LV ejection fraction, which in itself may be related to reduced activity levels. Further, our data account for activity levels well outside the peri-implantation window, which mitigates the impact of periprocedural complications on the relationship between activity time and mortality.

Our study is limited by the relatively small study population. We did not include other pacing devices with accelerometers as their algorithms for determining active time may differ from the 2 devices included in this study. We elected not to include patients with defibrillators so as to reduce the confounding effects of impaired cardiac function on activity levels. Balanced against these limitations are the quantitative nature of our data, the novelty of the findings and their potential impact on the care of patients post-pacemaker implantation.

Physical activity as measured by an implanted accelerometer is correlated with mortality—those who are less active have decreased survival independent of other risk factors. Our findings support the notion that care providers following patients with pacemakers could use these readily available data for risk stratification, to encourage increased physical activity, and to follow patient compliance with physical activity recommendations. Whether interventions to decrease inactive time can impact survival needs to be prospectively studied.

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Severity of Metabolic Syndrome as a Predictor of Cardiovascular Disease Between Childhood and Adulthood

The Princeton Lipid Research Cohort Study

The long-term ability of the metabolic syndrome (MetS) to predict cardiovascular disease (CVD) has been limited by the binary nature of traditional MetS criteria and by discrepancies among African Americans, who have low rates of MetS classification despite higher rates of death from CVD [1]. We previously used confirmatory factor analysis to formulate MetS severity z-scores for adolescents [2] and adults [3] that place differential weights on the individual MetS components to account for variation in how MetS is manifest by sex and racial/ethnic group. Our goal was to assess the ability of these scores to determine long-term risk for CVD.

The Princeton Lipid Research Cohort Study followed white and black (30.5%) individuals (55.5% female) over 3 phases: 1) the LRC (Lipid Research Clinic) (1973 to 1976) evaluated MetS measures on students in grades 1 to 12 [4]; 2) the PFS (Princeton Follow-Up Study) (1998 to 2003) evaluated complete MetS measures and reported CVD status on 629 LRC participants [4]; and 3) the PHU (Princeton Health Update) (2010 to 2014) assessed CVD outcomes via phone interviews and National Death Index query on 354 cohort members. CVD was classified as self-reported myocardial infarction, coronary artery bypass, other heart surgery, coronary revascularization procedure (angioplasty, stent placement), or stroke. MetS severity z-scores were calculated from each individual's measures of body mass index z-score (children/adolescents) or waist circumference (adults), systolic blood pressure, fasting triglycerides, and fasting glucose, based on equations specific to sex and racial/ethnic subgroup from LRC and PFS visits. Mean MetS z-scores were compared based on

participants' CVD diagnosis by the PFS or PHU. Logistic regression and receiver-operating characteristic (ROC) curves were used to evaluate the ability of MetS severity scores to predict future CVD.

MetS severity z-scores during childhood (LRC, mean 12.9 years of age) were lowest among those who never developed CVD, highest among those with early CVD (PFS, mean 38.4 years of age) and intermediate among those with later CVD (PHU, mean 49.6 years of age) (Figure 1). In predicting future CVD, ROC curves revealed that childhood MetS severity z-scores had areas under the curve of 0.91 and 0.65 by PFS and PHU, respectively, while MetS z-scores at PFS had area under the curve of 0.84 for subsequent CVD by PHU.

Using logistic regression, each 1.0 increase in childhood MetS severity z-scores carried elevated odds ratios of 9.8 and 2.4 for incident CVD by PFS and PHU, respectively ($p < 0.001$ and $p < 0.05$). When change in MetS severity z-score from LRC to PFS was added to baseline LRC z-score in the model, this carried a further elevated odds ratio of 3.4 for incident CVD between PFS and PHU ($p < 0.01$).

The long-term health consequences of obesity—including CVD—underscore the need for clinical tools to assist in risk prediction to target at-risk individuals for preventive therapy. We found that a sex- and race/ethnicity-specific MetS severity z-score may serve as such a tool in assisting disease prediction in 2 ways: 1) baseline MetS severity scores in childhood and in mid-adulthood predicted later CVD diagnosis; and 2) the *change* in score during the interval from childhood to adulthood was associated with future disease, even after adjustment for baseline scores. In this sense, this score overcomes limitations of traditional MetS criteria, which are based on individuals having abnormalities in ≥3 of the individual MetS components and are thus unable to assess for changes in MetS over time within an individual (besides its presence/absence)—and are unable to assess risk related to component values just below the population-based cutoff.

This score is associated with risk for CVD and may serve as a marker of the degree of the severity of metabolic derangements behind MetS. Such a score—potentially calculated automatically in an electronic health record system—could enable tracking changes in a given individual's MetS severity, both to assess response to specific therapies and to identify ominous increases in MetS severity as a marker of risk and a trigger for further intervention. Future research is needed to determine clinically useful cutoffs of particularly elevated risk and whether this score improves CVD risk prediction above traditional criteria on a sex and race/ethnic basis.

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FIGURE 1 Mean MetS Severity Scores (Mean, 95% Confidence Interval) by Adult CVD Status

Childhood (LRC [Lipid Research Clinic]) and adult (PFS [Princeton Follow-Up Study]) scores for 3 groups: 1) disease-free throughout; 2) early cardiovascular disease (CVD) (between LRC and PFS); and 3) later incident CVD (between PFS and PHU [Princeton Health Update]). Comparison with disease-free group: *$p < 0.001$. Comparison with incident disease between PFS and PHU: #$p < 0.05$. MetS = metabolic syndrome.

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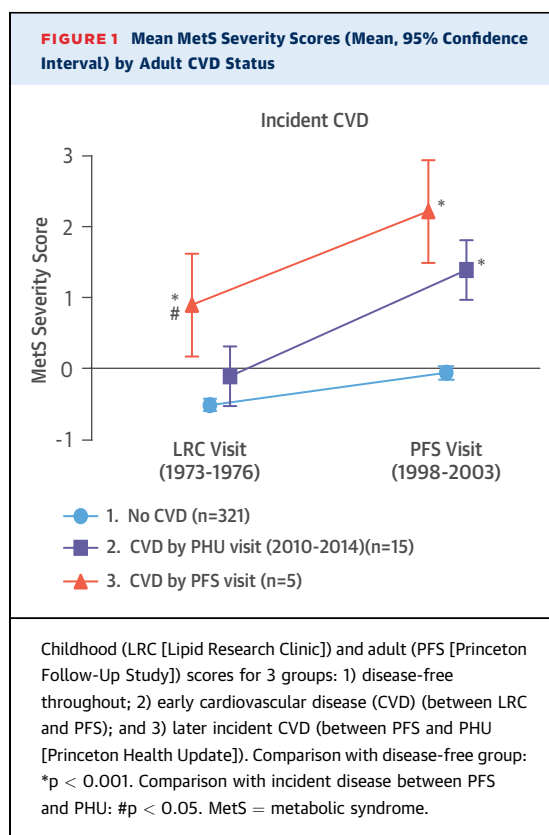
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Vulnerable Plaque

Absence of Evidence or Evidence of Absence

In their recent perspective, Arbab-Zadeh and Fuster explore the generally accepted concept that atherothrombotic events result from the interaction between systemic factors (inflammation and thrombosis) and local substrates (individual plaques). Although this notion has appeared in the literature for more than a decade, the authors emphasize the importance of overall atherosclerotic plaque burden rather than identification and characterization of vulnerable (or high-risk) plaque in cardiovascular (CV) risk prediction.

Fundamentally, the authors accept that "plaque ruptures and erosions are indeed responsible for most culprit lesions in patients with acute events" but express reservations about the feasibility of vulnerable plaque diagnosis, given the prevalence of subclinical plaque rupture events. However, several points are worth considering when evaluating the merits of the authors arguments:

1. Imaging studies associating vulnerable plaque with future CV events have generally not accounted for anatomic plaque burden as a confounder.

Similarly, studies of anatomic plaque burden have typically not adjusted for high-risk plaque features. Given this, and that most imaging studies account for similar CV and demographic risk factors, it is instructive to compare the predictive value of selected studies comparing anatomic burden to vulnerable plaque (Table 1). Notably, the adjusted risk estimates for death and/or major adverse cardiac events (MACE) are generally comparable for both plaque burden and plaque vulnerability characteristics. The study by Budoff et al. (1) represents the exception to this trend but was assessed in the extreme upper tier of coronary artery calcium (CAC) (>1,000), constituting <5% of the study population. Importantly, lower CAC in their study was associated with a risk of clinical events comparable to other studies at the same level of CAC.

The studies by Puchner et al. (2) and Criqui et al. (3) (Table 1) are particularly interesting in that they provide insight into the interplay between various prognostic factors in coronary artery disease (CAD): plaque burden and plaque vulnerability. Evaluating patients with chest pain using coronary computed tomography angiography (CTA), Puchner et al. (2) observed that high-risk plaque (defined as at least 1 of the following: positive remodeling, plaque with low Hounsfield units [<30], napkin-ring sign, spotty calcium) was predictive of acute coronary syndromes after adjustment for plaque burden (any coronary artery with a ≥50% or ≥70% stenosis). Criqui et al. (3) found that CV risk was inversely proportional to CAC density (i.e., vulnerable plaque features) at any level of CAC volume (i.e., plaque burden). These studies demonstrate the incremental prognostic value of characterizing features of individual plaque vulnerability in the

TABLE 1 Study Types and Cardiovascular Event Predictor

Plaque Burden			**Vulnerable Plaque Features**		
First Author (Ref. #)	**Population**	**Events**	**First Author (Ref. #)**	**Population**	**Events**
Budoff et al. (1)	N = 25,252 asymptomatic patients undergoing CAC	All-cause death: RR = 9.36 for CAC >1,000 and RR = 5.78 for CAC 400-699 (both p < 0.0001)	Puchner et al. (2)	N = 472 patients undergoing CTA for chest evaluation	ACS*: OR = 8.9 for "high-risk" plaque (p = 0.006)
Cho et al. (4)	N = 27,125 asymptomatic patients undergoing CTA and CAC	All-cause death: HR = 2.38 for death for CAC >400 (p = 0.014) and HR = 2.91 for multivessel CAD (p = 0.001)	Stone et al. (5)	N = 697 with ACS undergoing PCI + IVUS	MACE: HR = 3.35 for VH-TCFA (p < 0.001) and HR = 5.03 PB >70% (p < 0.001)
Criqui et al. (3)	N = 3,398 asymptomatic cohort undergoing CAC	CVD: HR =1.68 per SD increase in CAC volume (p < 0.001)			HR = 0.71 per increase in CAC density (p < 0.001)

*Remained significant after adjusting for anatomic plaque burden (CAD >50% stenosis).

ACS = acute coronary syndrome(s); CAC = coronary artery calcium; CAD = coronary artery disease; CTA = coronary computed tomography angiography; HR = hazard ratio; IVUS = intravascular ultrasound; MACE = major adverse cardiac event(s); MRI = magnetic resonance imaging; OR = odds ratio; PB = plaque burden; PCI = percutaneous coronary intervention; RR = risk ratio; TCFA = thin-cap fibroatheroma; VH = virtual histology.