# Prospective Risk Factors for Increased Central Augmentation Index in Men and Women

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**BACKGROUND**
Arterial wave reflections are important determinants of central pressure pulsatility and left ventricular afterload. The augmentation index (AIx) is the most widely used surrogate of arterial wave reflections. Despite multiple cross-sectional studies assessing the correlates of AIx, little prospective data exist regarding changes in AIx over time. We aimed to assess the predictors of changes in AIx over time in adults from the general population.

**METHODS**
We performed radial arterial tonometry assessments a median of $3.18 \pm 0.4$ years apart on 143 nondiabetic adult participants in the population-based PREVENCION study. Central AIx was obtained using the generalized transfer function of the Sphygmocor device.

**RESULTS**
Predictors of the change in AIx over time were investigated. Among men (n = 67), the change in AIx was predicted by abdominal obesity (standardized $\beta$ for waist circumference = 0.34; $P$ = 0.002), impaired fasting glucose (standardized $\beta$ = 0.24; $P$ = 0.009), and the change in heart rate (standardized $\beta$ = −0.78; $P$ < 0.001). Among women (n = 76), the change in AIx was predicted by non–high-density lipoprotein cholesterol (standardized $\beta$ = 0.33; $P$ = 0.001), C-reactive protein levels (standardized $\beta$ = 0.24; $P$ = 0.02), change in mean arterial pressure (standardized $\beta$ = 0.33; $P$ = 0.001), and change in heart rate (standardized $\beta$ = −0.52; $P$ < 0.001).

**CONCLUSIONS**
Metabolic and inflammatory factors predicted changes in AIx over time, with important sex differences. Metabolic factors, such as abdominal obesity and impaired fasting glucose, predicted changes in AIx in men, whereas C-reactive protein and non–high-density lipoprotein cholesterol levels predicted changes in women. Our findings highlight the impact of sex on arterial properties and may guide the design of interventions to favorably impact changes in late systolic pressure augmentation.

*Keywords:* augmentation index; blood pressure; hypertension; prospective; gender differences; wave reflections.

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Hypertensive target organs are exposed to aortic pressure rather than brachial pressure.[1] Wave reflections, which arise in peripheral arteries and return to the proximal aorta during mid-to-late systole, augment central systolic pressure.[1] Late systolic pressure augmentation has been linked to both structural (increased concentric remodeling) and functional (impaired diastolic relaxation) changes within the left ventricle.[2–5] The central augmentation index (AIx), determined by the relative height of the first and second systolic peaks of the aortic pressure profile, has been shown to predict cardiovascular events.[6,7] Furthermore, recent data show that wave reflections are strongly associated with the risk of incident heart failure in the general population.[6] Therefore, it is important to characterize the determinants of increased wave reflections and late systolic pressure augmentation in the general population.

Central pressure augmentation is markedly influenced by sex (with women having greater augmentation than men) and aging (with a nonlinear increase that is most pronounced until age 50 years).[8–10] Although multiple cross-sectional studies have assessed the correlates of AIx[9,11–13] and some prospective studies have assessed the effect of aging on AIx,[14–16] to the best of our knowledge, prospective data regarding the role of metabolic and inflammatory factors on AIx are not available. This is important because measurements of arterial function assessed at a single time point may not incorporate the lifetime exposure history of individuals. Additionally, identifying predictors of change in AIx may aid in the design of future interventions that favorably impact wave reflections. In this study, we aimed to assess the factors associated with changes in central AIx over an approximately

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3-year period among men and women from the general population. Prior work has shown that participants in the PREVENCION study demonstrate particularly high levels of late systolic pressure augmentation, making this a suitable population to investigate determinants of AIx.[9]

## METHODS

### Study population

This study included a subsample of adults enrolled in the PREVENCION study. The objectives, design, and details regarding the sampling strategy of the PREVENCION study have been published previously.[17–19] PREVENCION is a population-based study undertaken in Arequipa, Peru. A probabilistic sample of the adult population of Arequipa aged 20–80 years was enrolled. After initial contact with participants at their household, a comprehensive evaluation was performed, which included a cardiovascular risk assessment. Measurements of classic cardiovascular risk factors and tests of cardiovascular structure and function, including radial arterial tonometry, were performed.[17–23] A convenience subsample of study subjects (n = 145) whose households were in geographic proximity to the study center were selected to undergo an additional follow-up visit a median of 3.18 ± 0.4 years after the baseline visit. Although associations between diabetes and AIx have previously been demonstrated,[24] the low prevalence of diabetes in the PREVENCION study and our subsample (n = 2) led us to restrict analysis to nondiabetics. This study was approved by the ethics committee of the Santa Maria Catholic University and University of Pennsylvania Institutional Review Board. All subjects signed a written informed consent.

### Baseline biochemical measurements

Samples of venous blood were obtained after at least 8 hours of fasting, and serum was used for biochemical measurements. Total cholesterol, serum glucose, and triglycerides were measured enzymatically by automated methods (Cobas Mira Assay; Roche, Basel, Switzerland). High-density lipoprotein (HDL) cholesterol was measured after precipitation of apoB-containing lipoproteins. Impaired fasting glucose was defined as fasting blood glucose of 100–125 mg/dl according to current American Diabetes Association criteria.[25] Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl or pharmacological treatment for diabetes. C-reactive protein was measured using a high-sensitivity assay (Kamiya Biomedical, Seattle, WA). All laboratory variables were measured within 1 week of AIx determination. Waist circumference was measured the same day as the AIx determination.

### Pulse waveform analysis

In both the baseline and the follow-up visit, blood pressure was measured with the auscultatory method, as described previously.[17,18] Using a commercially available system (SphygmoCor Px, AtCor Medical, West Ryde, Australia), the radial artery pressure waveform was recorded with a high-fidelity Millar applanation tonometer (Millar Instruments, Houston, TX) and calibrated with auscultatory brachial

blood pressure measurements. A synthesized aortic pressure waveform was obtained from the radial pressure waveform using the generalized transfer function of the SphygmoCor device.[1,9] The merging point of the incident and the reflected wave (inflection point) was identified on the aortic pressure waveform. The first and second systolic peaks ($P_1$ and $P_2$) of the derived aortic pressure waveform were recorded, with the augmented pressure being the difference between the two.[9] Aortic AIx was defined as augmented pressure expressed as a percentage of aortic pulse pressure (peak systolic pressure minus end-diastolic pressure). The reproducibility of AIx was assessed in 20 subjects at the beginning of the study, and its coefficient of variation was found to be 4.7%.

### Statistical analysis

The annual change in AIx was computed as AIx from visit 2 minus AIx from baseline visit divided by time in years. The predictors of the change in AIx were assessed with multivariable linear regression. Because of known sex differences in AIx, our analysis was prespecified to be sex stratified. Individual candidate predictors tested included waist circumference, active smoking, HDL cholesterol and non-HDL cholesterol, C-reactive protein levels (a marker of subclinical inflammation), and the presence of impaired fasting glucose. All models were adjusted for height and age, given the previously reported change in AIx with aging.[8–10,26] Because AIx is highly dependent on mean arterial pressure and heart rate,[9] all models were also adjusted for the change in mean arterial pressure and heart rate between the baseline and the follow-up tonometry procedure. Variables that were not normally distributed were log-transformed. Adjusted regression coefficients for each predictor along with 95% confidence intervals (CIs) were obtained. In each regression model, standardized regression coefficients ($\beta$) were computed using $Z$ scores for the change in AIx and each of the predictor variables. Our study had 85% power to detect associations with a standardized regression estimate ≥0.2 at a significance of $\alpha = 0.05$. Statistical significance was defined as $\alpha < 0.05$. Statistical analyses were performed using SPSS for Windows version 17 (SPSS, Chicago, IL).

## RESULTS

There were no significant differences between participants of the parent PREVENCION study who were included vs. those not included in this study in age, sex, body height, weight, body mass index, waist circumference, non-HDL cholesterol, C-reactive protein, baseline AIx, prevalent hypertension, or impaired fasting glucose (all $P > 0.05$) There were small but statistically significant differences between subjects in this subsample and those in the overall PREVENCION study for HDL cholesterol (48.1 vs. 42.3 mg/dl, respectively; $P = 0.047$) and heart rate (67 vs. 65 bpm; $P = 0.003$).

Table 1 shows the general characteristics of men and women enrolled in this study. There were no significant differences between men and women in age, body mass index, non-HDL cholesterol, impaired fasting glucose, current smoking, C-reactive protein, or heart rate (all $P > 0.05$) (Table 1). As compared with women, men included in this

study demonstrated a higher body height, weight, waist circumference, and HDL cholesterol and lower levels of AIx (all $P < 0.05$) (Table 1). During follow-up, mean arterial pressure values for women and men were 94 mm Hg (interquartile range (IQR) = 84–101) and 93 mm Hg (IQR = 88–102), respectively, without significant sex differences ($P = 0.32$). Heart rate values during follow-up were 69 bpm (IQR = 63–77) and 65 bpm (IQR = 60–77) in women and men, respectively, without significant sex differences ($P = 0.59$). The changes in heart rate or mean arterial pressure over time were not significantly different between men and women (both $P > 0.05$).

### Predictors of AIx change in women

Among women (n = 76), the change in AIx was predicted by non-HDL cholesterol (standardized $\beta = 0.36$; $P = 0.001$), (log-transformed) C-reactive protein levels (standardized $\beta = 0.24$; $P = 0.02$), the change in mean arterial pressure (standardized $\beta = 0.33$; $P = 0.001$), and the change in heart rate (standardized $\beta = -0.52$; $P < 0.0001$). The model explained 47% of the variability in the change in AIx over time (Table 2). When subjects taking antihypertensive medications were excluded from the analyses, this did not appreciably change the results (data not shown).

### Predictors of AIx change in men

Among men (n = 67), the change in AIx was predicted by abdominal obesity (standardized $\beta$ for waist circumference = 0.33; $P = 0.002$) and impaired fasting glucose (standardized $\beta = 0.24$; $P = 0.008$). The change in heart rate was also predictive of the change in AIx (standardized $\beta = -0.77$; $P > 0.0001$), whereas the change in mean arterial pressure was not a significant predictor in the multivariable model. The multivariable model explained 60% of the variability in the change in AIx over time (Table 3).

When subjects taking antihypertensive medications were excluded from the analyses, this did not appreciably change the results (data not shown).

### DISCUSSION

We examined the role of various cardiovascular risk factors as predictors of change in aortic AIx over a median of 3.18 years among a subsample of the PREVENCION study. We found that abdominal obesity and impaired fasting glucose independently predicted an increase in wave reflections over time in men, whereas increased heart rate and age were associated with decreased AIx over time. In women, non-HDL cholesterol, C-reactive protein levels, the change in mean arterial pressure, and the change in heart rate emerged as independent predictors of the change in AIx.

Our study is novel in that we prospectively assessed predictors of a change in AIx over time. Although a single measurement of AIx provides valuable information, understanding how AIx changes over time in relation to changes in other parameters gives additional insight into the determinants of AIx. Although previous studies have prospectively assessed the

**Table 1.** Differences between men and women included in this study

| Variable | Men (n = 67) | Women (n = 76) |
|---|---|---|
| Age, y | 48 (32–64) | 50 (36.5–63.5) |
| Body height, m* | 167 (163–172) | 154 (150–159) |
| Body weight, kg* | 76.25 (67.63–84) | 62 (53–69.5) |
| Body mass index, kg/m² | 26.52 (24.31–29.74) | 26.11 (22.55–29.12) |
| Hypertension, % | 29.4 | 18.2 |
| Waist circumference* | 94.8 (88.1–101.4) | 86.5 (77.3–94.3) |
| Non-HDL cholesterol, mg/dl | 155.7 (132.8–178.8) | 153 (130.1–182.9) |
| Impaired fasting glucose | 5.9 | 6.5 |
| HDL cholesterol, mg/dl** | 46.2 (39.6–52.2) | 49.6 (44–55.4) |
| Current smoking, % | 5.9 | 1.3 |
| C-reactive protein, mg/L | 128.4 (58.5–278.1) | 136.7 (63.5–252.6) |
| Baseline AIx, %** | 25 (9.25–34.75) | 32 (24–38) |
| Heart rate, bpm | 65 (60–77) | 70 (63–77.5) |
| Systolic blood pressure, mm Hg | 120 (110–135) | 120 (110–130) |
| Diastolic blood pressure, mm Hg** | 80 (70–85) | 75 (70–80) |
| Mean arterial pressure, mm Hg | 94 (89–103) | 92.5 (85.3–99) |
| Antihypertensive medication use, % | 4.5 | 3.9 |

Values indicate median (interquartile range) or percentage.
Abbreviations: AIx, augmentation index; HDL, high-density lipoprotein.
*$P < 0.0001$.
**$P < 0.05$.

**Table 2.** Predictors of the change in augmentation index in women (model $R^2$ = 0.47)

| Independent variables | Estimate ($\beta$) | Standard error for $\beta$ | Standardized estimate ($\beta$) | P value |
|---|---|---|---|---|
| Age, per 10 y | −0.329 | 0.223 | −0.18 | 0.15 |
| Smoking | −1.497 | 2.504 | −0.06 | 0.55 |
| Waist circumference, cm | −0.013 | 0.028 | −0.05 | 0.65 |
| Impaired fasting glucose | −0.541 | 1.17 | −0.04 | 0.65 |
| Non-HDL cholesterol, mg/dl | 0.028 | 0.008 | 0.36 | 0.001 |
| HDL cholesterol, mg/dl | 0.006 | 0.035 | 0.02 | 0.86 |
| Change in mean arterial pressure, mm Hg | 0.28 | 0.08 | 0.33 | 0.001 |
| Change in heart rate, bpm | −0.437 | 0.076 | −0.52 | <0.0001 |
| (Log) C-reactive protein, mg/dl | 0.695 | 0.286 | 0.24 | 0.02 |

Abbreviation: HDL, high-density lipoprotein.

**Table 3.** Predictors of the change in augmentation index in men (model $R^2$ = 0.60)

| Independent variables | Estimate ($\beta$) | Standard error for $\beta$ | Standardized estimate ($\beta$) | P value |
|---|---|---|---|---|
| Age, per 10 y | −0.415 | 0.209 | −0.20 | 0.05 |
| Smoking | −0.846 | 1.262 | −0.06 | 0.51 |
| Waist circumference, cm | 0.103 | 0.032 | 0.33 | 0.002 |
| Impaired fasting glucose | 3.574 | 1.31 | 0.24 | 0.008 |
| Non-HDL cholesterol, mg/dl | −0.004 | 0.009 | −0.04 | 0.66 |
| HDL Cholesterol, mg/dl | 0.032 | 0.031 | 0.09 | 0.31 |
| Change in mean arterial pressure, mm Hg | 0.002 | 0.084 | 0.003 | 0.98 |
| Change in heart rate, bpm | −0.724 | 0.085 | −0.77 | <0.0001 |
| (Log) C-reactive protein, mg/dl | −0.493 | 0.297 | −0.15 | 0.10 |

Abbreviation: HDL, high-density lipoprotein.

role of aging and sex in the progression of central pressures over time,[14–16] our study is the first to assess the role of modifiable factors, such as metabolic abnormalities and subclinical inflammation, as determinants of changes in AIx over time.

After adjustment for the change in heart rate and mean arterial pressure between the two serial measurements,[1,8–10] additional factors measured at baseline predicted the change in AIx over time. In our prespecified sex-stratified analyses, the predictors differed between men and women. In men, abdominal obesity and impaired fasting glucose emerged as independent predictors of an increase in wave reflections. Prior cross-sectional work demonstrated that increased abdominal obesity was associated with decreased AIx. This finding may have been due to a decrease in transmural aortic pressure gradient and consequent lowering of the operating stiffness point of the aorta or to subclinical left ventricular dysfunction manifesting as a lower degree of pressure augmentation for any given reflection magnitude.[9,11–13,27] Our study, however, which assessed the changes in AIx over an approximately 3-year period, found that increasing abdominal circumference over time was associated with an increase in AIx. The prospective direct relationship between abdominal obesity and AIx suggests that obesity results in progressive arterial dysfunction, resulting in increased late systolic pressure augmentation.

Interestingly, despite the lower values of AIx associated with diabetes mellitus demonstrated in large population-based samples (including the parent population from this study),[9,28] impaired fasting glucose was associated with an increase in AIx over time in men. It is possible that once diabetes mellitus ensues, the resultant large artery stiffening leads to impedance matching between the aorta and muscular arteries, leading to a decrease in wave reflections.[29] Such a phenomenon was documented among subjects with established type 2 diabetes, but not among those with impaired fasting glucose, in a recent large study.[28] Further prospective studies are required to determine the relationships between impaired fasting glucose, abdominal obesity, and AIx.

We found that non-HDL cholesterol and C-reactive protein were associated with an increase in AIx in women over time. These findings are consistent with previous studies and suggest that subclinical inflammation and endothelial dysfunction may be causal determinants of increased wave reflections and late systolic pressure augmentation.[11,30] These results are also consistent with previous studies that have indicated that statin therapy, which reduces both subclinical inflammation and low-density lipoprotein cholesterol, reduces AIx.[31–33] The impact of statin therapy on AIx has been related to both its

lipid-lowering effect and the reduction in C-reactive protein levels.[31] Furthermore, increasing evidence suggests that statin therapy improves endothelial function due to enhanced nitric oxide production, potentially leading to a reduction in AIx.[31,32]

Our study has several limitations. The PREVENCION study population demonstrated greater levels of AIx than other population-based cohorts.[9,17,34–37] Although this may raise concerns regarding the generalizability of our findings, the greater levels of AIx also make this group uniquely suited for studying wave reflections. However, the determinants of change in AIx in this population may not be generalizable to populations with different ethnic backgrounds or living at different altitudes above sea level. Future longitudinal studies in other ethnic groups (ideally in multiethnic samples) are needed. We did not measure carotid–femoral pulse wave velocity, an index of large artery stiffness. Finally, AIx is a complex index affected not only by wave reflections but also by the reflected wave transit time, heart rate, and the ventricular ejection pattern. Therefore, future studies that use formal wave separation analyses will be important to assess the predictors of change in wave reflection magnitude over time.

In summary, metabolic and inflammatory factors predict changes in AIx over time, but there are important sex differences in these relationships. Abdominal obesity, impaired fasting glucose, and change in heart rate emerged as risk factors for an increase in wave reflections in men, whereas non-HDL cholesterol, C-reactive protein levels, change in mean arterial pressure, and change in heart rate emerged as predictors of the change in AIx among women. Our prospective findings support a biologically plausible cause–effect relationship between these metabolic and inflammatory abnormalities and increased wave reflections. These findings may guide the design of future interventions to favorably impact long-term changes in late systolic pressure augmentation.

## ACKNOWLEDGMENTS

## DISCLOSURE

The authors declared no conflict of interest.

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