A Linked Mixture Model of Coronary Atherosclerosis

A Preprint

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Abstract

Background & Objectives: Characterizing the progression of coronary atherosclerosis is a critical public health goal. The most common quantitative summary, the CAC score, is modelled by a variety of statistical methods, both as a predictor of coronary events and as an outcome of behavioral and population-specific risk factors. Little attempt has been made, however, to ground these statistical models in the underlying physiology of arterial aging, which would allow us to describe the onset and growth of CAC over a patient's life.

Methods: Using a stochastic growth model for arterial plaque accumulation, I identify severe under-estimation in the age of initial onset and rate of progression (doubling time) of CAC growth, and use this generative growth model to motivate new statistical approaches to CAC using mixture models of logistic and log-linear outcomes.

Results: Using 640 growth trajectory simulations (71,680 patients, 277,600 observations), I demonstrate substantial improvements in predictive accuracy of CAC onset and progression with linked hurdle-lognormal mixture distributions, compared with standard ln(CAC+1) or ln(CAC) models.

Conclusions: Using models that can account for patient-specific onset and progression rates, accurate descriptions of CAC trajectories can be made even in cross-sectional (single scan per patient) designs, with substantial clinical and epidemiological utility.

***K*eywords** Agatston Scores · Coronary Calcium · Bayesian Methods · Generative Inference

1 Background & Objectives

The coronary calcium (CAC) score was first proposed by Agatson, *et al.* [1] to quantify the amount of calcified plaque in the coronary arteries, and remains the standard metric for assessing arterial aging [2]. Three decades of research using large cohorts of patients, in both cross-sectional and longitudinal designs, has shown a patient's CAC score to be highly predictive of subsequent major coronary events [3–7], even among patients with few additional risk factors [8, 9]. Many studies have found CAC varies systematically by nationality [10, 11] and ethnicity [12–15], with some populuations showing very little CAC even into advanced age [16], leading to debates over whether atherosclerosis itself is a consequence of sedentary, industrialized lifestyles [17, 18].

Yet, despite its centrality in the study of atherosclerosis, the CAC score's significance in clinical practice is ambiguous [19, 20], and it lacks a consistent statistical model from study to study. A given analysis may employ ordered categorical [7, 21–23], linear [24, 25], log-linear [20, 26–28], quantile [29, 30] and proportional hazards [31–33] regression models, using CAC both as an outcome [5, 16, 34] or a predictor [32, 35]. With some exceptions, e.g. [25, 29, 36–39], the CAC score is almost always modeled as a cross-sectional value that varies between patients, rather than as the result of a growth process within an individual over the course of their lives.

To better connect the CAC score to the dynamic physiology of arterial aging, I propose a simple growth model for the onset and progression of calcified arterial plaques. Using high-throughput computational simulations (640 studies, 71,680 patients, 277,600 observations), this model can identify structural mis-specifications in many of the common log-linear models of CAC, and indicate specific statistical modifications which dramatically improve the predictive accuracy of CAC modeling across the life course.

2 Methods

2.1 A Generative Model of CAC Growth

Although CAC is modeled in the current literature by a large variety of methods, we can synthesize two key empirical details from which to build a generative growth model of CAC. First, calcified plaques typically appear in the coronary artery in middle age, with substantial variability between patients. Before this age of onset, t_0, patients given a computerized tomography scan would have a CAC score of 0. After the age of onset, an individual's CAC steadily accumulates at one or more plaque sites in the coronary artery, increasing at a non-linear pace set in part by variation in genetics, behavior, or risk exposures [8, 25, 36, 40]. Given this, let us assume that the rate of growth in CAC at a given moment t after the age of onset t_0 is proportional to both instantaneous risk factors and the current amount of coronary calcium, that is,

$$\frac{dy}{dx} = y(t)\, k(t), \tag{1}$$

for CAC score $y(t)$ and positive growth function $k(t)$. The CAC score y is thus given by the integral of all growth velocities since the age of onset t_0,

$$y(t) = \int_{t_0}^{t} y(x)\, k(x)\, dx \tag{2}$$

As we observe the score y change with time, we could estimate the shape of the rate function $k(t)$. However, since we ordinarily do not have more than one or a few CAC observations per person, we must instead appeal to the *average* CAC growth rate between t_0 and t, $k = (t - t_0)^{-1} \int_{t_0}^{t} k(x)\, dx$, a constant. We can then solve Equation 1 as

$$\ln y(t) = k\,(t - t_0) \quad \text{for any} \quad t \geq t_0. \tag{3}$$

Since rate k describes an exponential growth process, it is useful to re-express k as a *doubling time*. That is, we can describe the time $y + d$ at which the outcome score is doubled from a current amount y at time t as $\ln 2y = k\,(t + d - t_0)$, which is true if $d = (\ln 2)/k$. An example atherosclerosis trajectory for a single patient is given in Figure 1.

Allowing for a small amount of measurement error, we can estimate the average k for a set of observations by log-linear regression of CAC score y_j on patient age t_j using the above model. That is,

$$\begin{aligned} y_j &\sim \text{LogNormal}(\mu, \sigma) \\ \mu_j &= k\,(t_j - t_0), \end{aligned} \tag{4}$$

where μ_j represents the average CAC score at age t_j, which varies due to measurement error and other unobserved factors with standard deviation σ. Given a dataset recording a single individual's CAC trajectory over time, and the log-linear regression model $\mu_j = a + bt_j$, we could estimate the above model parameters as $t_0 = (-a/b)$, $k = b$ and $d = \ln(2)/b$.

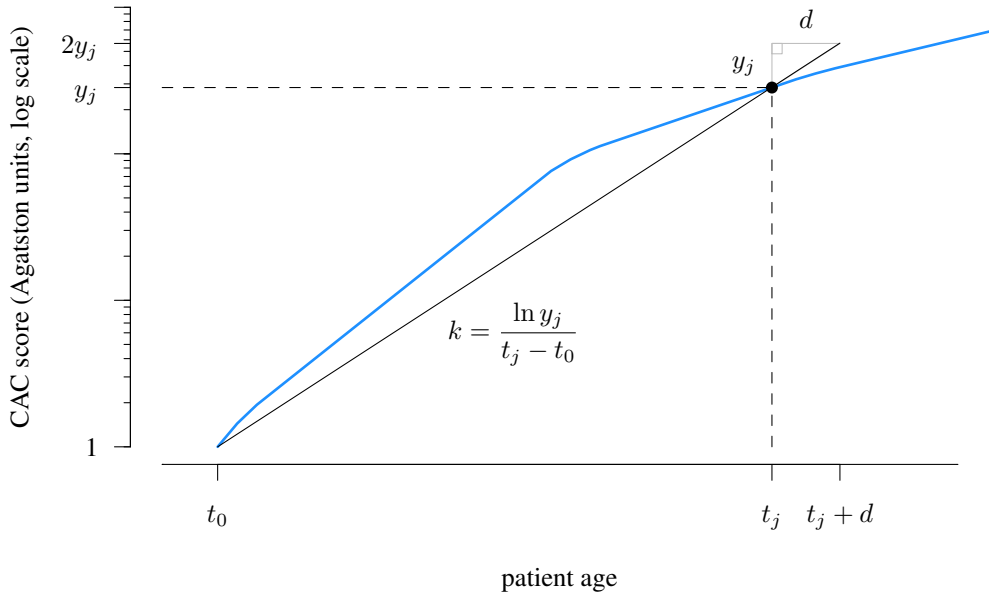

Figure 1: A single patient's coronary atherosclerosis progression over time, as measured by CAC score (blue). Onset at age t_0 is defined as the initial appearance of calcified plaque (CAC > 0), which is equivalent to a CAC score of 1 in most studies. Before t_0 the patient's CAC is 0. All CAC measurements after t_0 are given by Equation 2. In this growth trajectory, the patient's instantaneous CAC growth rate $k(t)$ intermittently decreases. Although neither the location of t_0 nor the rate function $k(t)$ are directly observable, average growth parameters can be estimated by log-linear regression Equation 4 (black line) for the location of t_0, an average k and doubling time $d = \ln(2)/k$

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2.2 Structural Under-estimation of Disease Onset and Progression

Studying CAC on the logarithmic scale was originally proposed by Agatston, *et al.* [1] and remains the most common statistical approach. However, the growth model described in Equation 4 indicates the existence of two major estimation biases with such models (Figure 2). Principally, the existence of distinct CAC age trajectories across patients is not a structural component of log-linear regression, which treats each patient-observation as following a single population average log-linear path from a single age of onset, t_0. As a consequence, standard regression models of CAC systematically under-estimate the age of atherosclerotic onset (Figure 2, left) and progression (Figure 2, right) in direct proportion to between-patient variability. Under realistic growth conditions, an inter-patient variatibility of only ± 3 years age of onset t_0 can induce estimation biases as severe as five decades.

An additional bias is introduced by studies that alter the scores of patients with no atherosclerosis (CAC = 0). Since 0 is undefined on the logarithmic scale, many studies first re-assign these patients a CAC score of 1 [5, 11, 15, 20, 27, 28, 34, 35, 41–43], indicating these patients have already begun atherosclerosis. The common justification given for the log-transform is to normalize the distribution of CAC [1, 11, 15, 32]. Yet depending on the cohort, a majority of patients may have a CAC score of 0. Consequently, such logarithmic outcome distributions are extremely zero-inflated, e.g. Figure 1 in [11]. By estimating the average growth rate k from a population in which some are growing CAC at rate k and others are not growing CAC at all, log-linear regression models introduce additional biases of about -5.9 years on t_0 (Figure 2, left, red) and an additional +1.0 year of CAC doubling time (Figure 2, right, red), versus studies that exclude non-atherosclerotic patients before performing the regression [14, 16, 25, 26, 44, 45].

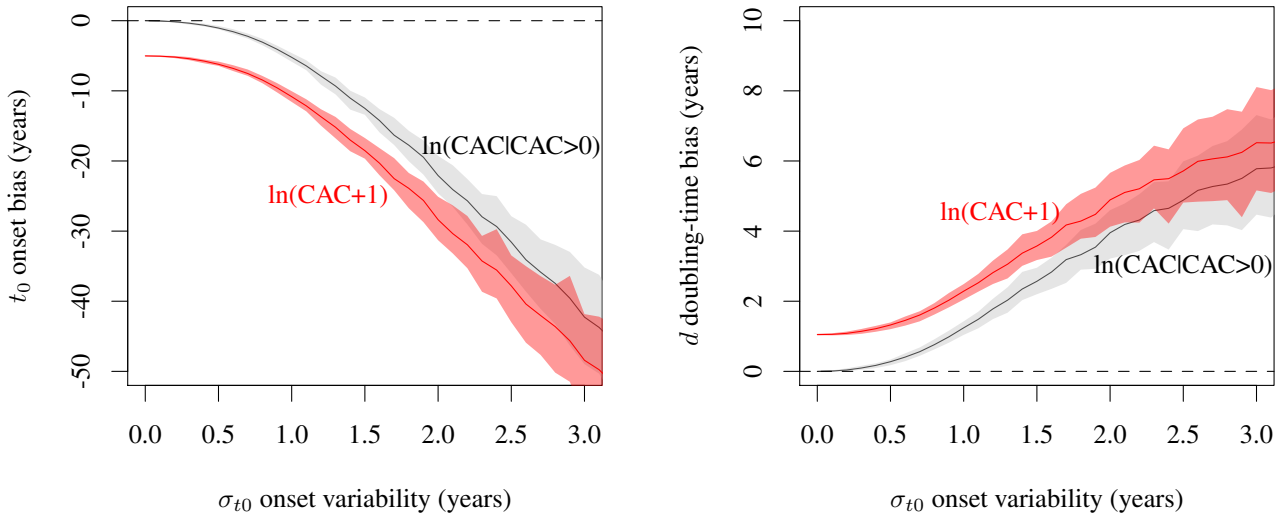

Figure 2: The relationship between inter-individual variance in t_0 and the bias in linear regression estimate of the age of onset (left) and the doubling time of CAC (right) for a sample of single observations from 5,000 patients. Controlling the standard deviation in individual t_0 variability, σ_{t0}, 300 cross-sectional datasets are randomly drawn from 5,000 patient growth trajectories. For each dataset, regression estimates are calculated in a log-linear regression of ln(CAC + 1) (red) or ln(CAC | CAC > 0) (black) on patient age, and the true onset age t_0 in the simulation is subtracted from onset estimates of $t_0 = -a/b$. Average estimates are shown with 89% confidence regions. The ln(CAC + 1) estimates are, on average, -5.9 years more biased than ln(CAC | CAC > 0) on t_0 and +1.0 year more biased in d over the observed range of σ_{t0}. Reproducible R code for this simulation and figure is available in the Supplementary Materials.

2.3 Alternate Statistical Specifications

To prevent inter-individual variation from manifesting as bias in statistical analyses, we can modify the log-linear model in Equation 4 with explicit CAC growth trajectories for each patient i by

$$\begin{aligned} y_j &\sim \text{LogNormal}(\mu_j, \sigma) \\ \mu_j &= k_i\,(t_j - t_{0i}), \\ t_{0i} &\sim \text{Normal}(t_0, \sigma_{t0}), \\ k_i &\sim \text{Normal}(k, \sigma_k). \end{aligned} \tag{5}$$

That is, the time of initial onset for each individual i, t_{0i}, is assumed to vary around some population-average age t_0 by standard deviation σ_{t0}, and similarly for individual-specific average growth trajectory k_i.

Rather than exclude patients who have no CAC, another approach is to employ generalized linear regression to model the probability CAC > 0 [3, 4, 7–10, 31, 39, 46–51]. If we define the log-odds that a patient's CAC score at observation j is non-zero as $\theta_j = \text{logit}(\Pr(y_j > 0))$, then for any individual i observed at age t_j,

$$\theta_j = \frac{t_j - \ell_i}{v} \tag{6}$$

$$\ell_i \sim \text{Normal}(\ell, \sigma_\ell)$$

The probability CAC is observed to be nonzero rises sinusoidally from 0 to 1 over the life course, reaching 50% probability at the inflection point age of ℓ_i for patient i. As above, we can expect ℓ_i to vary by individual according to parameters v and σ_ℓ, but also systematically by risk factors shared across individuals which can be incorporated into the model by logistic regression. Unlike log-linear models above, this approach can utilize all observations, including those for which $y_j = 0$, at the cost of being unable to distinguish non-zero CAC magnitudes.

Models of CAC > 0 can be combined with models of CAC magnitudes in so-called mixture models [52], first introduced in the literature by Kaplan, *et al.* [16] with the use of a zero-inflated Negative Binomial model. Such models incorporate two distinct probability distributions to describe both zero outcomes and non-zero magnitudes simultaneously. We here employ the related concept of a hurdle model, which allows an additional link between these two distributions. Specifically, in modeling the probability of CAC > 0 over the life course, we are simultaneously describing the age of onset as a random quantity. If we re-interpret the inverse-logit link as a cumulative distribution function, onset age must follow a Logistic probability distribution with mean ℓ_i and variance v. Therefore, both the hurdle and log-normal components of this mixture are estimating a common parameter in the individual onset age, t_{0i}, and we can link these stochastic nodes together via

$$t_{0i} \sim \text{Logistic}(\ell_i, v) \tag{7}$$

That is, the initial start times in the log-linear model are random quantities that follow the parameters of the hurdle model, such that the hurdle model's estimates of ℓ_i and v will pass forwards to add additional resolution on t_{0i} in the log-linear model, and the log-linear estimation of t_{0i} will help inform the locations of ℓ_i and b in the hurdle component (Figure 3). Taken together, this fully defines the linked hurdle-lognormal mixture model.[1]

2.4 Ranking Statistical Models by Simulation

In order to characterize gross performance differences between the above methods of studying CAC growth, I simulated 64 populations experiencing a variety of atherosclerotic growth scenarios. Growth trajectories from each population were sampled in 10 datasets, varying in the number of patients (from 1 to 500 patients), the number of observations per patient (in longitudinal or cross-sectional designs), the impact of risk factors of age and sex on initial onset and progression, and the mismatch between population properties and prior information. All simulations were performed in R v3.6.3 and models were fit with Stan by the `cmdstanr` library v0.3.0.9. A full list of the permutations is given in Table 2. We can summarize patient data for N = 71,680 patients seen over all 640 studies in Table 1. Each of the 14 models was fit to each of the 640 datasets, statistical estimates were calculated and extracted, and, given the true values for each individual trajectory were known, the bias of each parameter estimate was computed.

3 Results

Model battery performance is summarized in Table 3. In both cross-sectional and longitudinal designs, estimation of onset ages (population average t_0 and patient-specific t_{0i}) is least-biased in models incorporating binary outcomes for CAC > 0, including the linked hurdle log-normal and logistic regression models. The (un-linked) hurdle-lognormal and log-linear regression with patient-specific trajectories are consistently biased by nearly two decades across studies, while log-linear regression designs without individual trajectories are biased by at least three decades in estimating onset ages.

Sex specific risk-factor stratifications have small contrast coefficient biases for all models in longitudinal designs, with the largest bias produced by ln(CAC | CAC > 0) models at 3.2 (SE: 1.4) years. In cross-sectional designs, however, bias

[1] A complete list of variables is given in Table 4.

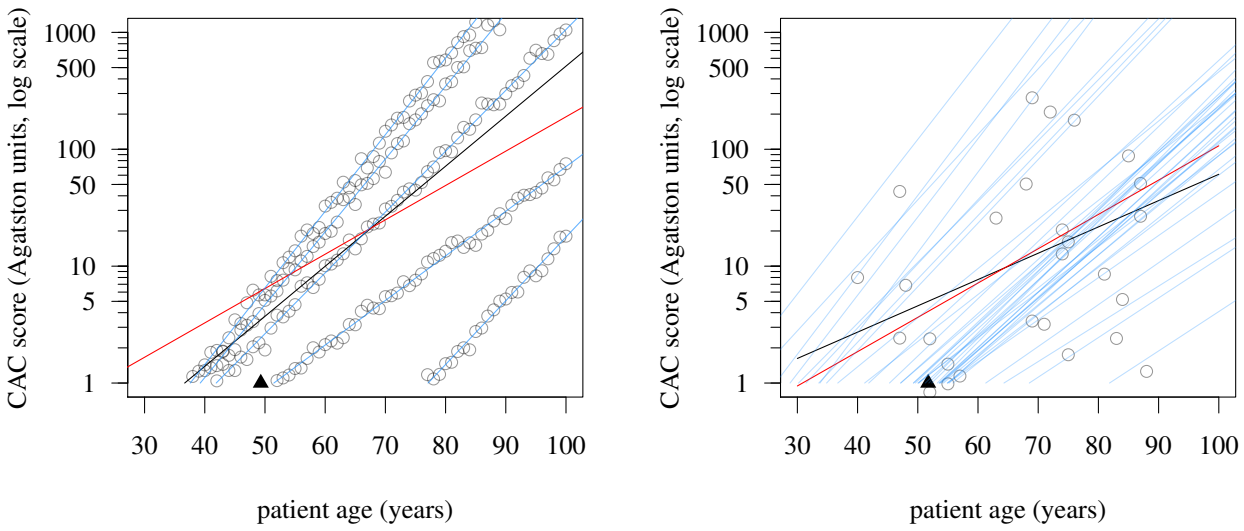

Figure 3: Observed CAC trajectories for 5 longitudinal study patients (left) and 100 cross-sectional patients with single observations each (right), with average counterfactual predictions from fitted ln(CAC) (black), ln(CAC + 1) (red) and linked hurdle-lognormal (blue) models. In each figure, true population average t_0 are indicated by black triangles.

Table 1: Characteristics of patients across 640 simulated CAC studies. Means (standard deviations) are given for t_0 and d. Here longitudinal studies involve 100 annual observations over the entire course of each patient's life (all individuals live to age 100), while cross-sectional studies simulate realistic CAC datasets by randomly sampling a single observation from each patient's adult measurements.

	Women	Men	Total
Number of Patients	36,089	35,591	71,680
Longitudinal	1,043	1,037	2,080
Cross-sectional	35,046	34,554	69,600
Number of Observations	139,346	138,254	277,600
Longitudinal	104,300	103,700	208,000
Cross-sectional	35,046	34,554	69,600
Onset t_0 (years)	48.9 (23.9)	50.2 (23.2)	49.5 (23.6)
Doubling time d (years)	2.7 (1.3)	2.9 (1.4)	2.8 (1.3)
CAC category (%)			
0	51.4	51.8	51.6
1 to 9	9.8	10.1	9.9
10 to 99	8.7	8.7	8.7
100 to 399	4.5	4.4	4.5
400 to 999	2.7	2.7	2.7
$\geq$ 1000	22.7	22.1	22.5

Table 2: Conditions across 640 simulated CAC studies. Here "longitudinal" studies involve 100 annual observations over the entire course of each patient's life (all individuals live to age 100), while "cross-sectional" studies simulate realistic CAC datasets by randomly sampling a single observation from each patient's adult measurements. Sex differences represent a common risk factor across studies and, if present in the population, may stratify the onset and progression by men versus women by a standard deviation of 10 years on t_0 and 112 years on d. Individual variation here is described by model parameter σ_{t0}. A "regularizing" prior reflects realistic ranges for each parameter prior to updating in Stan [52].

	Longitudinal	Cross-sectional
Total Studies	240	400
Inter-Individual Variation		
No Variation	90	0
$\pm$ 3 years on t_0	150	250
Sex Effect		
No sex difference in t_0	60	100
Sex difference in t_0	180	300
Sex difference in t_0, k	120	200
Prior Accuracy		
Regularizing Priors	30	50
Strong Priors	30	50
Perfect Priors	180	300
Study Size		
N = 1 Patient	80	0
N = 5 Patients	80	0
N = 20 Patients	80	80
N = 50 Patients	0	80
N = 100 Patients	0	80
N = 200 Patients	0	80
N = 500 Patients	0	80

is relatively higher for both logistic regression designs, but especially for the standard log-linear regression designs at -9.2 (SE: 4.5) and -8.0 (SE: 27.5) years. The linked hurdle log-normal yields on average the least biased estimates of a sex effect on age of onset, at -0.3 (SE: 0.7) years.

Estimates of the speed of atherosclerotic progression, measured as doubling times, are possible in log-linear models of CAC magnitudes. Estimation accuracy is high in longitudinal studies, but in cross-sectional studies, bias is lower for models that incorporate patient-specific individual trajectories. Models without these estimate slower rates of CAC growth, with a doubling-time bias of 7.5 (SE: 1.4) years for ln(CAC + 1) and 10.9 (SE: 4.8) years for ln(CAC | CAC > 0).

4 Discussion

Generally speaking, logistic and mixture models out-perform log-linear models in accurately estimating population and individual-specific ages of onset of CAC growth, and models that explicitly account for individual patient trajectories out-perform those that do not. These advantages are most pronounced in cross-sectional study designs, which constitute the vast majority of CAC datasets.

Because logistic models are able to accurately utilize the full range of patient observations, including the period before CAC growth begins, they are able to more-accurately characterize the onset of atherosclerosis compared to log-linear models, which must either exclude patients observed with zero CAC or incorrectly alter these scores to accomodate the logarithmic scale, producing large estimation errors.

Table 3: Estimation bias (mean and standard error) over all 640 studies.

model	design	t_0 bias	t_0 sex bias	d bias
logit(Pr(CAC > 0)) + RE	cross-sectional	-6.6 (3.7)	1.5 (3.7)	-
logit(Pr(CAC > 0))	cross-sectional	-7.8 (4.2)	2.1 (4.2)	-
linked hurdle-lognormal	cross-sectional	-8.2 (0.7)	-0.3 (0.7)	1.0 (1.2)
ln(CAC | CAC > 0) + RE	cross-sectional	-20.8 (1.1)	0.5 (1.1)	0.3 (0.1)
hurdle-lognormal	cross-sectional	-23.5 (3.7)	0.7 (3.7)	0.3 (0.1)
ln(CAC + 1)	cross-sectional	-28.8 (4.5)	-9.2 (4.5)	7.5 (1.4)
ln(CAC | CAC > 0)	cross-sectional	-49.9 (27.5)	-8.0 (27.5)	10.9 (4.8)
logit(Pr(CAC > 0))	longitudinal	-0.5 (0.7)	0.7 (0.7)	-
linked hurdle-lognormal	longitudinal	-0.9 (0.4)	0.5 (0.4)	-0.1 (0.0)
logit(Pr(CAC > 0)) + RE	longitudinal	-1.2 (0.4)	-0.4 (0.4)	-
hurdle-lognormal	longitudinal	-2.1 (0.6)	-1.2 (0.6)	-0.1 (0.0)
ln(CAC | CAC > 0) + RE	longitudinal	-2.3 (0.7)	-0.3 (0.7)	-0.1 (0.0)
ln(CAC | CAC > 0)	longitudinal	-22.2 (1.4)	3.2 (1.4)	0.9 (0.1)
ln(CAC + 1)	longitudinal	-31.0 (0.9)	1.0 (0.9)	3.0 (0.3)

Log-linear models are also observed to produce an large amount of bias in estimating the impact of risk factors across these simulation studies. This bias on age of onset can potentially mask measurable statistically significance, or even produce spurious significance values, in comparison to models that patient-specific hierarchical designs.

Although the innovations in model design described above show marked improvements in estimation accuracy, they come with increased costs, in terms of model complexity and computation time, and successful posterior updating of the full linked-hurdle log-normal may not be feasible for very large samples of patients. However, 3 indicates that comparable performance gains for specific parameters can be obtained by the use of simpler alternatives: for d, the ln(CAC | CAC > 0) + RE model, and for t_0 logistic regression models.

More generally, although the simulation studies presented here cover a broad range of realistic epidemiological scenarios for real populations, but are strictly limited to assessing the accuracy of statistical designs with respect to the generative model described by Equations 1 and 2. The true process of onset and progression is necessarily more complex and potentially more realistic improvements, such as the site-specific formation of individual calcified plaques, can potentially lead to further modeling innovations, and consequently greater improvements in estimation accuracy.

5 Conclusion

Review of the current literature shows subtantial variability in the methods of studying the CAC score, with multiple statistical designs employed even within the same study. Both because of this awkwardness, and because the CAC score aggregates over distributions of calcified plaque, several studies have suggested alternative metrics to studying atherosclerosis progression [19, 20]. However, the above computational meta-analysis shows substantial structural biases towards slower and earlier CAC growth and atherosclerosis progression. Modifications to these models that recognize individual-specific growth onset and progression rates are substantially more accurate in assessing individual and population-level growth parameters in realistic simulation studies with both longitudinal or cross-sectional designs, and so we can expect such models to similarly out-perform log-linear models in the analysis of real patient data.

6 Acknowledgments

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Table 4: Glossary of variables used.

Variable	Description
$k(t)$	instantaneous growth rate in CAC at age t
$y(t)$	true patient CAC score at age t
y_j	observed CAC score at observation j
t_j	patient age at observation j
t_0	population average age of onset
t_{0i}	age of onset for patient i
k	population average growth rate in CAC
d	population average dounling time in CAC
k_i	average growth rate in CAC for patient i
d_i	average doubling time in CAC for patient i
a	log-linear regression intercept
b	log-linear regression slope
v	logistic slope on logit(Pr(CAC > 0))
ℓ	expected population average age of onset
ℓ_i	logistic inflection point for logit(Pr(CAC > 0))
θ_j	log-odds of CAC > 0 for patient i in measurement j
σ	residual standard deviation on each CAC measurement y_j
σ_{t0}	standard deviation on t_{0i}
σ_k	standard deviation on k_i

7 Supplementary Materials

All statistical models and simulation data and software is available at https://github.com/babeheim/linked-calcium-growth under the CC BY-NC-SA 4.0 license.

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