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A Potential Role for Allostatic Load in Preeclampsia

Vanessa J. Hux, BS^{1,2} and James M. Roberts, MD^{2,3,4}

¹Vanderbilt University School of Medicine

²Magee-Womens Research Institute, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh

³Department of Epidemiology, University of Pittsburgh

⁴Clinical and Translational Science Research Institute, University of Pittsburgh

Abstract

Objective—Preeclampsia is a multisystemic disorder of pregnancy associated with maternal and fetal complications as well as later-life cardiovascular disease. Its exact cause is not known. We developed a pregnancy-specific multisystem index score of physiologic risk and chronic stress, allostatic load (AL), early in pregnancy. Our objective was to determine whether AL measured early in pregnancy was associated with increased odds of developing preeclampsia.

Methods—Data were from a single-center, prospectively collected database in a 1:2 individual-matched case control of women enrolled at <15 weeks gestation. We matched 38 preeclamptic cases to 75 uncomplicated, term deliveries on age, parity, and lifetime smoking status. AL was determined using 9 measures of cardiovascular, metabolic, and inflammatory function. Cases and matched controls were compared using conditional logistic regression. We compared the model's association with preeclampsia to that of obesity, a well-known risk factor for preeclampsia, by assessing goodness-of-fit by Akaike information criterion (AIC), where a difference >1-2 suggests better fit.

Results—Early pregnancy AL was higher in women with preeclampsia (1.25 +/- 0.68 vs. 0.83 +/- 0.62, $p=0.002$); women with higher AL had increasing odds of developing preeclampsia (OR 2.91, 95% CI 1.50-5.65). The difference between AIC for AL and obesity was >2 (AIC 74.4 vs. 84.4), indicating AL had a stronger association with preeclampsia.

Conclusion—Higher allostatic load in early pregnancy is associated with increasing odds of preeclampsia. This work supports a possible role of multiple maternal systems and chronic stress early in pregnancy in the development of preeclampsia.

Keywords

preeclampsia; allostatic load; stress; cardiovascular disease risk factors; racial disparities

Introduction

Preeclampsia is a multisystemic disorder of pregnancy clinically-diagnosed by hypertension and proteinuria and characterized by inflammatory activation and endothelial dysfunction. Preeclampsia occurs in approximately three percent of pregnancies in the United States and results in high maternal and perinatal morbidity and mortality. Risk factors for preeclampsia include obesity, pre-existing diabetes or hypertension, lower socioeconomic status, older maternal age, non-smoking status, and African American race.(1) Preeclampsia is also associated with at least a two-fold increase in risk for later-life cardiovascular disease (CVD).(2) Preeclampsia shares many risk factors with CVD; like CVD, it is complex and involves dysregulation within multiple maternal systems, including the cardiovascular, renal, and immunologic systems. It is also thought that preeclampsia develops as a result as an interaction of both maternal constitutional factors as well as abnormal placentation. (3) It is likely that there are many factors contributing to preeclampsia rather than a single pathway to disease.

In light of this, a useful approach to studying risk for preeclampsia would be one that assesses multiple systems. Allostatic load is an index of multisystem physiologic risk that is used as a measure of the cumulative toll of physiologic and psychological stress.(4) It assumes multisystemic interactions and incorporates subclinical biomarkers of neuroendocrine, inflammatory, metabolic, and cardiovascular function into a single index score.(5) Higher allostatic load is associated with many adverse health outcomes and is a better predictor of CVD than traditional individual measures.(6) Given that it is higher in African Americans and individuals of lower socioeconomic status(7), it also may contribute to persistent differences in health outcomes in these groups. The association between allostatic load and adverse health outcomes may also extend to adverse pregnancy outcomes. (8-11) No pregnancy-specific model of allostatic load exists. Since many of the analytes conventionally included in the allostatic load index change with pregnancy, it is necessary to select the appropriate time point and biomarkers and to determine pregnancy-specific cut-points for increasing risk. Because of its association with CVD and ability to assess multiple systems, we hypothesized that allostatic load could contribute to the pathogenesis of preeclampsia and thus would be elevated prior to clinically evident disease. The purpose of this study was to determine whether allostatic load measured early in pregnancy was associated with increased odds of developing preeclampsia and to evaluate whether allostatic load was better at predicting preeclampsia than a well-known risk factor, obesity.

Methods

Study design and participants

A 1:2 individual-matched case control study was conducted using data and plasma samples collected in the Prenatal Exposures and Preeclampsia Prevention (PEPP) study, a longitudinal and cross-sectional study of pregnancy, at the University of Pittsburgh in 1997-2001. Longitudinal subjects enrolled prospectively and completed demographic information and questionnaires on medical and reproductive history, smoking, and nutrition. At the time enrollment, no psychometric measures of stress were included in the questionnaires. The institutional review board approved this study, and all participants

provided written informed consent. Subjects also provided urine, serum, plasma, and cord blood samples. We identified preeclamptic cases with plasma samples collected prior to 15 weeks gestation and stored at -80 °C. Cases were matched to women in the same cohort with term (greater than or equal to 37 weeks), uncomplicated deliveries and plasma samples collected at less than 15 weeks gestation. We matched cases and controls on well-known risk factors for preeclampsia: age, smoking status, and parity. We defined each of the matching criterion as follows: age +/- 3 years, lifetime cigarette use of greater than 100 cigarettes, and primiparity.

Preeclampsia definition

Preeclampsia was defined by criteria recommended by the American College of Obstetricians and Gynecologists as women with new-onset hypertension and proteinuria after 20 weeks of gestation. Hypertension was defined at an absolute value of 140 systolic and/or 90 diastolic mm mercury. Proteinuria was defined as any one of the following: 1) urine protein in labor >1+ catheterized or >2+ void, 2) urine protein in labor >300 mg within 24 hours, or 3) urine protein-creatinine ratio >0.3.

Allostatic load

We determined the allostatic load index score for each subject using measurements obtained at and lab values from stored plasma samples collected at less than 15 weeks gestation. To calculate allostatic load, we used 9 components representative of 3 domains of systemic function. We used systolic blood pressure, diastolic blood pressure, and pulse pressure for the cardiovascular domain; pre-pregnancy body mass index (BMI), total cholesterol, high-density lipoprotein (HDL), and non-fasting triglycerides for the metabolic domain; and c-reactive protein (CRP) and interleukin-6 (IL-6) for the inflammatory domain. For each component, subjects received a single point for each component in the high-risk range. We calculated individual domain scores by summing the points for components in that domain and dividing by the total number of components in that domain. Therefore, each individual domain score could range from 0 to 1. The allostatic load score was a continuous measure derived as the sum of the 3 domain scores and ranged from 0 to 3.

High-risk values were determined using empirical and national survey data of values obtained during the first trimester of pregnancy and study-specific data when this information was not available in a national dataset. We determined high-risk quartiles using weighted 75th or 25th (HDL only) percentiles from the National Health and Nutrition Examination Surveys (NHANES) from 1999-2006 for systolic blood pressure, diastolic blood pressure, pulse pressure, total cholesterol, HDL, and triglycerides. We used data in NHANES obtained from women with positive urine pregnancy tests who self-reported being between 1 and 3 months of gestation. We analyzed these data using an appropriate protocol and weighting variables defined in the NHANES tutorial.(12) The World Health Organization guidelines defined obesity as a BMI greater than or equal to 30 kg/m², which we used for the high-risk cut-off of BMI. Given variability among different assay kits for inflammatory markers, we used the 75th percentile cut-offs of data from the PEPP study population. For CRP, we obtained a cut-off value using previously collected data on the majority of study subjects in this time period.(13) For IL-6, we randomly selected 150

subjects from among those enrolled during this first time period and measured IL-6 values. We determined a 75th percentile cut-off from those values.

Physiologic measures and bioassays

Systolic blood pressure, diastolic blood pressure, and pulse pressure were obtained from a single measurement at <15 weeks estimated gestational age. In patients with more than 1 recorded blood pressure measurement at <15 weeks gestation, we used the earliest measure. Pulse pressure was calculated as the difference between systolic and diastolic blood pressures. Pre-pregnancy BMI was determined from self-reported weight and measured height. If pre-pregnancy weight could not be recalled (N=1), we used weight at enrollment. We measured cholesterol, HDL, and triglyceride by colorimetric assays (Pointe Scientific). Coefficients of variation (COV) were 6.5%, 4.7%, and 2.3%, respectively. IL6 was measured with Human Immunoassay Kit (Quantikine), COV=15.0%. CRP was measured using an enzyme-linked immune assay protocol with primary and secondary antibody by Bethyl Laboratories, COV=6.9%.

Statistical analyses

We used conditional logistic regression to compare demographic variables, biomarker values, and allostatic load comparisons between the preeclamptic cases and matched control groups. Significance was considered as $p < 0.05$. In considering covariates, we included demographic components into the model that demonstrated a univariate relationship to the outcome with $p < 0.05$.

We did exploratory analyses to evaluate the model. We used conditional logistic regression in univariate analyses of the cardiovascular, metabolic, and inflammatory domains of allostatic load. Because obesity is a well-established risk factor for preeclampsia, we compared the *a priori* model of allostatic load to that of obesity. We used Akaike information criterion (AIC) to compare the allostatic load model to a model including only obesity. For comparing AIC of the models, we considered a difference in the values of at least 1-2 between the models as a difference in the goodness-of-fit with the lower AIC model being the better-fit model for the outcome preeclampsia.⁽¹⁴⁾ We also determined AIC for the domains and any significant individual components for the comparison to the allostatic load model. All statistical analyses were conducted using Stata Statistical Software, Version 12 (Stata Statistical Software: Release 12, College Station, TX: StataCorp LP).

Results

We initially identified 39 preeclamptics and 78 matched controls. Following examination of the blood pressure data, it was found that three study subjects in the control group lacked blood pressure data in early pregnancy. Because two of these subjects were matched to the same preeclamptic subject, this individual was also excluded from those analyses, reducing the number to 113 subjects or 38 preeclamptic women and 75 matched controls. There was a significant difference in gestational age at delivery ($p < 0.001$) between the preeclamptic and control groups. Gestational age at which plasma samples were collected and blood pressure

was measured were not different ($p=0.31$, $p=0.46$). Because preeclampsia in these subjects was not determined to be associated with race or any socioeconomic variables, these were not included in the model as covariates. Values for the high-risk cut-off points are presented in Table 2. Preeclamptic women had significantly higher allostatic load in early pregnancy compared to their matched controls (1.25 ± 0.68 vs. 0.83 ± 0.62 , $p=0.002$). Higher allostatic load in early pregnancy was also associated with increasing odds of developing preeclampsia (OR 2.91, 95% CI 1.50-5.65). In this study, 10 preeclamptic women delivered at less than 37 weeks and of those 3 delivered at less than 34 weeks. These may have resulted in a shorter data acquisition to diagnosis of preeclampsia than the data acquisition to normal delivery. To test if this was explaining the differences, we conducted a sensitivity analysis of only those preeclamptic women ($n = 28$) who delivered at term (at or beyond 37 weeks) and their matched controls. Based on usual obstetric management at this stage of gestation women are delivered shortly after diagnosis allowing us to use date of delivery as a surrogate for time of clinical diagnosis. The gestational ages at delivery for these preeclamptic women and controls were not different (39.3 ± 1.2 wks vs. 39.6 ± 1.2 wks, $p=0.82$). Allostatic load score remained higher in the women who went on to develop preeclampsia (1.30 ± 0.74 vs. 0.80 ± 0.65 , $p=0.005$), and higher allostatic load was associated with increasing odds of developing preeclampsia (OR 3.20, 95% CI 1.42-7.17).

In evaluating the individual domains of allostatic load, only the cardiovascular and metabolic domains were significantly associated with preeclampsia ($p=0.008$, $p=0.046$). Among the individual components of allostatic load, systolic blood pressure, diastolic blood pressure, and body mass index were significantly higher among women who later developed preeclampsia ($p=0.002$, $p=0.024$, and $p=0.030$, respectively). No other individual biomarkers measured in early pregnancy had an association with preeclampsia (Table 3).

The AIC for the allostatic load model and obesity was 74.4 and 84.4, respectively, suggesting that allostatic load was a better-fit model and had a stronger association with preeclampsia than obesity alone. In evaluating the model fit of domains of allostatic load, AIC values for the cardiovascular, metabolic, and inflammatory domains were 77.2, 82.6, and 83.4, respectively. Similarly, the AICs for significant individual components systolic blood pressure, diastolic blood pressure, and body mass index were 75.5, 78.8, and 81.6, respectively. Thus, based upon these scores all of these variables were poorer predictors of preeclampsia than AL.

Discussion

We found an association between higher allostatic load scores in early pregnancy and preeclampsia. Furthermore, we demonstrated that an *a priori* allostatic load model had a stronger association with preeclampsia than a well-known risk factor, obesity, as well as any single component of the allostatic load index. Consistent with other studies, systolic blood pressure, diastolic blood pressure, and body mass index were all significantly higher in women who later developed preeclampsia.(15, 16) However, these differences are minimal in comparison to allostatic load, and allostatic load remained a better fit model in predicting preeclampsia. These findings are suggestive of subclinical multisystem dysregulation present in early pregnancy in women that later develop preeclampsia. This study reveals yet

another similarity between preeclampsia and CVD, both of which are associated with elevated allostatic load. Furthermore, as allostatic load is also considered a physiologic measure of the cumulative impact of chronic stress, these results suggest that chronic stress, such as having a lower socioeconomic background or belonging to a marginalized racial group, may be associated with pregnancy outcomes. It may explain some of the persistent health disparities in pregnancy and health outcomes observed with race and socioeconomic status.

In this study, we developed a novel allostatic load model specific to early pregnancy. The model is specific to the time of pregnancy at which sampling is performed (early pregnancy < 15 weeks) and also for the domains tested and the biomarkers included in each domain. Two previous studies have examined allostatic load in pregnancy. Wallace and Harville measured allostatic load using 5 biomarkers at 26-28 weeks gestation and found no racial difference in the effect of allostatic load on birth outcomes.(17) Morrison *et al* compared measurements of allostatic load in non-pregnant and pregnant women in NHANES and observed higher allostatic load findings consistent with previous work in non-pregnant women but did not observe them in pregnant women.(18) Neither model accounted for physiologic changes in the values of the selected biomarkers that occur across pregnancy. They either used results of values obtained at any time during pregnancy (Morrison) or in late pregnancy (Harville). We specifically selected early pregnancy as we believed allostatic load in early pregnancy would most closely reflect pre-pregnancy values and cumulative stress. This decision was also guided by preliminary findings of our prior study demonstrating an association between higher allostatic load in non-pregnant women with a history of delivering a smaller infant at term.(19)

A particular strength of this study is that many of the high-risk value cut-offs came from well-characterized and representative existing national data, making the model generalizable beyond this specific population. Notably, these cut off values did not include those for inflammatory markers, which because of substantial variability in published values, were determined in the study population. An additional strength of this model is the ability for the components to be measured in stored, non-fasting samples. In preliminary examinations of NHANES data, even values for triglycerides, which are often measured in fasting samples but which were accepted in this study as non-fasting, had similar mean and variance in comparison to fasting values in the first trimester (Unpublished data, 2013). This aspect of the model facilitates its application to future work in other populations and in studying other pregnancy outcomes.

These findings fit our understanding of the pathophysiology of preeclampsia and of stress in that both are understood to be associated with dysregulation in multiple physiologic systems. The association of the metabolic, inflammatory, and cardiovascular domains measured in early pregnancy with later preeclampsia is consistent with the involvement of these systems when preeclampsia is clinically evident. The fact that the cutoff values are all within the range of normal clinical values and that a combination of these subclinical values is associated with preeclampsia is consistent with the multisystemic nature of the disorder. Given the increased risk for later-life cardiovascular disease and death, it is not surprising that higher values for allostatic load, a multisystemic assessment of physiologic risk, is

associated with preeclampsia. These findings are consistent with those of studies of allostatic load in the elderly population, which found higher allostatic to be associated with increased 7-year mortality, declining physical and cognitive function, and increased risk of a cardiovascular event. (20) It is especially striking that the combination of these subclinical components had a stronger association with preeclampsia than well-known risk factor obesity. This was evident in assessment of the predictive values.

Higher allostatic load in women that become preeclamptic is also consistent with previous work on subjective assessments of stress and anxiety disorders. Women with higher stress in the third trimester have higher uterine artery resistance(21), and women with mood and anxiety disorders have an increased risk of preeclampsia.(22) Bereavement in the months prior to pregnancy is also associated with increased risk of preeclampsia.(23) An animal model for preeclampsia has also been developed using chronic stress induced by overcrowding.(24) This previous work suggests a plausible association between stress and preeclampsia, and this study suggests that the cumulative burden of stress may impact risk. Conceptually, allostatic load is a reflection of chronic stress and dynamic physiologic adaptation to stress and life experience, *allostasis*. Allostasis, in contrast to homeostasis, encompasses dynamic changes in physiology, such as increases in blood pressure or cortisol; however, chronic stimulation or hypervigilance lead to wear and tear on the body, reflected by allostatic load, and hasten the development of disease. (4, 6, 25, 26) Thus, chronic stress may lead to increases in damage or premature aging of organ systems and predispose women under these conditions to develop preeclampsia. This study did not include any subjective measures of stress, and the study design and small sample size limited our ability to detect whether subjective stress or chronic stress proxies are associated with preeclampsia and/or higher allostatic load in our study population. However, this allostatic load model still demonstrates an association between allostatic load and preeclampsia. Further work is needed to validate this pregnancy-specific model as a measure of stress consistent with previous associations of allostatic load with stress.

This study has several limitations. Though this matched design has advantages and allows us to study a relatively rare syndrome in pregnancy while controlling for key risk factors, this study population was not representative as this study population was enriched for preeclamptic women (33%), and we selected matches based on demographics of preeclamptic women. We are also limited by the small size of this study. These limitations of the study design and size may explain why we failed to detect an association between preeclampsia and race or socioeconomic status. In addition, though we have demonstrated that we can develop an allostatic load model in pregnancy that uses routinely stored samples, we were limited in the ability to use analytes that are direct primary measures of stress and neuroendocrine function, such as norepinephrine or cortisol that require specialized collection and storage techniques. This limited the model to only three domains. We also cannot ignore the fact that allostatic load shares many common biomarkers with those associated with obesity and metabolic disease. In this small study it is nearly impossible to disentangle the relationship between the two although, we found that allostatic load was a better predictor than the major metabolic factor contributing to preeclampsia risk, obesity. This early pregnancy model suggests that some systemic derangement exists prior to

preeclampsia onset; however, we still cannot say whether these changes existed prior to pregnancy or if we have already begun to observe physiologic changes in biomarkers due to abnormal placentation. In the sensitivity analysis examining the effect of the measurement-delivery interval by excluding women who delivered preterm, the allostatic load score remain significantly higher in women who later developed preeclampsia. These findings indicate that differences between women with normal outcome or preeclampsia are not likely to be explained by differences between the duration of time from data acquisition to outcome. They are consistent with our hypothesis that these differences exist very early if not prior to pregnancy. An ideal study would measure allostatic load immediately prior to pregnancy as well, but because over half of pregnancies in the United States are unplanned, enrolling patients planning to become pregnant would not only prove difficult but also introduce selection bias.

In summary, this study demonstrates an association between allostatic load in early pregnancy and preeclampsia. The model supports the concept that multisystem pathways may lead to the development of preeclampsia. This pregnancy-specific model of allostatic load is novel and future steps include validating this model in other data sets and applying this model in the study of other adverse pregnancy outcomes. Specifically, given proposed pathways and relationships of stress to growth restriction (27-29) and preterm birth (30) as well as associations with later-life cardiovascular disease,(31) such work would be particularly relevant. A larger study of preeclampsia and allostatic load would be particularly useful in examining subtypes of preeclampsia such as severe or early-onset preeclampsia as well as maternal complications, such as eclampsia, HELLP syndrome, and maternal death. Finally, though calculation of allostatic load incorporates only physiologic biomarkers, the concept also includes genetic, environmental, and behavioral factors. Behavior is a modifiable risk factor, and in particular, behavioral changes and effective interventions may influence both allostatic load and risk of pregnancy outcomes. Future study of interventions in individuals with higher allostatic load, such as exercise, social support, sleep interventions, and stress reduction techniques, may suggest ways in which we can reduce risk of preeclampsia in high-risk populations.

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Table 1
Demographic features of study participants

	Preeclampsia (N=38)	Controls (N=75)	p-value*
Age [†] (yrs)	26.1 +/- 6.3	25.6 +/- 6.0	-
>100 Lifetime Cigarettes (%)	60.5	60.0	-
Primiparous (%)	78.9	78.7	-
Gestational Age at Sample Collection [†] (wks)	9.2 +/- 2.3	8.6 +/- 2.4	0.31
Gestational Age at Blood Pressure Measurement [†] (wks)	9.1 +/- 2.5	8.5 +/- 2.3	0.46
Gestational Age at Delivery [†] (wks)	38.0 +/- 2.8	39.6 +/- 1.2	<0.001
White (%)	71.1	74.7	0.89
Black (%)	26.3	24.0	0.89
Married/Marriage-like (%)	57.9	50.1	0.43
Education Completed (%)			0.99
Less than High School	10.5	10.7	
High School	47.4	46.7	
Some college/ Tech/ Associate's	15.8	17.3	
College and Beyond	26.3	25.3	
SES Index Score [‡]	5.3 +/- 2.3	4.9 +/- 2.1	0.25
Public Assistance (%)	15.8	14.7	0.84
Obese (%)	31.6	16.0	0.065
Self-report Diabetes or Hypertension (%)	7.9	4.0	0.4

* All comparisons were made using conditional logistic regression. P-values were excluded for matched characteristics.

[†] Shown as mean +/- standard deviation.

[‡] We used a socioeconomic index variable previously generated by averaging the component scores of three variables: occupation, income and education.(32) For each variable we computed the cumulative percentage distribution and the midpoint of the percentage interval for each level of the variable constituted the score for that level.(33) The final socioeconomic score (SES) was obtained by averaging these three scores and dividing by 10.

Table 2
High-risk value cut-offs and sources for components of allostatic load

Component	High Risk Value	Source	N
Systolic Blood Pressure (mmHg)	115	NHANES *	206
Diastolic Blood Pressure (mmHg)	69	NHANES	205
Pulse Pressure (mmHg)	55	NHANES	205
High-density lipoprotein (mmol/L)	< 50	NHANES	193
Total Cholesterol (mmol/L)	185	NHANES	193
Triglycerides, non-fasting (mmol/L)	118	NHANES	193
Pre-pregnancy BMI (kg/m ²)	30	WHO Guidelines [†]	N/A
C-Reactive Protein (mg/L)	4.31	PEPP Study [‡]	1511
IL-6 (pg/mL)	2.03	PEPP Study Subgroup [§]	150

* NHANES: National Health and Nutrition Examination Surveys conducted from 1999-2006. Weighted high-risk percentiles calculated using an 8-year mobile examination center (MEC) weight value determined from provided 2-year and 4-year MEC weight values.

[†] WHO: World Health Organization

[‡] PEPP Study: Pregnancy Evaluation and Preeclampsia Prevention Study cohort from 1997-2001.

[§] PEPP Study Subgroup: Randomly selected 150 available plasma samples collected at <15 weeks gestation in the PEPP Study.

Table 3
Mean, standard deviation, median, and interquartile ranges for individual biomarker components of allostatic load

Component	Preeclampsics		Controls		p
	Mean +/- SD*	Median [IQR [†]]	Mean +/- SD*	Median [IQR [†]]	
Systolic Blood Pressure (mmHg)	119 +/- 15	120 [110-130]	111 +/- 12	110 [100-120]	0.002
Diastolic Blood Pressure (mmHg)	72 +/- 8	70 [70-78]	68 +/- 8	70 [60-72]	0.024
Pulse Pressure (mmHg)	47 +/- 13	44 [40-56]	43 +/- 9	40 [38-48]	0.054
BMI [‡] (kg/m ²)	28.1 +/- 8.0	25.1 [22.5-33.9]	24.7 +/- 6.3	22.2 [20.6-27.4]	0.030
Triglycerides (mg/dL)	102 +/- 59	78 [59-127]	86 +/- 40	082 [54-106]	0.10
Cholesterol (mg/dL)	159 +/- 30	162 [132-178]	161 +/- 33	157 [136-180]	0.74
HDL [‡] (mg/dL)	48 +/- 10	46 [40-55]	51 +/- 12	50 [44-58]	0.10
CRP [‡] (mg/L)	5.6 +/- 7.6	2.7 [0.82-7.8]	4.2 +/- 6.9	1.8 [0.62-4.0]	0.35
IL-6 [‡] (pg/ml)	2.1 +/- 2.1	1.5 [0.8-2.5]	1.7 +/- 1.6	1.3 [0.8-2.0]	0.24

* SD: standard deviation

[†] IQR: Interquartile range; 25th percentile – 75th percentile

[‡] Component abbreviations: BMI = body mass index; HDL = high density lipoprotein; CRP = C-reactive protein; IL-6 = interleukin-6