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ORIGINAL RESEARCH

Prevalence of Abnormal Heart Weight After Sudden Death in People Younger than 40 Years of Age

Zachary J. Schoppen, MD; Lauren C. Balmert, PhD; Steven White, MD, PhD; Rachael Olson, BS; Ponni Arunkumar, MD; Lisa M. Dellefave-Castillo, CGC; Megan J. Puckelwartz, PhD; Alfred L. George Jr, MD; Elizabeth M. McNally, MD, PhD; Gregory Webster, MD, MPH

BACKGROUND: After sudden cardiac death in people aged <40 years, heart weight is a surrogate for cardiomegaly and a marker for cardiomyopathy. However, thresholds for cardiomegaly based on heart weight have not been validated in a cohort of cases of sudden cardiac death in young people.

METHODS AND RESULTS: We surveyed medical examiner offices to determine which tools were used to assess heart weight norms. The survey determined that there was no gold standard for cardiomegaly (52 centers reported 22 different methods). We used a collection of heart weight data from sudden deaths in the Northwestern Sudden Death Collaboration (NSDC) to test the 22 methods. We found that the methods reported in our survey had little consistency: they classified between 18% and 81% of NSDC hearts with cardiomegaly. Therefore, we obtained biometric and postmortem data from a reference population of 3398 decedents aged <40 years. The reference population was ethnically diverse and had no known cardiac pathology on autopsy or histology. We derived and validated a multivariable regression model to predict normal heart weights and a threshold for cardiomegaly (upper 95% CI limit) in the young reference population (the Chicago model). Using the new model, the prevalence of cardiomegaly in hearts from the NSDC was 19%.

CONCLUSIONS: Medical examiner offices use a variety of tools to classify cardiomegaly. These approaches produce inconsistent results, and many overinterpret cardiomegaly. We recommend the model proposed to classify postmortem cardiomegaly in cases of sudden cardiac death in young people.

Key Words: autopsy ■ cardiac ■ cardiomegaly ■ pediatric ■ sudden death ■ young

In the United States, estimates of the incidence of sudden cardiac death (SCD) range from 0.6 to 6.2 deaths per 100 000 people aged <35 years, accounting for ≈5000 annual deaths.[1–4] A 2013 expert consensus statement made a class I recommendation that all SCD decedents receive evaluation by an expert cardiac pathologist.[5] However, there is no gold standard that establishes a threshold for cardiomegaly in postmortem hearts.

Heart weight (or heart mass) is a fundamental cardiac measurement obtained during autopsy. A heavier-than-normal heart weight, or cardiomegaly, may be associated with cardiomyopathy, infiltrative diseases, or other primary and secondary cardiac disease. In living populations, elevated left ventricular heart mass is a well-established risk factor for mortality, with or without other established disease.[6–9] Elevated heart mass has been documented as a durable marker of risk in studies of diverse racial populations.[10,11] Several genetic causes of SCD are associated with cardiomegaly. For example, hypertrophic cardiomyopathy can result in increased heart weight. In contrast, heart weight is typically normal

Correspondence to: Gregory Webster, MD, MPH, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box 21, Chicago, IL 60611. E-mail: rgwebster@luriechildrens.org

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CLINICAL PERSPECTIVE

What Is New?

- We used a large heterogeneous population to derive a method to adjudicate abnormal heart weights in decedents aged 0 to 40 years.

What Are the Clinical Implications?

- Abnormal heart weight (cardiomegaly) must be accurately identified to improve diagnosis of genetic cardiomyopathies after sudden cardiac death in young people, potentially improving screening among surviving family members.

Nonstandard Abbreviations and Acronyms

NSDC	Northwestern Sudden Death Collaboration
SCD	sudden cardiac death

in inherited disorders of cardiac ion channels. Because heart weight may contribute relevant information to the ultimate cause of death, accurate determination of heart weight and cardiomegaly are important in the population aged 0 to 40 years, in which SCD from genetic causes is at its peak incidence. In particular, there may be differences in the yield and distribution of postmortem genetic causes based on the presence or absence of abnormal myocardial pathology.[12]

Pathologists have not established a gold standard to determine the threshold for cardiomegaly. There is no consensus about which biometric features should be used to determine normal or abnormal heart weight. Age, sex, body weight, height, body mass index, body surface area, and race have all been used as benchmarks.[13–15] In addition, some pathologists use nonindexed heart weight to define cardiomegaly. Nonindexed methods do not take features of body habitus into consideration. In a valuable study, Gulino et al[16] started to develop a database of SCD cases; they also detailed the best methods for preparing a heart for weighing, along with several other autopsy guidelines.

The primary objective of this study was to create and validate an independent model of heart weight and to establish a threshold for cardiomegaly. Our secondary objective was to use that model to evaluate cardiomegaly in cases of SCD in young people. Figure 1 summarizes our process.

METHODS

The data that support the findings of this study and the code to produce the online calculator are available from the corresponding author on reasonable request.

Survey Methodology

A survey was emailed to medical examiners and coroners from the 100 most populous counties in the United States. In addition, all medical examiners or coroners subscribed to the National Association of Medical Examiners electronic mailing list were contacted by email in February 2018. We surveyed these groups to create a mixed pool of large and small offices that were most likely to contain at least 1 expert pathologist, on the basis of either the large referral volume or an interest in the medical examiners academic society. Each office was asked to complete a 2-question digital survey: (1) identify the reference they used to determine cardiomegaly in the adult population and (2) identify the reference they used to determine cardiomegaly in the pediatric population. No compensation was offered, and all participation was voluntary.

Application of Survey Models

We used each method provided by a survey respondent to classify the incidence of cardiomegaly in the Northwestern Sudden Death Collaboration (NSDC) cohort. By doing so, we created a point estimate of cardiomegaly prevalence in the NSDC cohort for each method provided in the survey. This was done separately for survey results covering the adult population (≥20 years) and the pediatric population (<20 years).

Chicago Heart Weight Model

We reviewed all autopsies performed at the Cook County (Illinois) Medical Examiner's Office between 2014 and 2017 for decedents aged <40 years and whose deaths were classified as *homicide, suicide*, or *accident*. Age 40 was chosen in keeping with previously published approaches to sudden death in young populations.[17–20] For inclusion in the Chicago model, all cases had to be certified by the medical examiner with an extracardiac cause of death. We excluded cases if the autopsy reported cardiac disease as a secondary diagnosis; if there were gross or histologic cardiac abnormalities, including cardiac fibrosis; or if sudden unexplained death was a possibility. We also excluded cases for which data on the decedent's height, body weight, or heart weight were missing (5% of the cases that otherwise qualified). To increase the total number of pediatric hearts in the reference population, we extended the same screening to consecutive hearts from January 2018 to September 2019 for decedents aged ≤18 years. Hearts at the Cook County medical examiner are excised and weighed in keeping with current recommendations.[16]

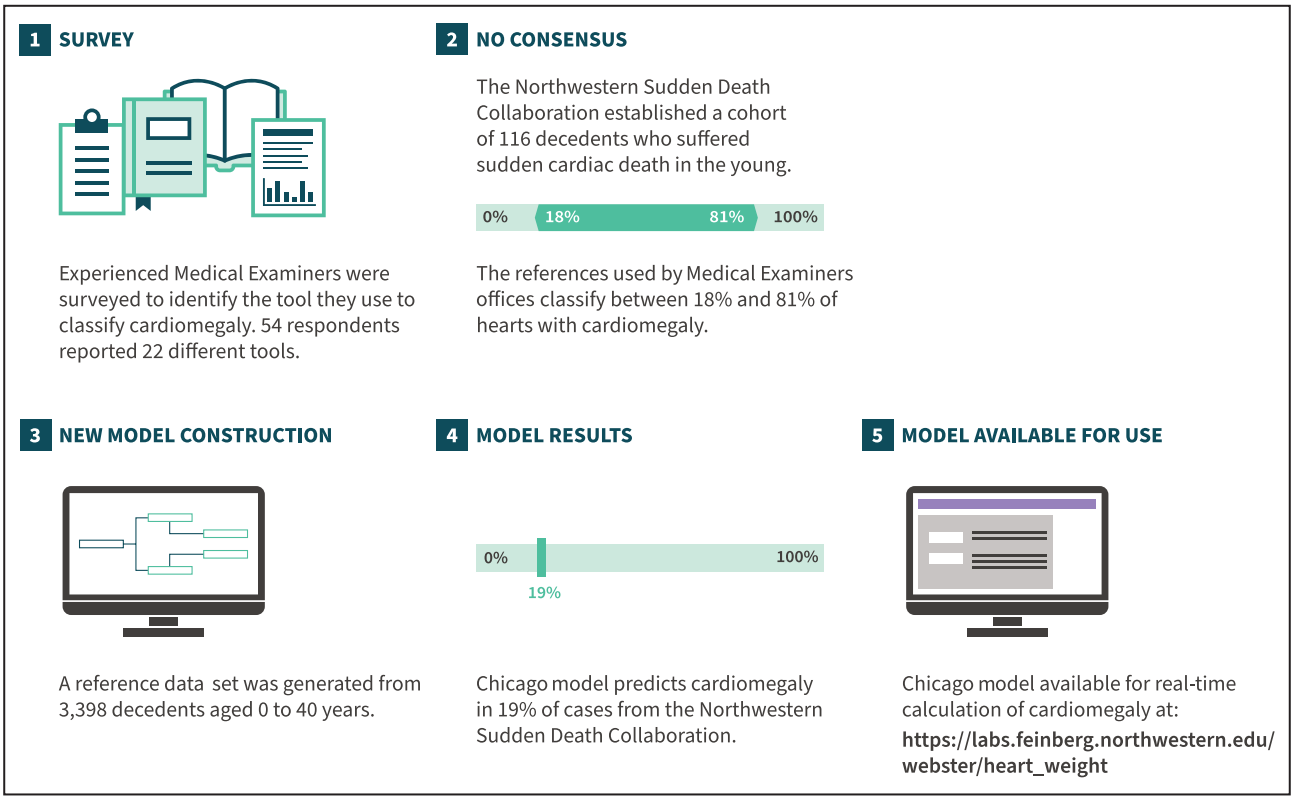

Figure 1. Workflow and key findings.
The Chicago model for postmortem cardiomegaly was generated from >3300 hearts from a large, urban, diverse population.

Statistical Analysis

We estimated a multivariable linear regression model to predict heart weight and the upper 95% CI limit. A cross-validation method was used to build the model: half of the data were randomly selected and used to build the model, and the other half were used to test the model. Common model-selection criteria including Akaike information criterion, Bayesian information criterion, and cross-validated mean squared error were used to evaluate and select the final model. Specifically, models considered age, sex, weight, height, and body mass index (weight [kg]/height [m^2]) as independent variables (Tables S1 and S2). Higher order terms, including quadratic and interaction terms, were also explored. A natural log transformation was applied to heart weight to improve model fit (Figure S1). Separate analyses were performed for adult and pediatric ages (separated at 20 years), but these independent analyses did not improve model fit; therefore, a continuous analysis across all ages was chosen as the final model (Figures S2 through S5). Observations with missing data on the outcome or predictors of interest were excluded before analyses (n=48). A sensitivity analysis considered exclusion of potential outliers, as identified by large residuals (less than –3 or >3; n=15); however, model results remained consistent. A quadratic model that included a second-order body weight term and interactions between height and weight was the best fit (Tables S2 and S3).

From this model, we established an equation for estimating the conditional mean heart weight and the corresponding upper 95% CI limit (equation 1). For the purposes of clarity, we have designated the model derived from these data as the *Chicago model* to predict and, ultimately, classify heart weight:

$$\text{Predicted upper 95\% CI limit for heart weight} = e^{(2.88-0.12\times\text{female}+0.0065\times\text{age}+1.09h+0.047w-0.018w\times h+0.000092h\times w^2-0.0002w^2+0.25)}, \quad (1)$$

where age indicates age at death in years, *h* represents measured body height minus the mean sample height (1.72 m), *w* represents body weight in kilograms minus the mean sample weight (83.48 kg), and female is 1 if female and 0 if male. The value 0.25 is used because it is the SE of the estimate multiplied by 1.65.

Northwestern Sudden Death Collaboration

The NSDC is a consortium of medical examiner and coroner offices that study SCD in young people. Northwestern University is the central coordinating

center. Cases were submitted to the NSDC from 24 counties in 12 states from 2015 to 2018. Cases were excluded if autopsy determined an extracardiac cause of death or if toxicology revealed lethal concentrations of foreign substances. Positive toxicology for recreational substances at sublethal concentrations, prescription medications at therapeutic concentrations, or medications used in emergency life support were not considered exclusion criteria. Whenever feasible, an independent review of tissue histology was performed by the NSDC. Heart weight was obtained from the autopsy report.

Institutional review board approval was obtained for human subject protection, and informed consent was not required.

RESULTS

Cardiomegaly Survey

We received responses from 54 offices. Most respondents were employed by medical examiner's offices (35/54, 65%) or coroner's offices (5/54, 9%). Two respondents worked for combined medical examiner/coroner offices (2/54, 4%). Twelve respondents (12/54, 22%) did not provide an administrative classification for their office. Responses were obtained from offices serving a range of population densities (8% with a catchment area >5 million people; 44% between 1 and 5 million people; 33% between 500 000 and 1 million people; and 14% with <500 000 people).

The 54 responding offices reported 22 different methods to determine cardiomegaly (Table 1).[21–31] Pediatric methods were provided by 39 of 54 offices (72%). The pediatric methods also did not agree, with 26 of 39 offices using those of Stocker et al,[21] 7 of 39 offices using those of Schulz et al,[22] and 6 of 39 offices using Scholz et al.[23]

Chicago Heart Weight Model

Survey respondents did not agree on a gold standard to determine cardiomegaly. In addition, the methods reported in the survey were often based on few hearts or on models not indexed to size, age, or other biometric characteristics (Table 1). Therefore, we established a reference population using a large, ethnically diverse catchment area. Demographics and biometrics for the 3398 decedents in the Chicago/Cook County reference population are shown in Table 2. The mean heart weight in the reference samples was 361.6 g (SD, 95.5 g; range, 34–930 g), and

Table 1. Methods of Determining Cardiomegaly Used by Survey Respondents

Method of Establishing Cardiomegaly	Code Used in Figure 2	Sample Size	Ages (y) of Decedents in Model	Reference (First Author)
Derived from heart samples	A			Karch[24]
>500 g	B			No reference
Derived from heart samples	C			Ludwig[25]
Derived from heart samples	D			Burke[26]
Derived from heart samples	E	765	20–99	Kitzman[27]
>450 g	F			No reference
>5 g/kg of body weight	G			No reference
>4 g/kg (female) and >5 g/kg (male)	H			No reference
>400 g	I			No reference
>350 g (female) and >400 g (male)	J			No reference
>2×body weight in pounds (in grams)	K			No reference
Derived from heart samples	L	926	21–69	Zeek[28]
Derived from heart samples	M			Connolly[29]
>4 g/kg (female) and >4.5 g/kg (male)	N			No reference
>350 g	O			No reference
Derived from heart samples	P	232 (male) 102 (female)	18–35	Molina[30,31]
>300 g (female) and >350 g (male)	Q			No reference
Additional pediatric methods, not included in figure				
Derived from heart samples			0–19	Stocker[21]
Derived from heart samples		701	0–1	Schulz[22]
Derived from heart samples		200	0–19	Scholz[23]

Where data were not available, cells were left blank. References did not always report sample size and ages of decedents from their model. "No reference" indicates that these thresholds were reported by coroners or medical examiners without reference to a cited derivation.

Table 2. Demographics for SCD Cases From the NSDC and From Normal Hearts

Variable	NSDC, n (%)	SD	Normal Hearts,* n (%)	SD
Heart weight, mean, g	355.9	189.7	361.6	95.9
Accident, mean, median			385.3 (386)	
Homicide, mean, median			346.6 (340)	
Suicide, mean, median			349.9 (338)	
Sex, n (%)				
Female	35 (30.1)		516 (15.2)	
Male	81 (69.9)		2882 (84.8)	
Age, mean, y	22.1	12.1	26.7	7.1
0–1 y (%)	13 (11.2)		22 (0.7)	
2–12 y (%)	11 (9.5)		66 (1.9)	
13–18 y (%)	15 (12.9)		450 (13.2)	
Height, mean, m	1.58	0.37	1.7	0.1
Weight, mean, kg	71.8	35.5	83.5	24.4
BMI, mean, stratified, kg/m^2 (%)				
Underweight (<18.5)	19 (16.4)		113 (3.3)	
Normal (18.5–24.9)	42 (36.2)		2220 (65.3)	
Obese (>25.0)	55 (47.4)		1065 (31.3)	
Pathologic findings (%)				
Sudden unexplained death	69 (67.6)			
Hypertrophic cardiomyopathy	19 (18.7)			
Arrhythmogenic cardiomyopathy	8 (7.8)			
Dilated cardiomyopathy	6 (5.9)			
Accident			1303 (38.3)	
Homicide			1931 (56.8)	
Suicide			164 (4.8)	
Race (%)				
White	67 (57.8)		1470 (43.3)	*P* value <0.01†
Black	45 (38.7)		1860 (54.7)	
Other	4 (3.4)		68 (2.0)	

BMI indicates body mass index; NSDC, Northwestern Sudden Death Collaboration; and SCD, sudden cardiac death.
*Normal hearts from the Chicago/Cook County medical examiner were used to derive the Chicago model.
†*P* value derived from χ^2 test.

there were small differences in heart weight when stratified by cause of death (homicide, suicide, accident) (Table 2).

Heart Weight in Cases of Sudden Death in the Young

The NSDC cohort contained 116 decedents with a mean age at death of 22 years (SD, 12.2 years). Most decedents were male (81/116, 70%) (Table 2). The mean heart weight was 355.9 g (SD, 189.7 g).

We used the heart weights from the sudden deaths collected by the NSDC to determine the incidence of cardiomegaly, using each of the methods provided by survey respondents. We determined the extent of the classification disagreement among the methods. Methods returned in the survey disagreed widely, classifying between 18% and 81% of the adult NSDC hearts as having cardiomegaly (Figure 2).

This wide discrepancy occurred among experienced centers. Responding medical examiners and coroners included many of the major population centers in the United States and covered a total catchment area of 69 million people.[32] Similarly, the 3 pediatric methods produced inconsistent results. The method of Stocker et al classified 74% of pediatric hearts in the NSDC with cardiomegaly, but the methods of both Scholz et al and Schulz et al classified 19% of pediatric hearts in the NSDC with cardiomegaly.

We then used the Chicago model (equation 1) to determine the prevalence of cardiomegaly among hearts in the NSDC test population. Observed heart weights above the estimated upper 95% CI limit, conditional on the factors of interest, were defined as

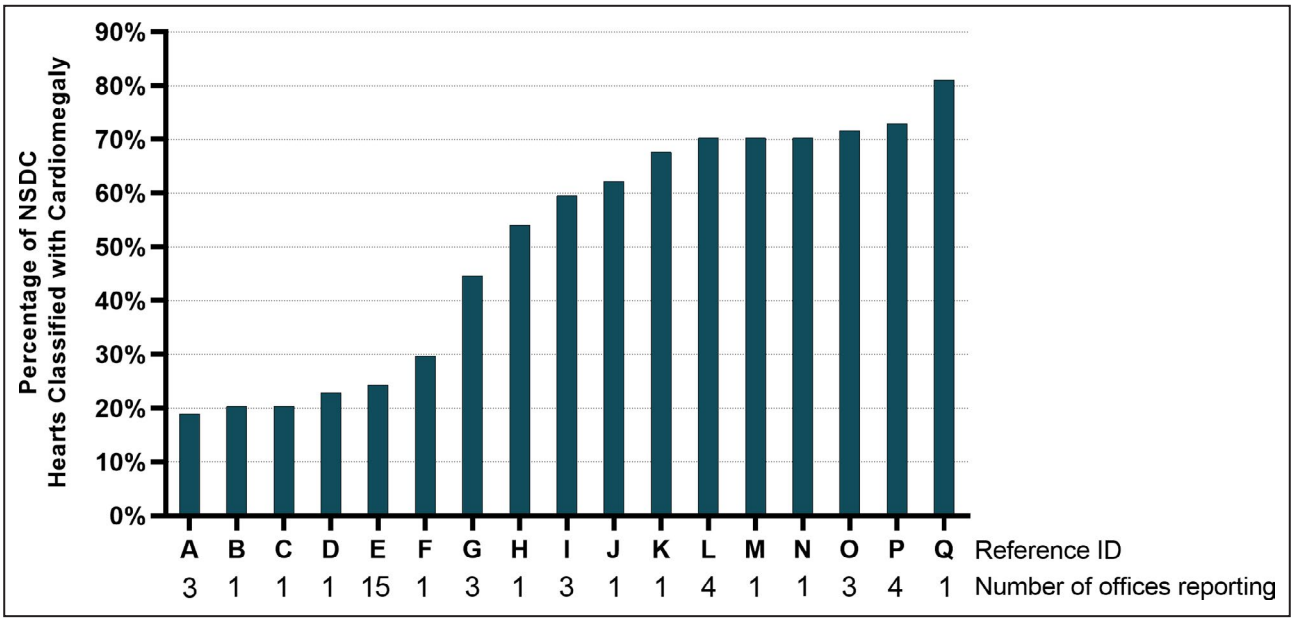

Figure 2. Variability between methods of classifying cardiomegaly.
Hearts from sudden deaths in young people in the Northwestern Sudden Death Collaboration (NSDC) were evaluated for cardiomegaly using 18 different references obtained by survey. The percentage of NSDC hearts classified by each method is on the ordinate. The number of medical examiner or coroner offices reporting each survey-derived method is listed below the identifier. (A) Karch and Drummer,[24] (B) heart weight >500 g, (C) Ludwig,[25] (D) Burke and Tavora,[26] (E) Kitzman et al,[27] (F) >450 g, (G) >5 g per kg body weight, (H) >4 g per kg body weight (female) or >5 g per kg body weight (male), (I) >400 g, (J) >350 g (female) or >400 g (male), (K) heart weight more than twice the body weight in pounds, (L) Zeek,[28] (M) Connolly et al,[29] (N) >4 g per kg body weight (female) or >4.5 g per kg body weight (male), (O) >350 g, (P) Molina and DeMaio,[30,31] (Q) >300 g (female) or >350 g (male). Data from references limited to pediatric age groups are not shown: Stocker et al,[21] Schulz et al,[22] and Scholz et al.[23]

cardiomegaly. The Chicago model determined a 19% incidence of cardiomegaly among the young population with SCD.

DISCUSSION

Current Methods for Determining Cardiomegaly Produce Inconsistent Results

The current expert consensus statements from the Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society recommend "expert cardiac pathology" in the setting of SCD in young people.[5] However, our survey did not record a consensus on how to define postmortem cardiomegaly. No gold standard exists. When we applied the tools provided by experienced pathologists, the prevalence of cardiomegaly ranged from 18% and 81% in a sample of hearts drawn from cases of SCD in young people. Medical examiner and coroner offices were selected for the survey because of their size and catchment area or because they belonged to an expert subspecialty society, suggesting that they represent a high-quality pool of expertise across the United States. The lack of a consistent threshold for cardiomegaly derived from these sources creates a challenge for cardiologists who may rely on this information in assessing risk for surviving family members.

As an alternative to these methods, we provide an equation to determine cardiomegaly that was derived and validated in a young population (aged 0–40 years) and tested against cases of SCD in a young population. This Chicago model was derived from a separate reference population that excluded cardiac causes of death. This model provides a method for cardiologists to compare all heart weights to a single reference standard, derived from an ethnically diverse population, and based on age, sex, body weight, and height.

Online Tool for Calculation of Cardiomegaly

Although we recognize that this equation is more difficult to use than a reference table, we believe it is more accurate than 2-dimensional tabular methods. An online calculator is provided to determine the threshold for cardiomegaly for decedents after SCD at an age <40 years (https://labs.feinberg.northwestern.edu/webster/heart_weight). This online calculator provides other reference thresholds, including the

ability to calculate a mean projected heart weight and thresholds at the 75th, 90th, and 99th percentiles.

Postmortem Cardiomegaly May Reflect Cardiomyopathy

The presence or absence of cardiomegaly is clinically relevant because it may affect the declared cause of death. Correct identification of the cause of death may affect the decision to obtain postmortem genetic testing. A correct pathologic diagnosis may affect the genes tested in the panel and may influence long-term surveillance recommendations for surviving relatives. In addition to direct clinical implications, the public health community is still working to determine the incidence, etiology, and impact of SCD in young people.[12,33] Inconsistent definitions of postmortem phenotype complicate this task. Finally, postmortem genetic testing (ie, molecular autopsy) is dependent on accurate genotype-phenotype correlations. Without a consistent framework for defining cardiac phenotype, it is difficult to compare genotype conclusions from study to study. The ethnically diverse reference population is particularly important for this reason. It is not possible to accurately categorize findings of uncertain significance unless both genotype and phenotype reference data are obtained from populations with diverse ancestry.

Although it is possible that this reference population could include people with undiagnosed genetic diseases associated with life-threatening arrhythmia, such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, these major arrhythmogenic causes of SCD have not been associated with findings on echocardiography that would affect heart weight and would not alter the calculations for cardiomegaly in the reference population.[34,35] Furthermore, the incidence of these disorders is sufficiently rare as to provide a negligible effect on the overall data set used to create the Chicago model.

Improved Benchmark

The most important contribution from this work is an improved benchmark to distinguish normal heart weight from cardiomegaly in cases of sudden death in young people. Our data are updated compared with prior standards, representing a larger number of data points (>3300 autopsies) and a more relevant age range for SCD in young people (0–40 years). These autopsies are from the diverse population of Chicago and Cook County, Illinois, making the model more generalizable to ethnically and demographically diverse populations. The previous models that medical examiners and coroners are using are derived from reference samples with few hearts or often from demographically narrow populations. The maximum number of hearts analyzed in any of the methods cited in our survey was 926 hearts. The remaining methods were based on fewer hearts or were not indexed to any reference population of hearts. For example, the model of Scholz et al was the most commonly cited method to determine cardiomegaly. Their data were derived from only 765 adult hearts and 200 pediatric hearts. In contrast, our tables were derived from >3300 pediatric and young adult hearts.

An additional advantage of this work is our focus on statistical models that are relevant for SCD in young people. Cardiac disease is the most common etiology in this population, both by autopsy data and by molecular autopsy data.[12,18,36–40] Therefore, we limited autopsies in our reference population to those who had died by accident, homicide, or suicide, and we specifically excluded those with a cardiac cause of death or demonstrable cardiac pathology. We propose that hearts that fall above the upper 95% CI limit of this reference population provide a reliable benchmark for cardiomegaly in cases of SCD in young people.

Population-Based Models Improve Consistency

We also note that our model is comparable to other population-based models intended to identify cardiomegaly based on biometrics and postmortem heart weight. The largest existing population model to determine postmortem cardiomegaly is based on 27 645 medicolegal autopsy cases in Sweden.[14] As a post hoc analysis, we determined the presence or absence of cardiomegaly in each heart by the Chicago model and the Swedish model. There was 100% concordance in classifying adult hearts from the NSDC cohort between the 2 models. The only discrepancies between the Chicago model and the Swedish model occurred in pediatric cases. These discrepancies are important because the Chicago model is based on reference cases of decedents aged 0 to 40 years, whereas the Swedish model did not use any pediatric data for model construction. This approach is a strength of the Chicago model in the setting of SCD in the young population. The 100% concordance in adult hearts reinforces the value of a population-based model using regression. The inclusion of pediatric cases in the Chicago model makes it more generalizable to the full age range for SCD in young people.

LIMITATIONS

Obesity may affect normal values for heart weight. Pericardiac fat was not excised before determining heart weight at autopsy in our normative population, but this is typical practice; thus, our data remain relevant. Obese patients occurred in our reference

population of traumatic deaths at the same frequency as in the general population.[41] We attempted to minimize the impact of obesity and heart disease coexisting by excluding any patients whose secondary cause of death included cardiovascular disease or cardiac fibrosis, but this remains a potential confounder of the data. Our population-based method of determining normal heart weight is indexed to people who have a typical distribution of pericardiac fat in Chicago in the years 2014–2019. In addition, this model presumes that hearts are trimmed in a standard manner before weighing—that is, the aorta and pulmonary artery were incised with a ≈1-cm margin—and all intracardiac clots were removed before weighing.

Race was reported by medical examiner or coroner offices as Black, White, or "Other," and we maintained these classifications without alteration. However, the underlying population is likely more complex. Chicago and the surrounding Cook County municipalities are the third-largest metropolitan area in the United States, with 5 194 675 people at the 2010 census.[32] The Chicago metropolitan area is ethnically and racially diverse (42.3% White, 24.0% Black, 25.5% Hispanic/Latino, 7.7% Asian, and 0.5% other race/ethnicity, which included Native American and Native Hawaiian/Pacific Islander).[32] Several studies examining specific subpopulations support the presence of subgroups in this cohort that are not able to be tabulated in this article.[13,42,43]

Finally, our model included few reference cases for ages 0 to 1. In the neonatal age group, the equation cutoffs should be interpreted with care, especially if prematurity or other factors are present.

CONCLUSIONS

The current methods used by medical examiners and coroners to determine heart weight do not provide a consistent diagnosis of cardiomegaly. These models were derived from older data, often with few hearts included in the derivation. The Chicago model is an improved method of determining cardiomegaly based on the upper 95% CI limit of heart weight in a large reference population between ages 0 and 40 years.

ARTICLE INFORMATION

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Affiliations

From the Division of Cardiology, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL (Z.J.S., R.O., G.W.); Department of Preventive Medicine (Biostatistics), Northwestern University Feinberg School of Medicine, Chicago, IL (L.C.B.); Cook County Medical Examiner's Office, Chicago, IL (S.W., P.A.); Department of Pharmacology (M.J.P., A.L.G.) and Center for Genetic Medicine and Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (L.M.D.-C., M.J.P., E.M.M.).

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The online calculator was programmed by the Weinstein Organization (Chicago, IL). Web hosting for the online calculator is currently provided by Northwestern University Feinberg School of Medicine. If the published link does not work, an updated link can be obtained from the corresponding author at rgwebster@luriechildrens.org or heartweight@bluewebster.com.

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Disclosures

None.

Supplementary Materials

Tables S1–S3
Figures S1–S5

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Supplemental Material

Table S1. Model building results.

Model	Predictors	VIF	AIC	BIC	CV-MSE
Step 1: Models including factors of interest and interaction terms					
1	Age, Sex, Weight, Height	All < 10	-1352.9	-1347.5	0.0282
2	Age, Sex, Weight, Height, BMI	BMI, Weight, Height > 10	-1558.5	-1553.1	0.0240
3	Age, Sex, Weight, Height, Weight*Height	All < 10	-1580.3	-1574.9	0.0239
4	Age, Sex, Weight, Height, BMI, weight*height	BMI, Weight, Height, Weight*Height > 10	-1572.7	-1567.2	0.0238
Step 2: Consideration of higher order terms (added to model 3)					
5	Age, Age^2, Sex, Weight, Height, weight*height	All < 10	-1564.3	-1558.9	0.0239
6	Age, Sex, Weight, Height, $Weight^2$ weight*height	All < 10	-1636.7	-1631.2	0.0231
7	Age, Sex, Weight, Height, $Weight^2$ weight*height, $Weight^2$*height	All < 10	-1645.2	-1639.8	0.0227
8	Age, Sex, Weight, Height, $Height^2$ weight*height	$Height^2$, Height*Weight > 10	-1582.9	-1577.5	0.0239
9	Age, Sex, Weight, Height, $Height^2$ weight*height, weight*$height^2$	$Height^2$, Height*Weight, $Height^2$*Weight > 10	-1576.3	-1570.9	0.0239
Step 3: Consideration of additional interaction terms with age (added to model 7)					
10	Age, Sex, Weight, Height, $Weight^2$ weight*height, $Weight^2$*height, Sex*Age	$Height^2$, Height*Weight, $Height^2$*Weight > 10	-1633.7	-1628.3	0.0227
11	Age, Sex, Weight, Height, $Weight^2$ weight*height, $Weight^2$*height, Weight*Age	Weight, $Height^2$, Height*Weight, Weight*Age, and $Height^2$*Weight > 10	-1629.3	-1623.8	0.0228
12	Age, Sex, Weight, Height, $Weight^2$ weight*height, $Weight^2$*height, Height*Age	Height, $Height^2$, Height*Weight, Height*Age, $Height^2$*Weight > 10	-1650.3	-1644.8	0.0229

VIF, variance inflation factor; AIC, Akaike information criterion; BIC, Bayesian information criterion; CV-MSE, cross-validated mean squared error; BMI, body mass index.

Table S2. Final model results (model 7 from Table S1).

Variable	Estimate	95% CI	P-value
Intercept	5.7346	(5.7046, 5.7647)	<0.0001
Age	0.006504	(0.0054, 0.0076)	<0.0001
Sex			
Male	Ref		<0.0001
Female	-0.1152	(-0.1365, -0.0940)	
Weight	0.007504	(0.0071, 0.0079)	<0.0001
$Weight^2$	-0.00005	(-0.00006, -0.00004)	<0.0001
Height	0.2046	(0.1097, 0.2995)	<0.0001
Height*Weight	-0.00296	(-0.00525, -0.00066)	0.0116
Height*$Weight^2$	0.000092	(0.000058, 0.00013)	<0.0001

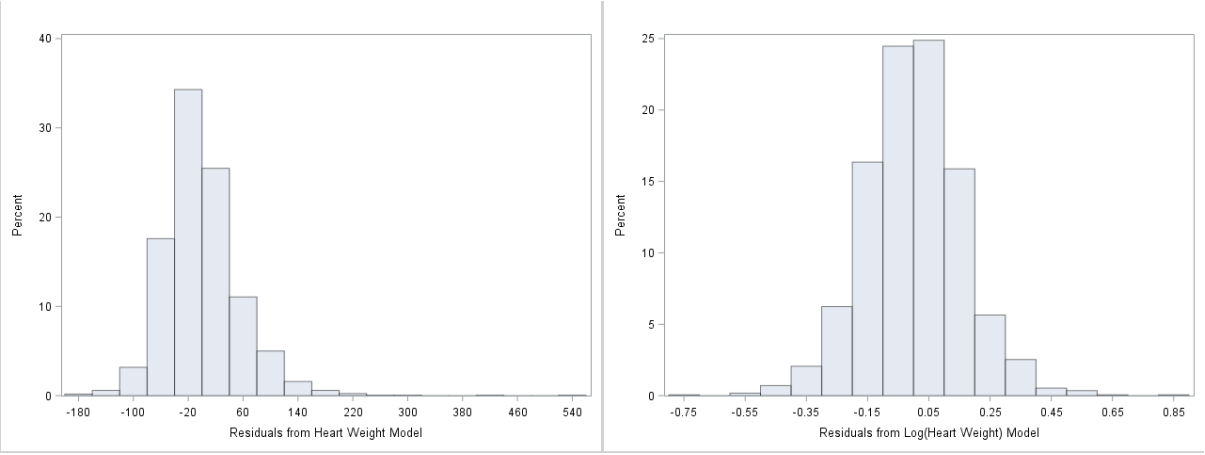
Table S3. Model removing potential outliers.

Variable	Estimate	95% CI	P-value
Intercept	5.7395	(5.7112, 5.7677)	<0.0001
Age	0.006205	(0.0052, 0.0072)	<0.0001
Sex			
Male	Ref		<0.0001
Female	-0.1180	(-0.1380, -0.0975)	
Weight	0.007502	(0.0071, 0.0079)	<0.0001
$Weight^2$	-0.00005	(-0.00006, -0.00004)	<0.0001
Height	0.2160	(0.1265, 0.3056)	<0.0001
Height*Weight	-0.00327	(-0.00544, -0.0011)	0.0031
Height*$Weight^2$	0.000088	(0.000057, 0.00012)	<0.0001

We estimated a multivariable linear regression model to predict mean heart weight and the upper 95% confidence interval limit using data on autopsies performed at the Cook County Medical Examiner's Office (2014-2017). A cross-validation method was used to build the model, where half of the data were randomly selected and used to build the model and the other half were used to the test the model. Common model selection criteria including Akaike information criterion (AIC), Bayesian information criterion (BIC), and cross-validated mean squared error (CV-MSE) were used to evaluate and select the final set and form of independent variables. Variance inflation factors (VIF) were also considered to identify issues with multicollinearity.

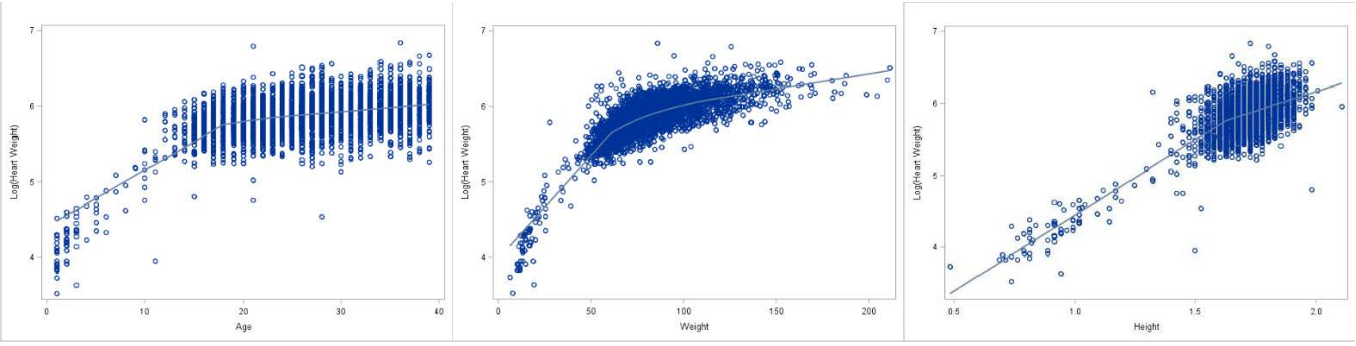
Specifically, we began with a series of models considering age, sex, weight, height, body mass index (weight (kg)/height (m^2)), and the interaction between weight and height (Table S1, Step 1). Continuous variables were centered at their respective means. Residuals were assessed after fitting the initial model including age, sex, weight, and height as independent variables. A log transformation was applied due to concerns with normality of residuals. We have included histograms of the model residuals from the original scale heart weight model (Figure S1, left) and log transformed heart weight model (Figure S1, right). Subsequent models were fit using the log transformed outcome.

Figure S1. Histograms of Model Residuals from Step 1.



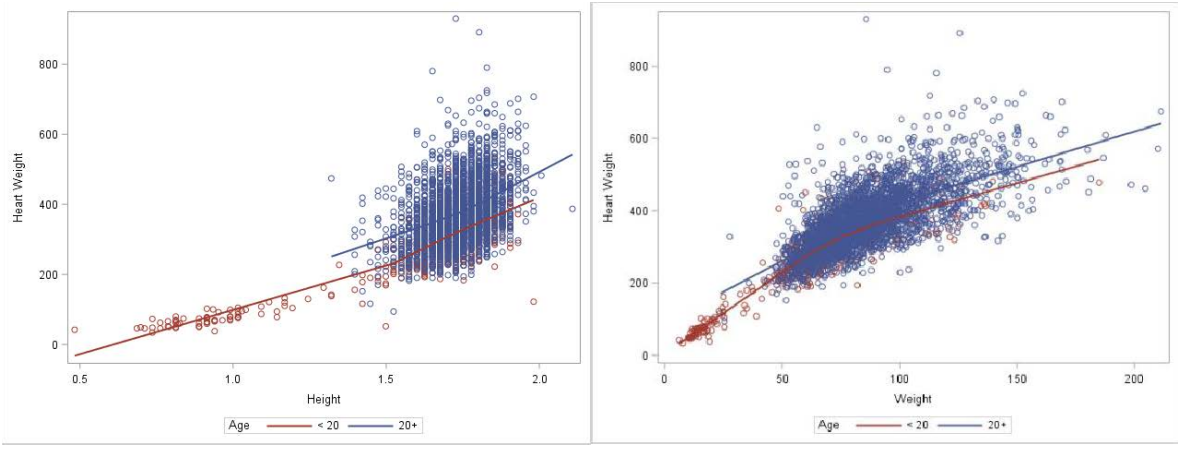
Models with highly correlated independent variables, as identified by a variance inflation factor greater than 10, were removed from consideration. The remaining model with the lowest AIC, BIC, and CV-MSE was selected. As descriptive scatterplots (Figure S2) indicated, potentially higher-order relationships between age, weight, height and the heart weight outcome existed. Therefore, we then considered adding higher-order terms.

Figure S2. Scatterplots of age, weight, and height versus log [heart weight].



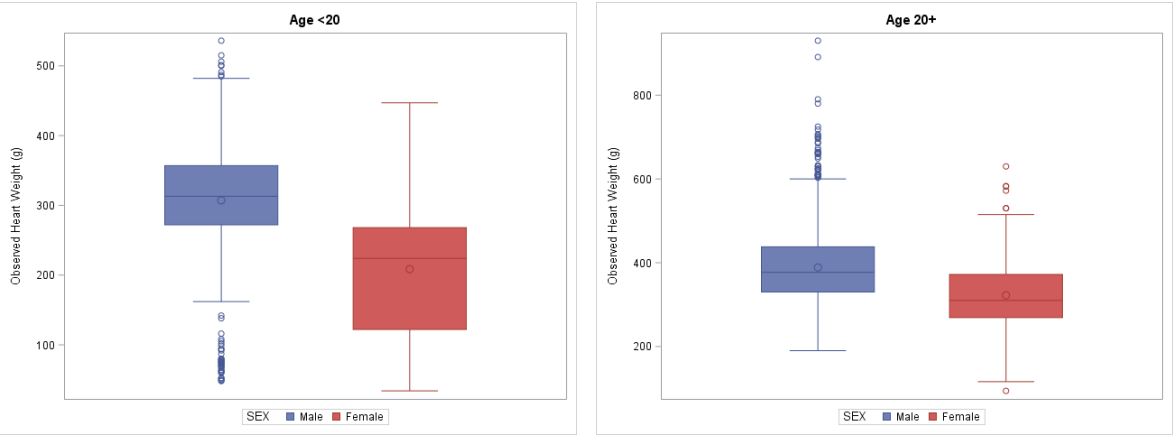
We considered age^2, height^2, and weight^2 in an iterative process (Table S1, Step 2). Further investigation of interactions with age (Table S1, Step 3) were performed to assess whether the effects of these factors on heart weight may be different for different ages. Consideration of interactions with age, which may warrant stratification by age group, was further explored with visualizations of associations by age group (<20 vs 20+). Scatterplots overlaid with Loess curves and boxplots did not provide suggest different effects of height, weight, or sex or heart weight for different age groups (Figures S3 and S4). Furthermore, models incorporating interactions with age did not improve model fit, but caused additional concerns with multicollinearity. Thus, stratification of models by age group and interactions with age were not reported.

Figure S3. Scatterplots of height and weight versus heart weight.



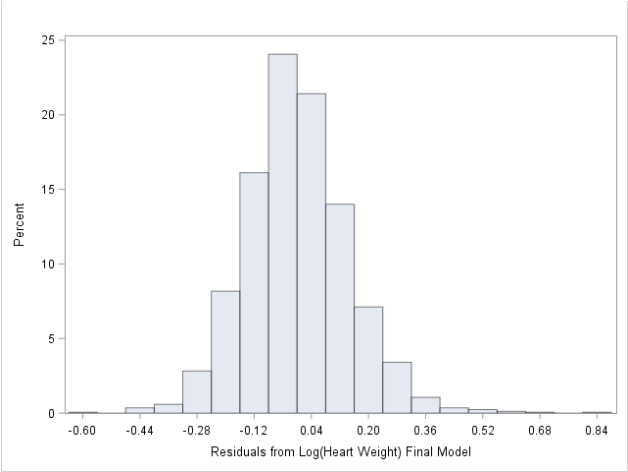
Loess curves added, stratified by age < 20 years (red) and age ≥ 20 years of age or older (blue)

Figure S4. Box plots of observed heart weight, stratified by sex and age.



The final model was ultimately selected by the lowest AIC, BIC, and CV-MSE, without violation of multicollinearity concerns (Table S1, Model 7). Residuals were also assessed for the final model (Figure S5).

Figure S5. Histogram of Residuals from Final Model.



From the final selected model, we established an equation for estimating the conditional mean heart weight and corresponding upper 95% confidence interval limit based on the estimated coefficients and standard error (Table S2).

Equation for upper 95th limit of heart weight (Equation 1 from manuscript)

$$= e^{2.88 - 0.12*female + 0.0065*age + 1.09h + 0.047w - 0.018w*h + 0.000092h*w^2 - 0.0002w^2 + 0.25}$$

Where *age* = age at death in years; h = (body height in meters – 1.72), which is the measured height minus the mean sample height; w = (body weight in kilograms – 83.48), which is the measured weight minus the mean sample weight; and *female* = 1 if female and 0 if male. The value 0.25 is used because it is the standard error of the estimate multiplied by 1.65.

Finally, a sensitivity analysis considered exclusion of potential outliers, as identified by large residuals, < -3 or > 3 (n=15); however model results remained consistent (Table S3). We then applied the final equation to the NSDC cohort. Observed heart weights above the upper 95% confidence interval limit, conditional on age, sex, weight, and height, were defined as cardiomegaly.