# Accelerated coronary atherosclerosis not explained by traditional risk factors in 13% of young individuals

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**Importance** Most individuals who die of sudden cardiac death (SCD) display very advanced lesions of atherosclerosis in their coronary arteries. Thus, we sought to identify and characterize a putative subpopulation of young individuals exhibiting accelerated coronary artery atherosclerosis.

**Objective** Our analysis of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study—which examined 2651 individuals, obtaining quantitative measurements of traditional risk factors for coronary heart disease (CHD)—aimed to identify individuals with advanced coronary artery lesions, and to determine whether risk factors could account for such rapid disease progression, or not.

**Design** Using the cross-sectional PDAY study data, an exploratory de facto analysis stratified the population by age and observed number of coronary raised lesions and examined these groups *via* Poisson regression modeling. A separate de novo approach utilized Poisson mixture modeling to generate low- and high-growth groups based on measurements of traditional risk factors, and identified factors contributing to disease progression.

**Participants** Participants, n = 2651 individuals aged 15–34, who had died of non-cardiac death, were recruited *post mortem*. Tissues and other samples were harvested for analysis (details in previously published PDAY studies).

Main Outcome(s) and Measure(s). Using quantitative measurements of raised coronary lesions and traditional risk factors of CHD, we sought to identify which risk factors account for disease progression.

**Results** A group of ~13% of the PDAY population exhibits accelerated coronary atherosclerosis despite their young age. Several traditional risk factors were associated with increased odds of inclusion in this subgroup, reflecting current understanding of these markers of disease. However, only age was a significant contributing factor to the observed coronary lesion burden.

**Conclusions** While a range of traditional risk factors contribute to an individual's inclusion to the identified subgroup with accelerated atherosclerosis, these factors, with the exceptions of age, are not able to predict an individual's lesion burden. Moreover, unattributed variances in observations indicate the need to study novel risk factors.

## Short summary

Hypothesis The extent of coronary atherosclerotic disease is limited and homogeneous within youth, and its progression can be accounted for by traditional risk factors in this population.

**Findings** A subpopulation (~13%) of the Pathobiological Determinants of Atherosclerosis in Youth cohort exhibited accelerated coronary artery atherosclerosis. While several traditional risk factors contribute to an individual's inclusion in this subgroup, these factors, with the exceptions of age, do not predict accurately an individual's lesions burden. Critically, unattributed variances in observations indicate the need for the identification of novel risk factors.

**Meaning** Screening of the general population at a young age for high-risk group membership could provide opportunity for disease prevention and avoidance of the worse complications such as myocardial infarction and sudden cardiac death later in life. (Am Heart J 2019;208:47-54.)

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Coronary heart disease (CHD) involves inflammation that causes the formation and growth of atherosclerotic plaques within the coronary tree.[1] For several decades, medical researchers and clinicians have focused on elucidating the underlying mechanisms of atherosclerosis and on the identification of risk factors and biomarkers for CHD. Even so, recognition of specific individuals at particular risk for serious and even deadly complications associated with CHD (*e.g.*, myocardial infarction (MI), sudden cardiac death (SCD), *etc.*) remains a major clinical challenge.

Many large prospective studies have attempted to elucidate connections between suspected "traditional" risk factors and their potential prognostic capabilities for cardiovascular related events. For example, the PROSPECT study of 697 individuals in the United States and Europe demonstrated that baseline demographics including age, sex, and race presented modest correlations with lesion formation and subsequent acute coronary events.[2] Moreover, the inclusion of clinical risk factors such as the history of diabetes and modifiable risk factors marginally increased this correlation.[3] The ARIC study consisting of nearly 16,000 individuals, examined measures of subclinical atherosclerosis and reported similar findings.[4] However, the majority of these large prospective studies placed focus on the enrollment of individuals already exhibiting acute coronary events and belonging to groups between the ages 50 and 65 years. The INTERHEART study included over 26,000 cases and controls, predominantly from these older aged groups, and demonstrated that a small number of risk factors were responsible for over 90% of the population attributable risk of acute MI for both men and women, suggesting that modification of risk factors in younger populations might be capable of reducing or preventing future coronary events.[5]

In contrast to most other population studies, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) was a study of 2651 younger individuals (between the ages of 15 and 34) who died of non-CHD-related causes.[6] The study sought to determine the relationship of known CHD risk factors with the observed extent of atherosclerosis. Specifically, in addition to the measurement of a number of traditional risk factors of CHD, the right coronary artery (RCA) of these individuals was analyzed for the presence of raised lesions (a collective term that includes simple fibrous plaques as well as complicated fibrous plaques exhibiting calcification, hemorrhage, ulceration, or thrombosis). For our analysis, we have selected raised lesions of atherosclerosis as the key marker for severity of CHD. Raised lesions define the disease burden within coronaries, which in turn has been established with overwhelming evidence as the best predictor of clinical outcome for an individual.[7] In contrast, the search for "high risk lesions" within coronaries did not produce information that surpasses the assessment of the coronary disease burden (either invasively or non-invasively) for a particular individual.[7]

In this current work, we have analyzed the unique PDAY cohort and probed for the existence of a subset of individuals exhibiting accelerated atherosclerosis in their coronary arteries at a young age, exemplified by the presence and extent of raised lesions. We identify this potentially high-risk group using two approaches: de facto (based strictly on the observed number of coronary raised lesions and an individual's age) as well as de novo (using regression modeling to partition the population based on recorded data for all of the measured traditional risk factors). Finally, we determined which risk factors—or combination of risk factors—can account for inclusion into this potentially high-risk subpopulation and contribute to accelerated disease progression.

## Methods

Detailed descriptions of the methods of collection and original analysis of subject samples have been published previously.[6,8,9] Importantly, individuals selected for the PDAY study represented those who had died of accidents, suicides, or homicides, and were otherwise in good health, lacking comorbidities such as cancer, heart disease or diabetes (commonly associated with atherosclerosis). An exploratory analysis began with the segregation of the total population of 2651 individuals into two main groups: a Comprehensive Cohort of 739 individuals (possessing complete observations for all measured risk factors with the exception of serum concentrations of C-reactive Protein, CRP), and the Partial Cohort of the remaining 1912 individuals. These cohorts were stratified by age, and a putative high-growth subgroup was identified in each cohort using the following de facto segregation method. For each age group within each cohort, the distribution of the number of raised lesions was examined, and observations found in the right tail of these distributions (representing those individuals with the highest prevalence of disease within their age group) were selected to form the high-growth group. Segregation of the groups from these distributions was selected to occur at the point $Q_3 + 1.5(Q_3 - Q_1)$, where $Q_3$ and $Q_1$ are the third and first quartiles of the distribution, respectively. Poisson regression was performed on the resulting low- and high-growth groups identified in each cohort. Because this analysis was exploratory only, multiple imputation was not performed. Moreover, because a substantial number of individuals were lacking data on serum levels of CRP (57% in the overall PDAY population, 71% in the Partial Cohort), this covariate was not included in this exploratory analysis. Remaining covariates to be retained in each fit model were determined using backward elimination.

**Table I.** Characteristics of data from exploratory analysis

| Variable | All observations | Comprehensive cohort | Partial cohort |
|---|---|---|---|
| N | 2651 | 739 | 1912 |
| Number in high-growth partition (%) | 345 (13.3%) | 93 (12.6%) | 252 (13.2%) |
| Number of raised lesions (Mean, SD) | 0.3810 (1.002) | 0.3789 (0.9683) | 0.3818 (1.015) |
| Race—White (N, %) | 1276 (48%) | 349 (47%) | 927 (48%) |
| Sex—Male (N, %) | 2001 (75%) | 549 (74%) | 1452 (76%) |
| Cholesterol, mg/dL (Mean, SD) | 194.4 (59.2) | 191.6 (60.27) | 196.5 (58.35) |
| HDL, mg/dL (Mean, SD) | 53.68 (21.06) | 53.45 (20.72) | 53.92 (21.41) |
| LDL, mg/dL (Mean, SD) | 136.8 (54.11) | 138.1 (56.39) | 135.7 (51.78) |
| Glycosylated hemoglobin, (Mean %, SD) | 6.537 (1.072) | 6.526 (0.9659) | 6.543 (1.118) |
| BMI (Mean, SD) | 25.22 (5.211) | 25.06 (5.260) | 25.28 (5.193) |

In addition to the exploratory analysis, de novo group identification was achieved using a two-group Poisson mixture model that was fit to the entire data set of 2651 observations. In this approach, the model itself was responsible for identifying those individuals belonging in the low- and high-growth subgroups, providing a more objective means of analysis following the population division. All analyses were performed using R 3.3.0.[10] The two-group Poisson mixture model fitting used the flexmix package version 2.3-14.[11] The process of multiple imputation was utilized in the two-group Poisson mixture model to account for observations with missing values, allowing them to be incorporated into the model.[12] Multiple imputation was handled with the mice package, version 2.30.[13] For additional details pertaining to model selection and methodology, see the Supporting Material.

## Results

### Exploratory analysis

Due to the high amount of missingness within the entire PDAY dataset, the 2651 members of the PDAY population were initially segregated into the 739-member Comprehensive Cohort presenting complete observations (with the exception of CRP), and the remaining 1912-member Partial Cohort. Table I summarizes the characteristics of data available for the entire PDAY population as well as the Comprehensive and Partial Cohorts.

Individuals within each cohort with an increased number of raised lesions (in comparison to others of their age group) were separated into a high-growth group for each cohort (see Methods). Poisson regression estimates for the parameters used to measure the number of raised lesions in each of these de facto identified high-growth groups appear in Table II (whereas full results including estimates of parameters in the models for the low-growth groups from each cohort can be found in e-Table 2 of the Supporting Material). Importantly, of the analyzed risk factors, age was the only parameter retained as significant in the prediction model estimating the number of raised lesions for individuals of the high-growth groups within both the Comprehensive and Partial Cohorts. Individuals of average age in the high-growth group of the Comprehensive or Partial Cohorts would be expected to have 1.892 or 1.812 raised lesions, respectively. For an individual in the Partial Cohort, a one-year increase in age would increase this value to $1.812*1.060*1.006 = 1.93$ raised lesions, while a four-year increase in age would result in $1.812*1.060^{4}*1.006^{16} = 2.52$ raised lesions. Although the models for the high-growth groups of the Comprehensive and Partial Cohorts are highly similar, the models for the low-growth groups of each cohort demonstrated marked differences in parameters that were retained as significant in addition to wide confidence intervals of determined effect estimates (see Supporting Material). To further refine our analysis, a two-group Poisson mixture model was applied to the entire PDAY population such that an individual's membership to the low- or high-growth groups could be achieved in a de novo manner.

### Two-group Poisson mixture model

Using a two-group Poisson mixture model, the PDAY population was segregated into low- and high-growth groups *via* logistic regression (Figure 1). Complete model fitting for group selection including the contribution of analyzed risk factors is given in Table III. These parameter estimates are aggregated from the estimates obtained with 100 imputed data sets (see Supporting Material for additional information). Those 100 model fits consistently identified 234 individuals as belonging to the high-growth group, with an additional 164 individuals sometimes included in the high-growth and sometimes included in the low-growth group. Thus, the identified high-growth group comprised between 8.8% and 15.0% of the study population. In comparison, a total of 345 individuals were identified as belonging to the high-growth group in the prior exploratory analysis utilizing de facto segregation. Of the 234 individuals consistently included into the high-growth group identified in this more objective de novo approach, 179 (76%) had also been identified in the initial de facto analysis. Overall, this

**Table II.** Parameter estimates for high-growth group by cohort

| Group | Parameter | Effect estimate (number of lesions scale) | 95% CI |
|---|---|---|---|
| Comprehensive Cohort | Intercept[a] | 1.892 | (1.611, 2.223) |
| | Age (y) | 1.078[b] | (1.045, 1.112) |
| Partial Cohort | Intercept[a] | 1.812 | (1.615, 2.033) |
| | Age (y) | 1.060[b] | (1.040, 1.080) |
| | $Age^2$ ($y^2$) | 1.006[b] | (1.003, 1.009) |

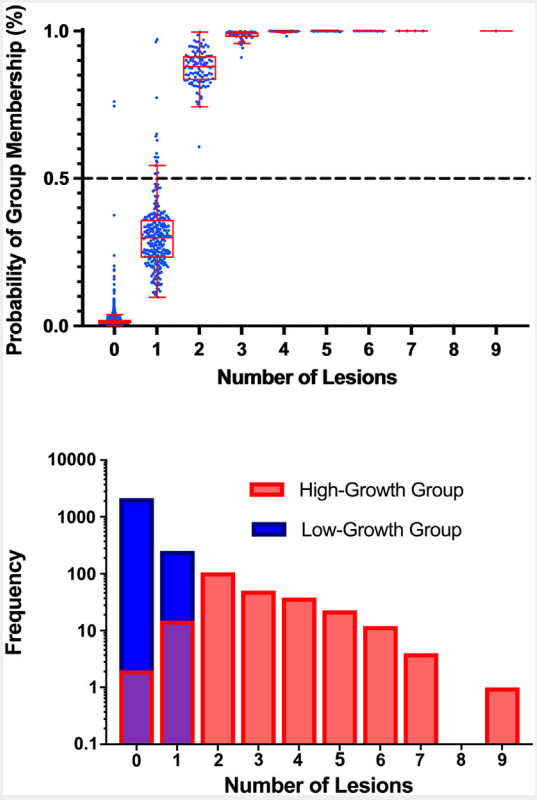
a Intercept represents lesion number for subjects of average age for given cohort
b Multiplier

**Table III.** Group selection model fitting, odds of individual inclusion to high-growth group

| Parameter | Effect estimate (odds scale) | 95% CI |
|---|---|---|
| Intercept[a] | 0.1281 | (0.0894, 0.1837) |
| Age (y) | 1.125[b] | (1.063, 1.1903) |
| Sex (Female) | 0.4417[b] | (0.2771, 0.7041) |
| Cholesterol (mg/dL) | 1.007[b] | (1.003, 1.0105) |
| HDL (mg/dL) | 0.9848[b] | (0.9729, 0.9968) |
| Glycosylated Hemoglobin (%) | 1.278[b] | (1.078, 1.515) |
| BMI | 1.070[b] | (1.037, 1.103) |

a Intercept represents odds of inclusion in high-growth group for men with average risk factor levels
b Multiplier

**Figure 1**




Separation of Low- and High-Growth Groups: (Top) Median probability of high-growth group membership. Each plotted point represents one of the 2651 observations in the PDAY data set and depicts the median probability of high-growth group membership among the 100 imputations for that observation. Box whiskers extend to 1.5 x interquartile range. The threshold for high-growth group classification is 50% and shown as a dashed line. (Bottom) Histogram of group classification with logarithmic scale for y-axis. Note that some observations have probabilities of high-growth group membership >50% for some imputations even if the median for that observation is <50%.

high-growth group had more men, individuals with slightly lower HDL, and slightly higher total cholesterol, glycosylated hemoglobin, and BMI than the low-growth group, as might be expected. Serum CRP levels were investigated for potential contributions to group membership but were not found to improve the model of group membership. Moreover, the effect of the included risk factors remained modest. The odds of inclusion to the high-growth group for a man of average age and average measurements for the risk factors listed in Table III are 0.1281, or approximately 1:8. A three-point increase in BMI increases these odds of high-growth group membership to only $0.1281*1.070^3 = 0.157$ or approximately 1:6, while a ten-point increase in total cholesterol increases the odds of high-growth membership to $0.1281*1.007^{10} = 0.137$, or approximately 1:7. In other words, while these parameters improved the fit of the model, their actual effects on the probability of membership in the high- or low-growth group were limited.

Similar to the exploratory analysis, the Poisson mixture model also examined estimates for the number of raised lesions for individuals in the high- and low-growth groups. These estimates are given in Table IV. At the population average age of 24.8 years, men in the low-growth group with average measurements of BMI would be expected to have on average 0.092 lesions, while men in the high growth group with average measurements of CRP would have 1.995 lesions. This represents an average of a staggering 22-fold increase in lesion formation in the high-growth group. By age 34, men in the low-growth group (with average BMI) would be expected to have on average 0.238 ($=0.092*1.111^{9}*1.058^{0}$) lesions, while those in the high-growth (with average CRP) group would be expected to have 2.84 ($=1.995*1.040^{9}*1.189^{0}$) lesions on average, a 12-fold increase. These results are even more pronounced for females, with a lower expected number of coronary lesions in members of the low-growth group, but no predicted effect of sex in the high-growth group. Interestingly, reflecting the initial

**Table IV.** Parameter estimates for low- and high-growth group from Poisson mixture model.

| Group | Parameter | Effect estimate (number of lesions scale) | 95% CI |
|---|---|---|---|
| Low-Growth | Intercept[a] | 0.09183 | (0.06693, 0.1260) |
| | Age (y) | 1.111[b] | (1.0581, 1.1670) |
| | Sex (Female) | 0.5774[b] | (0.3596, 0.9272) |
| | BMI | 1.058[b] | (1.028, 1.089) |
| High-Growth | Intercept[a] | 1.995 | (1.644, 2.422) |
| | Age (y) | 1.040[b] | (1.009, 1.071) |
| | $\log_{10}$(CRP) ($\log_{10}$(mg/L)) | 1.189[b] | (0.9195, 1.537) |

a Intercept represents lesion number for men of average age and average BMI for the low-growth group, and lesion number for subjects of average age and average $\log_{10}$(CRP) for the high-growth group
b Multiplier

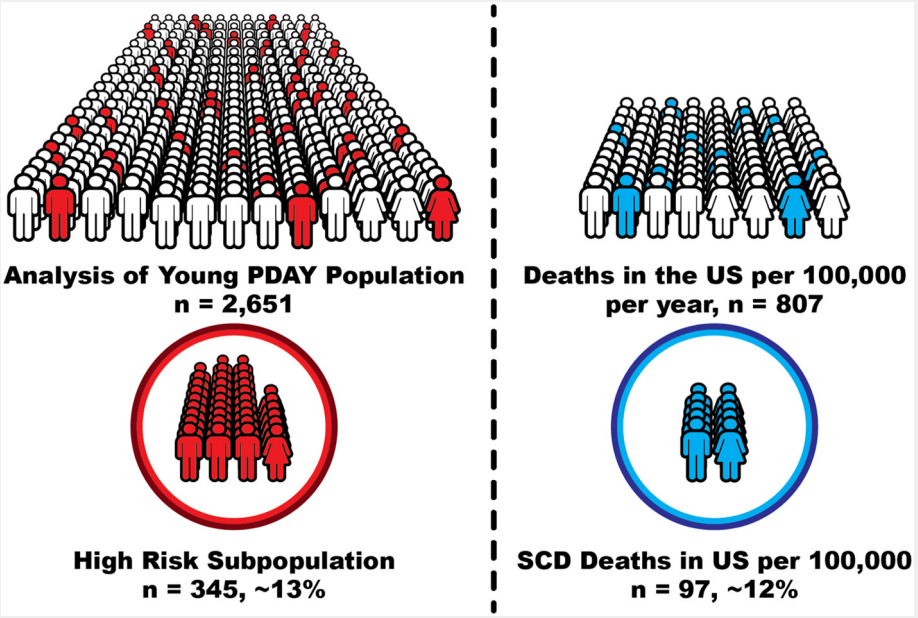
findings of the exploratory analysis, age remains the predominant variable for the estimation of the number of lesions in an individual of the high-growth group. Instructively, CRP was retained in the model to estimate lesion growth for the high-growth group, but its effects are modest. The model estimates that an individual in the high-growth group of average age and average levels of serum CRP would have 2.07 ($=1.995*1.040*1.189^{0}$) lesions. By comparison, the expected number of raised lesions for a high-growth group member of average age—but with a serum CRP level double that of the average—would increase only to 2.19 ($=1.995*1.040*1.189^{0.30}$) lesions (for additional information on calculating the effect of serum CRP on estimated numbers of lesions, see Supporting Material). Finally, it was observed that the number of lesions recorded for some individuals identified as belonging to the high-growth group noticeably exceeded the expected number of lesions predicted by the model. This important finding suggests that there may yet be unaccounted-for risk factors driving disease progression in this subset of the population.

## Discussion

Herein, we have reported the development of data-driven models (de facto and de novo) for the analysis of coronary artery atherosclerotic plaques and traditional CVD risk factors. Critically, our de novo model is capable of reliably segregating a young population of individuals with no known co-morbidities into 2 groups so-called low- and high-growth groups, that exhibit dramatically varying levels in atherosclerotic plaque burden. We have selected to exclusively examine the presence and extent of raised lesions, rather than flat lesions (such as fatty streaks), as a means to identify truly advanced atherosclerosis.[7] Using this developed model, we have identified a subset of individuals belonging to a high-growth group that represents approximately 13% of the young population, and exhibits markedly accelerated atherosclerosis within their coronary arteries, as assessed by measuring raised atherosclerotic lesions. By age 25, individuals of the identified high-growth group exhibit on average a 22-fold increase in lesion formation in their right coronary artery when compared to the remaining population. Moreover, this high-growth group continues to display accelerated disease progression through the oldest ages examined. Importantly, we demonstrated that although a number of the studied traditional risk factors contribute to an individual's group membership, none of these risk factors, with the exception of age, contributed to the estimation of the number of raised lesions that members of the high-growth group would exhibit.

In a prior study on SCD, we concluded that a proportion of approximately 12% of an aged population is at risk of SCD (Figure 2).[14] Our new report has identified a high-growth group relative to raised coronary lesions, such that 13% of a young population, with no known CHD, exhibits a level of coronary lesion severity that would cause individuals to be prone to SCD.[14,15] While it is tempting to speculate that these two similarly-sized groups may represent a single, high-risk human subpopulation, there is no fundamental reason to assume that these two populations represent the same individuals. It should be emphasized that the models generated in the present study cannot be directly extrapolated to ages beyond the range directly observed in this young population. The purpose of the model that we have produced is not to predict how disease within particular individuals of the PDAY population may have progressed into the future. Instead, we have identified a population already exhibiting accelerated atherosclerosis in their youth, and showed that known risk factors contributing to this condition could not account for the severity of detected lesions. It is likely that any similarity between the high-growth group identified in the current work and the group of individuals exhibiting SCD in the general population would be confined to just size. While both groups experience accelerated disease, the disease process might be quite different and thus governed by rather specific risk factors. Factors influencing the incidence of SCD are exceptionally diverse, extend way beyond simple atherosclerotic plaque burden, and

**Figure 2**




Comparison of Young and Aged Populations: A group of approximately 13% of the PDAY population of young individuals was identified as exhibiting markedly accelerated atherosclerosis. Population data and previous computational models have identified a similar proportion (approximately 12%) of aged populations as suffering from SCD. However, the results of the current work are not intended to suggest that these two populations represent the same individuals, only that these two populations represent similar proportions of the total population, and that the younger population exhibits advanced atherosclerosis for their age.

involve processes related to thrombotic diathesis, rhythm disorders, and other complex systems. Nevertheless, the relevance of raised lesions in the coronaries of SCD patients is demonstrated by the fact that they are present in greater than 80% of the SCD deaths in adults.[14] Moreover, the effects of particular risk factors in a young population could be different in an aged population. Specifically, while age was found to be of critical importance for disease progression in young individuals, its effects would likely be blunted or reduced in an aged population. Additionally, prolonged exposure to other traditional CHD risk factors may have a more pronounced effect in aged populations compared to the young individuals studied herein. All of this stated, the current study indicates that there is a sizable population of young individuals (a subpopulation equivalent in size to the group experiencing SCD) that experiences accelerated atherosclerosis early in life (Figure 2).

It is also important to note here that the studied PDAY population may not be fully representative of today's modern population of youth. The selection criteria of the PDAY study precluded any individuals with existing health conditions and comorbidities of atherosclerosis (diabetes, *etc.*), and relied on a population that was otherwise considered healthy. Moreover, in the general population, the prevalence of such conditions (including obesity) in youth has increased since the original PDAY study was conducted. Consequently, it is likely that the proportion of the population of youth identified with accelerated atherosclerosis within the PDAY study may be an underestimate of the true proportion in a modern population. As such, our results strongly invite that efforts be made to screen for this putative high-risk subpopulation prospectively at as young an age as possible—beyond what is currently recommended for the general population of children and young adults. Identification of these individuals at risk early could have a tremendous effect on disease prevention and on avoiding deadly outcomes, through more efficient disease management and treatment.

The results of this work also illustrate the importance of continuing to explore for new and unique potential risk factors and predictors of CHD. Potential candidates are as diverse as they are numerous, including increased plasma levels of homocysteine, the presence of cells exhibiting a senescence-associated secretory phenotype (SASP), accumulation of misfolded protein (amyloid-beta), small molecules derived from the gut microbiome, and numerous single nucleotide polymorphisms (SNPs).[16-20] It was recently reported that clonal hematopoiesis of

indeterminate potential (CHIP), a process that implicates the functional degeneration of the bone marrow, represents another such potentially causal factor for CHD and subsequent MI.[21] This work highlights the importance of bone marrow cells in the continuous maintenance of the homeostasis of arterial tissues,[22,23] including coronaries, and exemplifies the need to continue to uncover unique CHD biomarkers, and to develop new methods of identifying individuals or groups at greatest risk of CHD.

An important finding of the present work is that in addition to identifying a group of individuals with generally advanced atherosclerosis, a number of individuals were identified that exhibited substantially higher numbers of raised lesions than predicted by the developed model. Consequently, it may be that disease progression in the identified high-growth group is driven by one or more of these unexplored risk factors or by yet entirely unrecognized risk factors. Ultimately, all of these studies illustrate the importance of non-traditional risk factors in disease progression and identification of individuals not traditionally considered to be at risk. As an example, inherited single nucleotide polymorphisms (SNPs) may also contribute to the yet unexplained acceleration of disease in these individuals, as atherosclerosis and its thromboembolic consequences in young individuals seem to be more dependent on genetic modifiers than for older individuals.[24,25] While many SNPs confer only minor increases in CHD risk individually, the combined synergistic effect of multiple SNPs contributes significantly to the genetic susceptibility of coronary atherosclerosis.[24]

Our results demonstrate that elevated CRP contributes only modestly to determining the estimated number of lesions for individuals of the high-growth subset of the population. However, there was a high degree of missingness for CRP data that was handled *via* multiple imputation. Hence, it is difficult to draw precise information regarding the contribution of CRP to disease progression in the current model. As stated previously, although this risk factor was retained as improving the fit of the model, its effect on model predictions were marginal.

## Conclusions

The present work has identified an important group of young people for which atherosclerotic disease is accelerated beyond what traditional risk factors are capable of explaining. The results of this work suggest the need for identification of new biomarkers at the molecular and genetic level. Moreover, it also points out to the need to further explore the mechanisms responsible for normal endogenous arterial repair, from inflammation to bone marrow integrity, and the contributions of peripheral blood and local arterial environments. In this way, we may identify novel risk factors that result in failure to repair or to resolve atherogenic inflammatory processes,[26] failure that can be exacerbated by processes of arterial aging,[27] and thus promote premature and devastating atherosclerosis.[26,27] Subsequent development of novel therapeutic interventions, in combination with the known armament of therapeutic strategies (lifestyle changes, pharmaceuticals, and procedures), may prevent, retard, reduce, or block the development of new lesions, potentially reversing the process of atherosclerosis and preventing the onset of MI and/or other coronary events such as SCD. Ultimately, these advances could save numerous lives.

## Disclosure statement

Pascal J. Goldschmidt-Clermont serves on the Board of Director of Mednax (NYSE: MD), a provider of health solutions company, including for neonates, children ad adults.

## Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.005.

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