

Maternal Supraphysiological Hypercholesterolaemia Identifies a Distinct Atherogenic Lipid Profile in Pregnancy

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Abstract

Maternal lipid metabolism undergoes marked physiological changes during pregnancy. Maternal supraphysiological hypercholesterolaemia (MSPH) where cholesterol levels exceed physiological limits, has been associated with adverse cardiovascular outcomes in both mother and offspring, but data from Asian populations are limited. We aimed to characterise the lipid profile and assess the cardiovascular risks associated with MSPH, in a multi-ethnic Singaporean cohort.

In this prospective observational study, term pregnant women without comorbidities were recruited in a tertiary maternity hospital in Singapore. Lipid profiles, apolipoproteins, oxidised low-density lipoprotein (oxLDL), atherogenic index of plasma (AIP), endothelial dysfunction markers, and antioxidant capacity were compared between MSPH and physiological hypercholesterolemia (MPH) groups.

Among 32 participants, 31.3% had MSPH. These women exhibited significantly higher total cholesterol, LDL-C ($p<0.001$), ApoB, ApoCII, ApoCIII, and oxLDL levels ($p<0.05$). OxLDL correlated strongly with LDL-C ($r=0.82$) and ApoB ($r=0.70$). A greater proportion of MSPH women had elevated AIP (70% vs 50%), indicating higher risk for cardiovascular disease (CVD), while endothelial dysfunction and antioxidant markers were comparable.

MSPH affects 30% of metabolically uncomplicated pregnancies and is associated with elevated cardiovascular risks. Pregnancy can serve as a window for early cardiovascular risk identification and lipid screening during pregnancy will be useful in this stratification.

Introduction

Maternal lipid metabolism undergoes marked physiological adaptation during pregnancy to support fetal development, with progressive increases in circulating cholesterol and triglycerides^{1–3}. This adaptive process is referred to as maternal physiological hypercholesterolemia (MPH) and is characterised by total cholesterol (TC) levels within a defined gestational range of ≤ 7.24 mmol/L at term^{1–3}. However, a subset of pregnancies exhibit maternal supraphysiological hypercholesterolemia (MSPH, TC at term > 7.24 mmol/L), characterised by excessive elevation of TC without overt metabolic disease^{4–6}. This condition is primarily associated with increased LDL-C level, although the mechanism behind its occurrence is still unknown.

Evidence indicates that MSPH is associated with larger atherosclerotic lesions in the arteries of fetuses and children of these women, together with an increased severity of myocardial infarction in adulthood compared to MPH offspring^{2,7,8}. A recent study also reported elevated levels of lipid peroxidation in the serum of MSPH women along with a pro-atherogenic profile of maternal LDL-C, which contribute to a pro-oxidative environment compared to MPH⁹. While MSPH has been reported in approximately 25–35% of pregnancies in Western and South American cohorts^{9,10}, data from Asian populations remain sparse. Ethnic differences in lipid metabolism and cardiometabolic risk profiles highlight the need for population-

specific evaluation^{11,12}. Furthermore, most existing studies have focused primarily on lipid concentrations, with limited exploration of downstream cardiovascular risk markers. Beyond conventional lipid measurements, apolipoprotein profiles and derived indices such as the ApoB/ApoA-I ratio and atherogenic index of plasma (AIP) provide a more integrated assessment of atherogenic risk. Whether MSPH is associated with alterations in these markers in Asian populations remains unclear. This study aimed to characterise the lipoprotein phenotype and cardiovascular risks associated with MSPH, with a focus on ApoB-containing particle burden, oxidised low-density lipoprotein (oxLDL), and triglyceride-derived indices in a Singapore cohort.

Results

A total of 32 women were recruited. Of these, 10 women (31.3%) met the criteria for MSPH, while 22 women (68.7%) were classified as having MPH. The maternal age, BMI and weight gain between the women at term with MSPH and MPH were 31.0 ± 2.8 vs 32.0 ± 3.8 years old, 25.1 ± 1.9 vs 26.3 ± 2.7 kg/m² and 10.5 ± 3.5 vs 11.6 ± 4.0 kg respectively (Table 1), without statistically significant differences between them. The two groups also have comparable systolic and diastolic blood pressures (111.2 ± 8.4 vs 115.4 ± 10.2 mmHg and 69.6 ± 11.4 vs 73.2 ± 9.3 mmHg respectively) as well as birthweight of their newborns (3131.3 ± 338.0 g vs 3179.4 ± 346.9 g). All the above indicate a matched cohort with comparable baseline characteristics. There is also no significant difference between the two population in terms of mode of delivery ($p = 0.71$).

Table 1
Clinical Demographics of Participants

Age, years	MSPH (10)	MPH (22)
	31.0 ± 2.8	32.0 ± 3.8
BMI, kg/m ²	25.1 ± 1.9	26.3 ± 2.7
Prepregnant weight (kg)	52.8 ± 7.1	55.4 ± 7.1
Weight at Time of Labour (kg)	63.4 ± 8.19	68.2 ± 8.7
Weight gain	10.5 ± 3.5	11.6 ± 4.0
G.A.@ delivery (weeks)	37.9 ± 1.2	38.4 ± 1.2
Systolic Blood Pressure (mmHg)	111.2 ± 8.4	115.4 ± 10.2
Diastolic Blood Pressure (mmHg)	69.6 ± 11.4	73.2 ± 9.3
Baby's Birthweight (g)	3131.3 ± 338.0	3179.4 ± 346.9
Ethnicity	N (%)	
Chinese	8 (80)	16 (72.7)
Malay	2 (20)	4 (18.2)
Indian	-	-
Others	-	2 (0.1)
Mode of Delivery	N (%)	
Vaginal Delivery	5 (50)	13 (59.1)
Caesarean Section	5 (50)	9 (40.9)

Women with MSPH have significantly higher TC levels compared to women with MPH (8.9 ± 1.3 vs 6.5 ± 0.6 mmol/L, $p < 0.001$). LDL-C levels were also significantly elevated in the MSPH group (4.8 ± 1.3 vs 3.2 ± 0.7 mmol/L, $p < 0.001$). Triglycerides and HDL-C levels while higher in women with MSPH were not statistical significant (Fig. 1). Women with MSPH exhibited significantly higher serum levels of ApoB, ApoCII, and ApoCIII compared to women with MPH ($p < 0.05$). Although the ApoB/ApoAI ratio was higher in the MSPH group (1.78 ± 0.37 vs 1.49 ± 0.49 in the MPH group), this difference did not reach statistical significance (Table 2).

Table 2
Apolipoproteins levels of participants as determined by Luminex. Apo B, CII and CIII were significantly elevated in participants with MSPH. **p = 0.004, * p = 0.01

Apolipoproteins (g/L)	MSPH (10)	MPH (22)
Apo A1	1.23 ± 0.22	1.16 ± 0.3
Apo B	2.16 ± 0.55	1.64 ± 0.39**
Apo CII	0.28 ± 0.10	0.19 ± 0.06**
Apo CIII	0.57 ± 0.41	0.43 ± 0.09*
Apo E	0.09 ± 0.37	0.08 ± 0.03
Apo B/ ApoAI Ratio	1.78 ± 0.37	1.49 ± 0.49

sICAM-1 measured 136.34 ± 35.51 ng/ml in serum of women with MSPH, which was comparable to 140.52 ± 31.54 ng/ml in women with MPH. sVCAM-1 levels were also comparable at 183.75 ± 105.84 ng/ml in women with MSPH and 190.75 ± 72.96 ng/ml in women with MPH. The total antioxidant capacity assessed by FRAP assay demonstrated comparable levels between groups (1177.34 ± 123.16 uM in MSPH group vs 1144.80 ± 233.13 uM in MPH group) (Fig. 2).

Mean AIP values were similar between groups (0.23 ± 0.23 in MSPH vs. 0.22 ± 0.20 in MPH; not statistically significant). Nevertheless, a high AIP, reflecting an increased risk for cardiovascular disease, was more prevalent among women with MSPH (70%) than among those with MPH (50%) (Fig. 2iv, p-value = 0.009). Overall, more than half of the study population (56.3%) demonstrated a high AIP regardless of hypercholesterolaemia status. There were no statistically significant differences in sICAM-1, sVCAM-1, or FRAP levels between women with high AIP (> 0.24) and those without. Oxidised LDL in MSPH women averaged 112.1 ± 25.4 U/L, representing a 34% increase compared with the 83.3 ± 19.7 U/L in the women with MPH (Fig. 2v, p-value < 0.002). There was a strong correlation of oxLDL with LDL ($r = 0.82$) and ApoB ($r = 0.70$, $p < 0.001$) and not with AIP, TG or HDL ($r = 0.27$, 0.28 and -0.18 respectively, $p > 0.05$).

Discussion

In this study, we report that maternal supraphysiological hypercholesterolemia (MSPH) is present in approximately one-third of otherwise metabolically uncomplicated pregnancies at term at a tertiary maternity hospital. By the restrictive inclusion criteria's of our cohort, we aimed to isolate the contribution of supraphysiological hypercholesterolaemia itself to cardiovascular risk in pregnancy. The clinical characteristics of the cohort such as BMI, blood pressure, body weight, weight gain during pregnancy and offspring's birthweight were comparable (Table 1), suggesting that the difference observed in cardiovascular risks could be mainly attributed to the observed lipid levels. The incidence of

31% is consistent with reports from Western, specifically South American populations^{9,10}, suggesting that MSPH is a common pregnancy-associated condition across diverse ethnic groups including Asians.

Typically, a high AIP indicates increased risk for CVD¹³, although it is also established that levels of lipoprotein particles and lipids increase greatly, approximately 50% more for cholesterol and 200% for triglycerides at delivery which would likely be in the atherogenic range when compared to non-pregnant levels in women of comparable ages without medical co-morbidities^{14,15}. Hence, elevated AIP is common in late pregnancy due to physiological hyper-triglyceridaemia, and its prognostic significance in this setting should be analysed with this caveat in mind. Mean AIP of MSPH women in our cohort (0.23) is lower than that of the South American cohort⁹ (0.267) but there was ultimately no significant difference in the absolute mean AIP between the two populations in both cohorts. In terms of proportion, 50% of the women with MPH and 70% of women with MSPH in our study demonstrated a high AIP which is rather similar to the South American cohort (47.06 in MPH and 65.22 in MSPH) with a significantly higher proportion of MSPH women with AIP indicative of high risk for CVD ($p = 0.009$).

In our cohort, MSPH was associated with a distinct atherogenic lipid phenotype characterised by elevated LDL-C, increased ApoB-containing lipoproteins, and higher oxidized LDL levels, indicating an increased burden of proatherogenic particles. Despite comparable clinical characteristics between groups, women with MSPH exhibited biochemical features consistent with increased atherogenic risk. The elevation in ApoB, ApoCII, and ApoCIII further highlights the contribution of lipoprotein particle number and composition beyond conventional lipid measures. Consistent with prior studies, apolipoprotein-based indices provide a more integrative assessment of cardiovascular risk than lipid concentrations alone^{16–18}.

The ApoB/ApoA1 ratio represents the balance of proatherogenic and antiatherogenic lipoproteins and is strongly correlated with increased coronary risks¹⁹. Women with MSPH in our cohort have a higher ratio (1.78) as compared to the women with MPH (1.49), although this difference did not reach statistical significance, likely due to the limited sample size. Our observed ratio of 1.49 is comparable to the value of 1.43 reported in the MPH population of a Chilean cohort, whereas the ratio of 1.78 is substantially lower than 2.43 reported for the MSPH population of the same Chilean cohort¹⁰. All our ratios are much higher than that reported in a cohort in Southeast China comprising 98% of Han ethnicity²⁰. In that China study, the average ApoB/ApoA1 ratio of women sampled within 24 hours of delivery is only 0.7, with values of TC, TG, LDL-C and HDL-C similar to that of our MPH population. Their antiatherogenic ApoA1 level of 1.8g/L is higher than our cohort (MPH: 1.16, MSPH:1.23) while their atherogenic ApoB level of 1.2g/L is lower than our cohort (MPH: 1.64, MSPH:2.16), highlighting the higher ratios and increased cardiovascular risk particularly in our MSPH patients²⁰.

While LDL is necessary for normal body function, high levels can lead to accumulation of lipids on the walls of the arteries, causing atherosclerosis. Oxidised LDL, where LDL has undergone oxidation by free radicals and other oxidative agents, has also been shown to be a sensitive marker of CVD^{21–23}. We

found higher levels in women with MSPH ($p < 0.002$), with strong correlation with LDL and ApoB levels ($r \geq 0.7$, $p < 0.001$) and not with AIP, TG or HDL-C ($r = 0.27, 0.28$ and -0.18 respectively, $p > 0.05$). This pattern suggests that oxLDL levels were predominantly driven by LDL particle burden rather than TG-rich dyslipidaemia or HDL-related antioxidant capacity. ApoB levels reflects the number of circulating atherogenic lipoprotein particles; thus, the strong association between ApoB and oxLDL supports a substrate-driven oxidative model whereby increased LDL availability proportionally increases oxidized lipoprotein formation. In our cohort, the lack of correlation between AIP, TG or HDL with oxLDL suggests that the primary determinant of LDL oxidation is unlikely to be TG-driven metabolic changes and suggests the absence of a distinct systemic oxidative stress syndrome in our cohort.

Contrary to expectations, we did not observe differences in endothelial dysfunction markers or total antioxidant capacity between the women with MSPH and MPH ($p > 0.6$ for sVCAM-1, sICAM-1 and FRAP) as shown in other cohorts¹⁰. Additionally, there were no differences in these markers when comparing the women without and with high (> 0.24) AIP indices. This observation suggests that raised AIP may be an early manifestation that precedes endothelial dysfunction and hence, longitudinal follow up may be of importance.

Our findings suggest the presence of two distinct lipid axes at term pregnancy: an LDL/ApoB-driven pathway associated with MSPH and oxidised lipoproteins, and a TG/HDL-driven pathway reflected by AIP, which may represent broader metabolic adaptation rather than direct atherogenic processes and MSPH appears characterised by an ApoB-associated increase in oxidised lipoproteins, supporting a substrate-driven mechanism of LDL oxidation.

Current obstetric practice does not routinely incorporate lipid screening during pregnancy, and elevated cholesterol levels are often dismissed as physiological. This identification of MSPH as a common condition associated with adverse cardiovascular risk markers raises the possibility that pregnancy represents a critical window for cardiovascular risk stratification in women²⁴ and long term follow up of them may be important to determine their risk postpartum.

Strengths of this study include the exclusion of major metabolic confounders, a multi-ethnic Asian population and the comprehensive assessment of cardiovascular risk markers. Limitations include the modest sample size and the cross-sectional design which precludes causal inference and long-term outcome assessment. Larger longitudinal studies are required to determine whether MSPH predicts future CVD in both mothers and offsprings. Generalisability to population with demographics beyond our study should also proceed with caution.

MSPH remains an under-recognised condition with increased risk of CVD and potentially important long-term implications. Our findings contribute to a growing body of evidence linking maternal lipid dysregulation with future cardiovascular risk in both mother and offspring^{1,2,7-9}. This should guide our care for pregnant women, including close monitoring of lipid levels during pregnancy, early identification of women at risks and following up on the dyad postpartum for the at risk group. Larger longitudinal

studies are also needed to determine the implications of MSPH on long-term maternal and offspring cardiovascular health that will aid from targeted monitoring and follow-up strategies during and after pregnancy.

Materials and Methods

Ethics Approval

The current study was reviewed and approved by the SingHealth Centralized Institutional Review Board (CIRB 2013/215/D). Informed written consent was obtained for all participants before their participation in the study at KKIVF Centre, KK Women's and Children's Hospital. All experimental procedures were performed in accordance with the relevant guidelines and regulations.

Inclusion and Exclusion Criteria

Our inclusion criteria are women delivering at term in KK Women's and Children's Hospital. Women were excluded if they had maternal obesity at term, excessive gestational weight gain, pregestational or gestational diabetes mellitus, preeclampsia, fetal growth restriction, previous clinical history of hypercholesterolemia or other significant maternal medical conditions. Exclusion criteria were deliberately stringent to minimise confounding by established cardiometabolic conditions.

Sample Collection and Processing

Maternal blood was obtained from brachial venupuncture at admission. Lipid (TC, high density lipoprotein (HDL), LDL, and triglyceride (TG)) levels measured by the clinical laboratory in KK Women's and Children's Hospital using standardised assays. Serum was obtained by centrifugation at 1000g for 10min after allowing the blood to clot for 30min. The serum was then stored at -80°C in aliquots till used in batches for measurements determination as follows.

Apolipoproteins Determination

Apolipoprotein(Apo) AI, ApoAII, ApoB, ApoCII, ApoCIII, and ApoE levels were determined in maternal total serum from MPH and MSPH women by Luminex using the MILLIPLEX Human Apolipoprotein Magnetic Bead Panel—Cardiovascular Disease Multiplex Assay (APOMAG-62K; Merck Millipore, Billerica, MA, USA), as described²⁵. The ApoB/ApoAI ratio was calculated as an established surrogate marker of atherogenic risk^{26,27}.

Endothelial Dysfunction Determination

Endothelial dysfunction markers; soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) levels were determined in maternal total serum from MPH and MSPH women by enzyme-linked immunosorbent assays (ELISA) kits (Human ICAM-1/CD54 Allele-specific Quantikine ELISA Kit and Human VCAM-1/CD106 Quantikine ELISA Kit, respectively; R&D Systems, Minneapolis, MN, USA), as described²⁸.

Determination of Total Antioxidant Capacity in Serum

Antioxidant status was assessed by the ferric reducing ability of plasma (FRAP), as described²⁹. Briefly, 750 µL of FRAP solution (300 mmol/L of acetate buffer, 10 mmol/L of 2,4,6-tri(2-pyridyl)-1,3,5-triazine solution, and 20 mmol/L of FeCl₃·6H₂O in a 10:1:1 ratio) was mixed with 75 µL H₂O and 25 µL of serum and then incubated at 25°C for 30 min. The absorbance was determined at 593 nm. A standard curve of FeSO₄ was prepared for the quantitative determination of FeSO₄ as Fe²⁺ equivalents produced in the samples.

Cardiovascular Risk Markers

1. A. ApoB/ApoAI Ratio^{19,30} was calculated from the values of ApoB and ApoAI obtained in the maternal total serum from MPH and MSPH women as an established surrogate marker of atherogenic risk.
2. B. Atherogenic Index of Plasma was determined as the logarithmically transformed ratio of the molar concentrations of TG and HDL-C ($\log(\text{TG}/\text{HDL-C})$)^{13,31}. AIP values less than 0.11 was considered as low cardiovascular risk, between 0.11 and 0.24 as intermediate risk, and over 0.24 as high cardiovascular risk^{32,33}.
3. C. Oxidised LDL levels were determined by ELISA (Oxidised ELISA kit, Mercodia AB, Uppsala, Sweden) in duplicates as per manufacturers' instructions.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Comparisons between the MPH and MSPH groups were performed using Student's t-test (if normality of distribution is established) or the Mann–Whitney U test as appropriate. Categorical variables were compared with Fisher's exact test. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA).

Declarations

Funding Declarations

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Author Contributions

YF and JKYC study conceptualization and funding. YF designed and performed the experiments. AL, MC, FY and SL provided supervision. ES, JKYC consented patients and collected data. All authors read, reviewed and approved the final version of the article.

Data Availability Statement

The authors confirm that the data supporting the findings are available within the article. Please contact the corresponding author for more information.

Additional Information

The authors declare no conflicts of interest.

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Figures

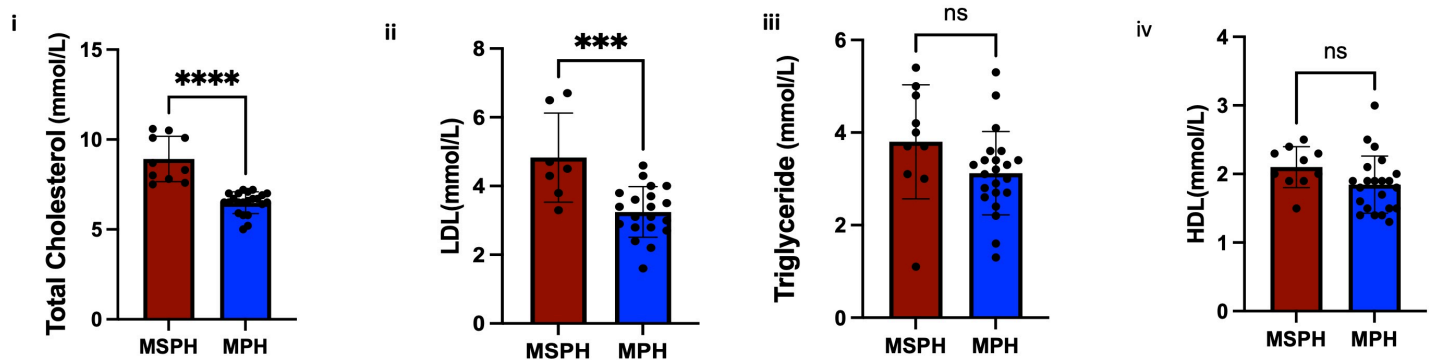


Figure 1

Lipid Profile of participants with and without MSPH. Total cholesterol (i) and LDL-C (ii) were found statistically elevated in participants with MSPH ($p \leq 0.0005$). Triglycerides (iii) and HDL-C (iv) while higher in the MSPH group, were not statistically significant.

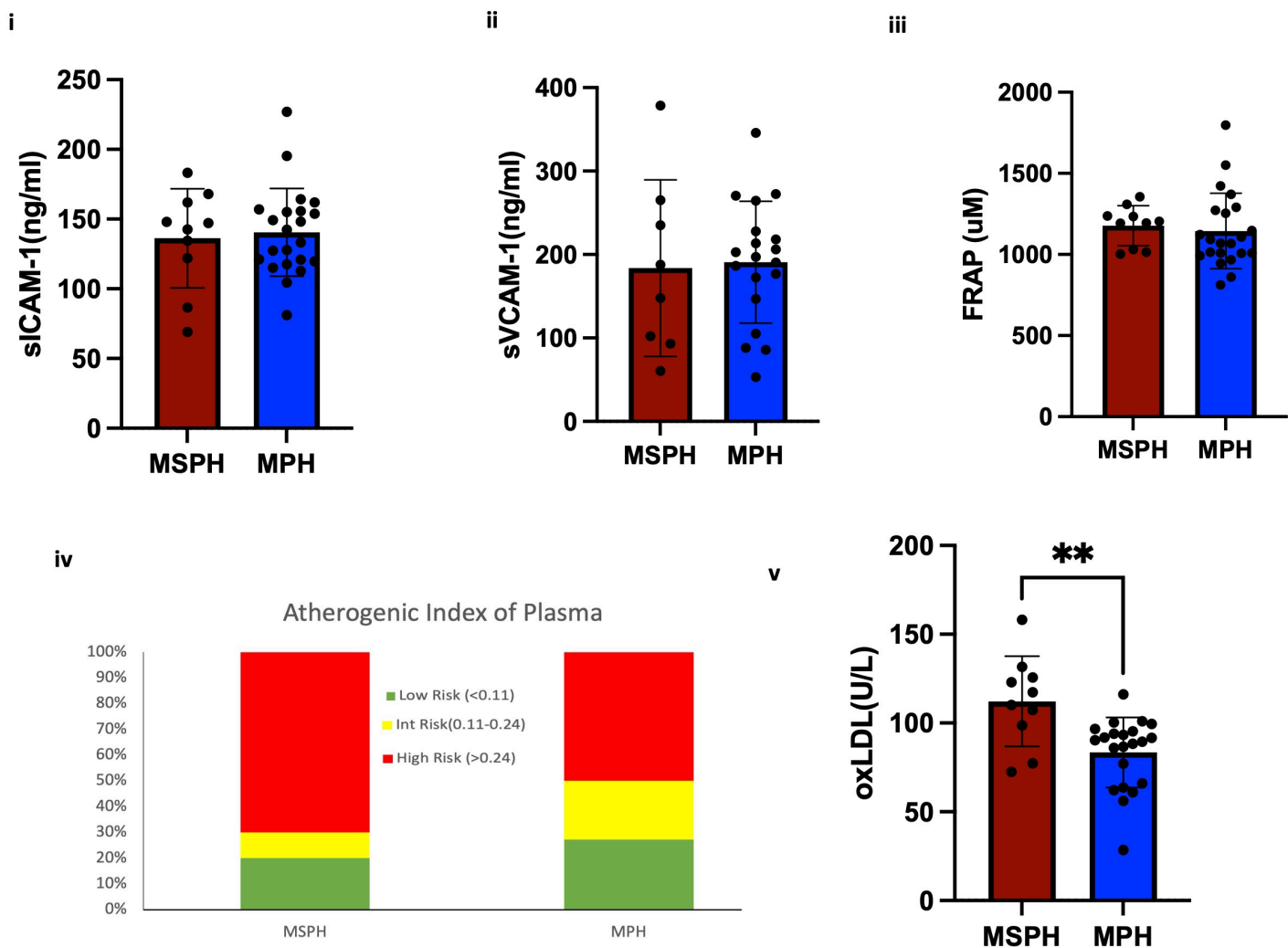


Figure 2

Endothelial Dysfunction, Antioxidant Capacity and Cardiovascular Risk comparison between women with MSPH and MPH. No statistically significant difference was found between the 2 groups for sICAM-1 (i), sVCAM-1 (ii) and antioxidant capacity (iii). Statistically higher proportion of women with MSPH have a AIP indicative of high risk of CVD (iv) ($p = 0.009$) and higher oxLDL levels (v) ($p < 0.002$).