). **(E)** Women: Δestradiol versus ΔLDL-C (ρ=-0.22, p=0.542, n=10). **(F)** Men: Δneutrophil % versus ΔLDL-C (ρ=+0.51, p=0.089, n=12). Least-squares regression lines are shown for visualization only.

neutrophil pool is diminished [7]. In the present human study, reduced neutrophils coinciding with elevated LDL specifically in the high-estradiol ovulatory window is consistent with a speculation in which a peripheral, neutrophil-associated route of LDL handling operates at homeostatic neutrophil counts and is transiently diminished when neutrophils fall. The absence of any relationship between Δestradiol and ΔLDL argues against the assumption that estradiol independently drives both variables.

The co-occurrence of falling neutrophil counts and rising LDL at ovulation is consistent with several mechanistic hypotheses. Neutrophils internalize native and oxidized LDL particles, participate in reverse cholesterol transport through myeloperoxidase-dependent pathways, and their apoptotic clearance by hepatic Kupffer cells and liver sinusoidal macrophages may feedback on hepatic lipid handling [3, 17]. The periovulatory recruitment of peripheral neutrophils to ovarian tissue, where neutrophilic granulocytes accumulate 8-fold in the thecal layer during ovulation [18], may reduce the peripheral neutrophil pool and thereby diminish the rate of peripheral LDL uptake. Pernes et al. [4] have further shown that lipid availability reciprocally regulates hematopoietic output.

Our finding that neutrophil percentage decreased at ovulation, with a parallel but non-significant decline in absolute count, contrasts with a study by Nowak et al. [16], who reported that WBC count and neutrophil count increased around ovulation in 37 healthy cycling women. This discrepancy may reflect differences in the phase-confirmation process, timing of blood sampling relative to the LH peak, or the phase-specific inflammatory microenvironment. The post-LH-surge period is characterized by complex immune remodeling in which circulating neutrophils are actively recruited to the follicle, potentially depleting the peripheral pool transiently even as bone marrow output increases. The net change in peripheral blood will depend on which of these processes dominates at the exact sampling moment. Our protocol,

Table 4. Sex comparisons at each sampling phase (Mann-Whitney U)

Variable	Women	Men	U	p	r_rb
Menstrual/Time-1					
LDL-C (mg/dL)	73.5	105.0	31	0.038	-0.52
HDL-C (mg/dL)	61.8	51.1	106	0.049	+0.48
Neutrophil %	63.2	57.5	108.5	0.034	+0.52
Neutrophil count ($\times 10^9$/L)	4.2	3.6	104.5	0.059	+0.46
WBC ($\times 10^9$/L)	6.7	5.9	94	0.202	+0.31
Ovulatory/Time-2					
LDL-C (mg/dL)	91.0	95.0	57.5	0.622	-0.13
HDL-C (mg/dL)	68.3	55.1	111	0.006	+0.68
Neutrophil %	55.5	57.4	51	0.372	-0.23
Neutrophil count ($\times 10^9$/L)	3.3	4.4	49.5	0.324	-0.25
WBC ($\times 10^9$/L)	6.4	6.8	52	0.406	-0.21

Medians; r_rb=rank-biserial (positive=higher in women). LDL-C: Low-density lipoprotein cholesterol; WBC: White blood cell; HDL-C: High-density lipoprotein cholesterol.

Table 5. Within-subject correlation of leukocyte-subset change with ΔLDL-C, women (n=10)

Δ metric	ρ versus Δ LDL	p
Neutrophil count (primary)	-0.40	0.249
Neutrophil % (secondary)	-0.52	0.120
Lymphocyte count	+0.01	0.980
Monocyte count	-0.09	0.806
Eosinophil count	-0.16	0.667
Basophil count (caution)	+0.41	0.234
Estradiol	-0.22	0.542

Spearman ρ. Neutrophil (absolute) is primary, percentage secondary. LDL-C: Low-density lipoprotein cholesterol.

which used LH surge detection and aimed to sample within 24–48 h of the surge, may have captured an earlier peri-ovulatory window than some prior studies. This biological uncertainty underscores the importance of within-subject designs, which mitigate inter-individual variability and isolate the paired change in each participant.

The increase in mean absolute lymphocyte count from 1.85 to 2.22×10^9/L (p=0.024) may reflect cycle-dependent changes in leukocyte trafficking or hormonal modulation, although the present measurements cannot establish these mechanisms. An increased lymphocyte contribution also complicates interpretation of the fall in neutrophil percentage, particularly because the decline in absolute neutrophil count was not statistically significant. Cycle-related lymphocyte changes are not consistent across studies. Nowak et al. [16] reported stable lymphocyte counts across menstruation, ovulation, and the mid-luteal phase. In our cohort, changes in lymphocyte count and LDL-C were not significantly correlated (Spearman ρ=+0.01, p=0.980; n=10), so the concurrent lymphocyte increase does not itself demonstrate a relationship with LDL-C.

The sex-specific convergence of LDL levels is another noteworthy finding. In the complete paired LDL-C samples, 10 women and 12 men (Table 1), group mean LDL-C concentrations were 77.4 mg/dL in women and 99.2 mg/dL in men at menstruation/Time-1 and 89.5 and 96.8 mg/dL, respectively, at ovulation/Time-2. These correspond to descriptive differences between group means of approximately 21.8 and 7.3 mg/dL. This convergence was specific to LDL (HDL-C remained significantly higher in women at both phases) and supports the interpretation that the ovulatory phase represents a window in which the sex advantage in LDL-C is transiently attenuated. From an evolutionary perspective, the transient LDL rise at ovulation may serve to mobilize cholesterol substrates necessary for steroidogenesis, a well-recognized physiological demand of the periovulatory period [8]. Sex-biased lipid-handling gene expression [19] may provide the substrate on which cyclic hormonal change acts.

Several limitations of this study require explicit acknowledgment. First, the sample size (11 women, of whom 10 contributed paired LDL measurements, and 13 men) provides adequate power only for large effect sizes. The moderate inverse neutrophil–LDL correlation observed here ($\rho \approx -0.40$–-0.52) did not reach statistical significance at this n, so it must be treated as a trend requiring confirmation, and the sample also limits the precision of all correlation estimates and precludes subgroup analyses by BMI, body fat, or CRP tertile. Second, the observational design precludes causal inference; common upstream signals (e.g., ovarian cytokines, LH) could independently affect neutrophils and lipoproteins. Third, peripheral counts cannot distinguish true clearance changes from compartmental redistribution. Fourth, LDL subfraction and neutrophil functional assays were not performed.

Conclusion

In healthy young women, a periovulatory neutrophil decline coincides with an LDL-C rise, and the two changes tend to vary inversely and selectively within participants, a trend that is not explained by estradiol and is absent in men. The pattern is compatible with a neutrophil-associated contribution to LDL turnover modulated across the cycle. Interventional and functional studies in larger cohorts are required to test causality and mechanism.

Ethics Committee Approval: This study was approved by the Marmara University Clinical Research Ethics Committee (09.2020.1051 – 16.10.2020).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: During the preparation of this work, the author(s) used Gemini solely to improve the English language, grammar, and readability of the manuscript.

Authorship Contributions: Concept – MS, BCY; Design – MS, BCY; Supervision – MS, BCY; Resource – MS, BCY; Materials – MS, BCY; Data Collection and/or Processing – MS, TA, MMK, BCY; Analysis and/or Interpretation – MS, TA, MMK, BCY; Literature Search – MS, TA, MMK, BCY; Writing – MS, TA, MMK, BCY; Critical Reviews – MS, TA, MMK, BCY.

Acknowledgments: This study is derived from the medical specialisation thesis of Mustafa Sevim, titled "The Effect of the Number of Circulating Neutrophils on Blood LDL Level", accepted by Marmara University Faculty of Medicine. The authors thank Alper Yildirim, Yelda Toy, Cagla Unlu, Emine Nur Avci, Yagmur Islek and Akay Ekmekci for their support in the initial phase of the study.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Rosales C. Neutrophil: a cell with many roles in inflammation or several cell types? Front Physiol 2018;9:113. [CrossRef]
2. Mortaz E, Alipoor SD, Adcock IM, Mumby S, Koenderman L. Update on neutrophil function in severe inflammation. Front Immunol 2018;9:2171. [CrossRef]
3. Geng S, Zhang Y, Lee C, Li L. Novel reprogramming of neutrophils modulates inflammation resolution during atherosclerosis. Sci Adv 2019;5:eaav2309. [CrossRef]
4. Pernes G, Flynn MC, Lancaster GI, Murphy AJ. Fat for fuel: lipid metabolism in haematopoiesis. Clin Transl Immunology 2019;8:e1098. [CrossRef]
5. Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. Trends Immunol 2010;31:318-24. [CrossRef]
6. Fraunberger P, Hahn J, Holler E, Walli AK, Seidel D. Serum cholesterol levels in neutropenic patients with fever. Clin Chem Lab Med 2002;40:304-7. [CrossRef]
7. Sevim M. The effect of the number of circulating neutrophils on blood LDL level [medical specialization thesis]. Istanbul: Marmara University School of Medicine; 2023. Available at: https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=GoJ1rKE4SgJUkomyAKpRxRyJEu0R1I28K6E0wXFEpHP2Rna3dZbg2Z5Mhr3mqh
8. Pellegrini M, Pallottini V, Marin R, Marino M. Role of the sex hormone estrogen in the prevention of lipid disorder. Current Medicinal Chemistry 2014;21:2734-42. [CrossRef]
9. Marlatt KL, Redman LM, Beyl RA, Smith SR, Champagne CM, Yi F, et al. Racial differences in body composition and cardiometabolic risk during the menopause transition: a prospective, observational cohort study. Am J Obstet Gynecol 2020;222:365.e1-18. [CrossRef]
10. Josefsson E, Tarkowski A, Carlsten H. Anti-inflammatory properties of estrogen. I. *In vivo* suppression of leukocyte production in bone marrow and redistribution of peripheral blood neutrophils. Cell Immunol 1992;142:67-78. [CrossRef]
11. Geraldes P, Gagnon S, Hadjadj S, Merhi Y, Sirois MG, Cloutier I, et al. Estradiol blocks the induction of CD40 and CD40L expression on endothelial cells and prevents neutrophil adhesion: an ERalpha-mediated pathway. Cardiovasc Res 2006;71:566-73. [CrossRef]
12. Minor BMN, LeMoine D, Seger C, Gibbons E, Koudouovoh J, Taya M, et al. Estradiol augments tumor-induced neutrophil production to promote tumor cell actions in lymphangioleiomyomatosis models. Endocrinology 2023;164:bqad061. [CrossRef]
13. Chiang JYL, Ferrell JM. Up to date on cholesterol 7 alpha-hydroxylase (CYP7A1) in bile acid synthesis. Liver Res 2020;4:47-63. [CrossRef]
14. Lavoie JM. Dynamics of hepatic and intestinal cholesterol and bile acid pathways: The impact of the animal model of estrogen deficiency and exercise training. World J Hepatol 2016;8:961-75. [CrossRef]
15. Casanova-Acebes M, Pitaval C, Weiss LA, Nombela-Arrieta C, Chèvre R, A-González N, et al. Rhythmic modulation of the hematopoietic niche through neutrophil clearance. Cell 2013;153:1025-35. [CrossRef]
16. Nowak J, Borkowska B, Pawlowski B. Leukocyte changes across menstruation, ovulation, and mid-luteal phase and association with sex hormone variation. Am J Hum Biol 2016;28:721-8. [CrossRef]
17. Kumar S, Dikshit M. Metabolic insight of neutrophils in health and disease. Front Immunol 2019;10:2099. [CrossRef]
18. Brännström M, Mayrhofer G, Robertson SA. Localization of leukocyte subsets in the rat ovary during the periovulatory period. Biol Reprod 1993;48:277-86. [CrossRef]
19. Naqvi S, Godfrey AK, Hughes JF, Goodheart ML, Mitchell RN, Page DC. Conservation, acquisition, and functional impact of sex-biased gene expression in mammals. Science 2019;365:eaaw7317. [CrossRef]