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None to Declare.

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Abstract:

Purpose: Blood pressure, cardiac output, and ventricular volumes correlate to various subject features such as age, body size, and exercise intensity. The purpose of this study is to quantify this correlation through regression modeling. *Methods:* We conducted a systematic review to compile reference data of healthy subjects for several cardiovascular parameters and subject features. Regression algorithms used these aggregate data to formulate predictive models for the outputs - systolic and diastolic blood pressure, ventricular volumes, cardiac output, and heart rate - against the features - age, height, weight, and exercise intensity. A simulation-based procedure generated data of virtual subjects to test whether these regression models built using aggregate data can perform well for subject-level predictions and to provide an estimate for the expected error. The blood pressure and heart rate models were also validated using real-world subject-level data. *Results:* The direction of trends between model outputs and the input subject features in our study agree with those in current literature. *Conclusion:* Although other studies observe exponential predictor-output relations, the linear regression algorithms performed the best for the data in this study. The use of subject-level data and more predictors may provide regression models with higher fidelity. *Significance:* Models developed in this study can be useful to clinicians for personalized patient assessment and to researchers for tuning computational models.

Keywords:
Systematic Review, Regression Modeling, Simulation Studies, Blood Pressure, Cardiac Output, Ventricular volume

Abbreviations:

BSA	–	Body Surface Area (m^2)
BMI	–	Body Mass Index (kg/m^2)
MET	–	Metabolic Equivalent (exercise intensity)
SD	–	Standard Deviation
EDV	–	End-Diastolic Volume (ml)
ESV	–	End-Systolic Volume (ml)
RMSE	–	Root-Mean-Squared Error
NRMSE	–	Normalized Root-Mean-Squared Error (normalized to mean value)
Data-O	–	the original aggregate data compiled from the systematic review process
Sample-O_{aggr}	–	a single aggregate data point from Data-O
Model-O	–	the regression models built using Data-O
Data-S	–	the simulated aggregate data generated using the simulation studies procedure
Model-S	–	the regression models built using Data-S
FRIEND	–	Fitness Registry and the Importance of Exercise National Database
Model-F	–	the regression models built using subject-level data from FRIEND

Systematic Review and Regression Modeling of the Effects of Age, Body Size, and Exercise on Cardiovascular Parameters in Healthy Adults

Introduction:

Subject features such as age, body size, and exercise intensity correlate with blood pressure [1–4], blood flowrate [5–7], ventricular volumes [8–11], and other hemodynamic parameters [12–14]. These are some of the most important and fundamental cardiovascular parameters which provide important clinical information regarding the cross-sectional health status and longitudinal health trajectory of a subject [15–19].

Clinicians have developed consensual pathologic thresholds for many of these cardiovascular parameters. However, despite the potential utility, a more personalized approach of evaluating gradations of these parameters within the normal and abnormal ranges is not widely used [20]**.** While a threshold approach is easier to study with clinical trials, a more granular understanding of patient-specific parameters could encourage better personalized medicine.

Multivariable regression models provide specific numerical values of the cardiovascular parameters given subject features. They also provide the ability to assess the strength of predictors used which makes the models physically interpretable and provides clinicians the ability to easily integrate them into the current standard of care. By utilizing an array of reference data, these models can provide a specific benchmark regarding normal values for cardiovascular parameters, thereby improving diagnostic resolution in the clinical setting.

Computational modeling often uses patient-specific measurements as well as literature-reported values for model construction [21–25]. Previous studies have combined literature data such as cardiac chamber volumes [22] and blood flow rates and pressures [23–25] with patient-specific data to generate models. Values in the literature given for healthy subjects are generally in the form of percentiles or ranges [26–28] and not specific numerical values. Predictions from the multivariable regression equations can provide useful targets for model tuning. For parameters where patient-specific data is not available, the predictions from such regression models can impute the missing information for patient-specific tuning.

Previous studies have reported the reference ranges of cardiovascular parameters for healthy adults [26,27], with some also reporting the correlation coefficients which only describe the trends between the cardiovascular parameter versus the predictors [1,5,7,29–37]. However, studies in current literature generally did not report explicit multivariable regression models. The majority of the articles which report regression equations for healthy adults were single variable linear regression models. These models used subject-level data and provided models for stroke volume (SV) [10,38,39], cardiac output [6,10,38,39], heart rate [38,39], and left ventricular end-diastolic and end-systolic volumes (EDV and ESV) [10,27]; however, age [6,10,27], height [6,38], weight [6,38,39], and body surface area (BSA) [6,10,38] used as predictors in these prior studies were applied separately for the cardiovascular parameters.

While the use of multiple predictors for regression modeling of these cardiovascular parameters is not common, a few publications have utilized this method. One multiple regression model built on subject-level data for left ventricular EDV [40] provided the linear coefficients against age, height, weight, and sex. In another study, an indirect form of multiple regression [1] provided the change in systolic and diastolic pressure against weight and body mass index (BMI) after adjusting for age, height, education, waist circumference, etc. As for non-linear models, a 5-knot-restricted cubic splines regression [3] used subject-level systolic and diastolic pressure data

to build models against height. For right ventricular volumes (i.e., EDV, ESV, and stroke volume) [34], an exponential multi-variable relation used age and BSA as the predictors.

In this study, a systematic review compiled the current literature reporting measurements of ventricular volumes, blood pressure, and cardiac output under resting and exercise conditions in relatively healthy subjects. Next, we used various linear and non-linear regression algorithms on this data to build predictive models for these cardiovascular parameters. Sex [41] and race [42] also affect the cardiovascular parameters; however, not enough data was available to include them in the current analysis. Other predictors such as percent body fat [43], pulmonary artery systolic pressure [44], ventricular mass [45], pericardial fat volume [32], and respiratory mechanical properties [46] are only obtained through advanced measurement not readily available and thus were not included in regression modeling. By including only age, body size, and exercise intensity as predictors, it is not possible to predict the exact value of the cardiovascular parameters of interest, however, due to the correlation of the predictors with the parameters, the formulated regression models can provide a realistic estimate of those parameter values.

Since our systematic review pooled together data from the studies selected, the data we used for regression modeling corresponds to a larger population than any single study referenced in this review. Most of these studies (**Table 1**) either directly collected subject data or referred to subject data compiled from institutional collaborations for data collection [32,47–49]; whereas in this study, the models generally used aggregate data. A simulation-based statistical method was used to evaluate the performance of the regression algorithms built on aggregate data for subject-level predictions. For a few of the cardiovascular parameters, we obtained subject data [50–52] in order to perform a direct comparison between regression models built on aggregate data versus those built on subject data.

In summary, the models from this study provide numerical reference values of key cardiovascular parameters for a subject characterized by the values of the predictors. We also report the trends of the cardiovascular parameters versus predictors. The models contain a combination of age, body size, and exercise intensity as predictors and estimate reference cardiovascular parameters for a subject or cohort of interest providing a more personalized approach to patient diagnosis.

Methods:

We collected data for regression modeling by conducting a comprehensive literature search for databases reporting cardiovascular parameter data for healthy subjects (as described in the Literature Search section). The search for subject-level databases provided data for systolic pressure, diastolic pressure, and heart rate only; while aggregate data for all the cardiovascular parameters of interest were available. We built regression models for all of the parameters using the aggregate data (Regression Modeling section). In order to assess the performance of these regression algorithms for providing subject-level predictions, we generated subject-level data (Simulation Studies section) based on the aggregate data statistics and repeated the regression procedure on the simulated data to obtain reference results for comparison (Model Comparison section). Finally, we used the real-world subject-level data (available only for systolic pressure, diastolic pressure, and heart rate) to validate our modeling procedure and to obtain additional regression models built directly from subject-level data.

Literature Search:

This study selected data for each cardiovascular parameter in accordance with the PRISMA [53] guidelines by using the advanced search in the PubMed database. **Table 1, Table 2, and Fig.**

1. summarize the search process, search strings used, the number of articles selected, and the quantity of data compiled.

During the literature screening process, only articles that reported data about relatively healthy adults were included. Studies focusing on subjects with one or more major health conditions (e.g., pulmonary hypertension, valve regurgitation, etc.) likely to have a significant effect on the cardiovascular parameters of interest were considered only if they also reported data on healthy control subjects as comparators. The articles included used a variety of imaging modalities for measurements. The purpose of the articles included was either to investigate which variables in the study affect the cardiovascular parameter of interest, to compare controls to subjects with a health condition, or to investigate the effect of interventions on the cardiovascular parameter of interest.

Articles were excluded if the age of the participants was not reported. For every article, we excluded the data for subjects less than 16 years of age. The predictors – height, weight, body surface area (BSA), and body mass index (BMI) – are all indicators of body size and correlate to each other; thus any two of these predictors are enough to calculate the other predictors from the BSA formula by Mosteller [90] and the formula for BMI (weight(kg) / height(meters)^2). Articles that did not provide enough information to calculate the body size variables were excluded. For every article, we excluded data for subjects with mean BMI greater than 85th percentile (36 kg/m^2) [91], as well as data for blood pressure and cardiac output if it was not possible to determine the corresponding exercise intensities. As the articles with data on ventricular volumes along with exercise were limited in number [87,88], we did not include metabolic equivalents (MET) as a predictor for ventricular volumes. We considered journal articles published before 31 December 2018 and restricted the language of the articles to English.

We used the guidelines provided in the revised Cochrane risk-of-bias tool for randomized controlled trials [92] to identify the risk of bias for individual studies with respect to performance, detection, attrition, reporting, and any other type of biases, and classified the studies as having a low risk, high risk, or unclear concerns of bias (**Table 1**). The articles with high risk were not used for regression modeling.

The data in the form of sample size, the mean and standard deviation (SD) of the predictors and the cardiovascular parameter were manually extracted from the selected articles. This entire dataset is referred to as Data-O in this paper. Each article reported one or more aggregate data points (Sample-O_{aggr}).

TABLE 1

TOTAL AVAILABLE DATA COMPILED FROM THE SYSTEMATIC REVIEW

Sr No	Author (Year)[ref#]	Cardiovascular Parameter								Risk of Bias	Search String
		SysBP	DiasBP	LVEDV	LVESV	RVEDV	RVESV	CO	HR		
1	Wang et al. (2018)[4]	✓	✓						✓	Low	Aortic Pressure (MeSH) + Exercise (Keywords)
2	Schultz et al. (2013)[54]	✓	✓						✓	Low	Aortic Pressure (MeSH) + Exercise (Keywords)
3	Hulkkonen et al. (2014)[47]	✓	✓							Low	Aortic Pressure (MeSH) + Exercise (Keywords)
4	Robinson et al. (1988)[55]	✓	✓						✓	Low	Aortic Pressure (MeSH) + Exercise (Keywords)
5	Shim et al. (2011)[56]	✓	✓					✓	✓	Low	Aortic Pressure (MeSH) + Exercise (Keywords)
6	Chia et al. (2015)[57]	✓	✓						✓	Low	Ventricle Volume (MeSH) + Aging (Keywords)
7	D'Alto et al. (2017)[13]	✓	✓						✓	Low	Ventricle Volume (MeSH) + Aging (Keywords)
8	Ashrafpoor et al. (2015)[58]			✓	✓					Low	Ventricle Volume (MeSH) + Aging (Keywords)
9	Nio et al. (2017)[59]			✓	✓					Low	Ventricle Volume (MeSH) + Aging (Keywords)
10	Bernard et al. (2016)[60]			✓	✓					Low	Ventricle Volume (MeSH) + Aging (Keywords)

Sr No	Author (Year)[ref#]	Cardiovascular Parameter								Risk of Bias	Search String
		SysBP	DiasBP	LVEDV	LVESV	RVEDV	RVESV	CO	HR		
11	D'Andrea et al. (2017)[61]			✓	✓					Low	Ventricle Volume (MeSH) + Aging (Keywords)
12	Menting et al. (2016)[62]			✓	✓					Low	Ventricle Volume (MeSH) + Aging (Keywords)
13	Yeon et al. (2015)[63]			✓	✓					Low	Ventricle Volume (MeSH) + Body Size (Keywords)
14	Bhambhani et al. (2018)[31]			✓	✓					Unclear	Ventricle Volume (MeSH) + Body Size (Keywords)
15	Nikitin et al. (2006)[64]			✓	✓					Low	Ventricle Volume (MeSH) + Body Size (Keywords)
16	Maffessanti et al. (2013)[34]			✓	✓					Low	Ventricle Volume (MeSH) + Body Size (Keywords)
17	Kuznetsova et al. (2016)[9]			✓	✓					Low	Ventricle Volume (MeSH) + Body Size (Keywords)
18	Benda et al. (2016)[65]			✓	✓					Unclear	Ventricle Volume (MeSH) + Exercise (Keywords)
19	Rao et al. (2015)[66]			✓	✓					Low	Ventricle Volume (MeSH) + Exercise (Keywords)
20	Rojek et al. (2015)[8]			✓	✓					Low	Ventricle Volume (MeSH) + Exercise (Keywords)

Sr No	Author (Year)[ref#]	Cardiovascular Parameter								Risk of Bias	Search String
		SysBP	DiasBP	LVEDV	LVESV	RVEDV	RVESV	CO	HR		
21	Schmidt et al. (2015)[44]			✓	✓					Low	Ventricle Volume (MeSH) + Exercise (Keywords)
22	Lane et al. (2014)[67]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
23	Park et al. (2003)[68]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
24	Celentano et al. (2003)[41]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
25	Maceira et al. (2006)[27]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
26	Scalia et al. (2010)[69]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
27	Maggioni et al. (2012)[70]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
28	Lee et al. (2016)[71]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)

Sr No	Author (Year)[ref#]	Cardiovascular Parameter								Risk of Bias	Search String
		SysBP	DiasBP	LVEDV	LVESV	RVEDV	RVESV	CO	HR		
29	Yang et al. (2017)[72]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
30	Hollingworth et al. (2012)[73]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
31	Fujimoto et al. (2012)[74]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
32	Lin et al. (2014)[75]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
33	Vormbrock et al. (2014)[29]			✓	✓					Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
34	Aquaro et al. (2017)[76]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + Aging (Keywords)
35	Lei et al. (2017)[77]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + Body Size (Keywords)
36	Stojanovska et al. (2014)[78]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + Body Size (Keywords)

Sr No	Author (Year)[ref#]	Cardiovascular Parameter								Risk of Bias	Search String
		SysBP	DiasBP	LVEDV	LVESV	RVEDV	RVESV	CO	HR		
37	Le Ven et al. (2016)[79]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + Body Size (Keywords)
38	Prakken et al. (2010)[80]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + Body Size (Keywords)
39	Wilson et al. (2011)[81]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
40	Bohm et al. (2016)[82]			✓	✓	✓	✓			Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
41	Maceira et al. (2006)[26]					✓	✓			Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
42	Foppa et al. (2016)[49]					✓	✓			Low	Ventricle Volume (MeSH) + [Aging + Body Size + Exercise] (Keywords)
43	Staunton et al. (2015)[83]							✓		Low	Cardiac Output (MeSH) + Age (Keywords)
44	Xing et al. (2017)[5]							✓		Low	Cardiac Output (MeSH) + Age (Keywords)
45	McGuire et al. (2001)[84]							✓	✓	Low	Cardiac Output (MeSH) + [Aging + Body Size + Exercise] (Keywords)

Sr No	Author (Year)[ref#]	Cardiovascular Parameter								Risk of Bias	Search String
		SysBP	DiasBP	LVEDV	LVESV	RVEDV	RVESV	CO	HR		
46	Ogawa et al. (1992)[85]							✓		Low	Cardiac Output (MeSH) + [Aging + Body Size + Exercise] (Keywords)
47	Vella et al. (2012)[86]							✓	✓	Low	Cardiac Output (MeSH) + [Aging + Body Size + Exercise] (Keywords)
48	Esfandiari et al. (2014)[87]							✓		Low	Ventricle Volume (MeSH) + Exercise (Keywords)
49	Roberts et al. (2018)[88]			✓	✓			✓		Low	Ventricle Volumes MeSH + Together
50	Barrett-O'Keefe et al. (2015)[89]								✓	Low	Aortic Pressure (MeSH) + Exercise (Keywords)

SysBP: systolic blood pressure, DiasBP: diastolic blood pressure, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, RVEDV: right ventricular end-diastolic volume, RVESV: right ventricular end-systolic volume, CO: cardiac output, HR: heart rate, MeSH: Medical Subheadings.

TABLE 2

TOTAL AVAILABLE DATA COMPILED FROM THE SYSTEMATIC REVIEW

	No. of Articles	No. of Sample-O_{aggr}	Total sample size
Systolic Pressure	7	43	2195
Diastolic Pressure	7	43	2195
Heart Rate	9	38	1178
Left Ventricular EDV	34	98	6811
Left Ventricular ESV	34	98	6811
Right Ventricular EDV	10	38	2523
Right Ventricular ESV	10	38	2523
Cardiac Output	8	36	703

EDV: End-Diastolic Volume; ESV: End-Systolic Volume

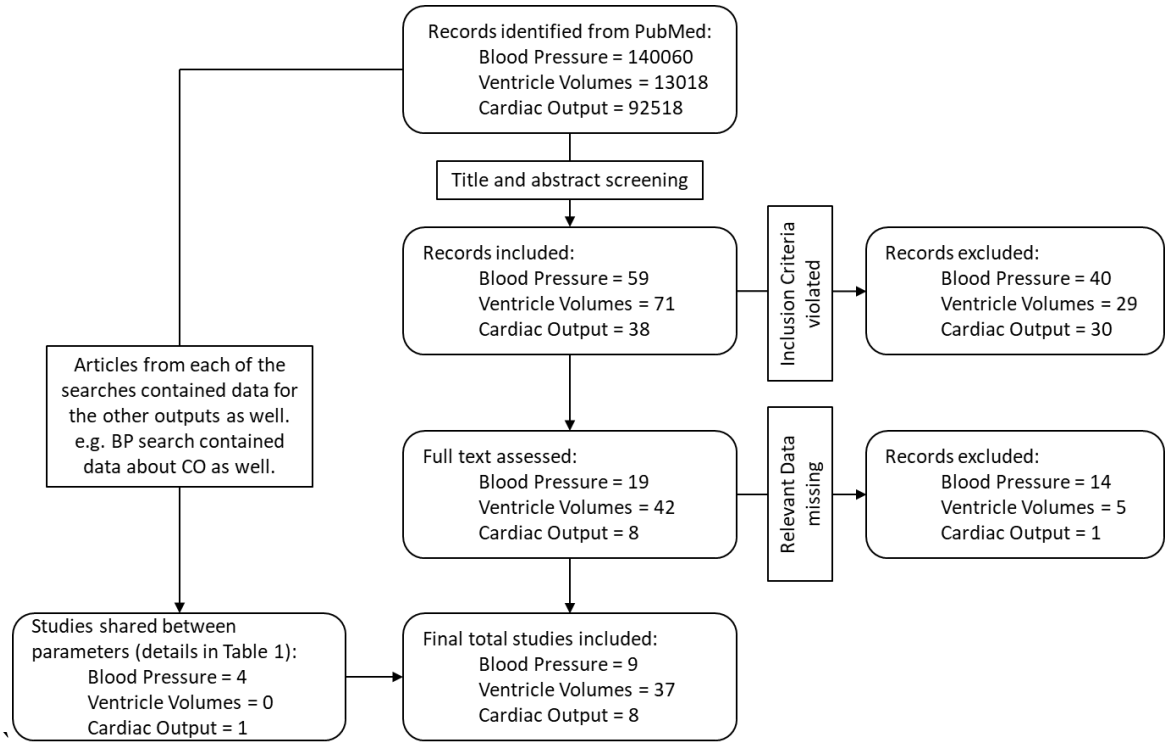

Figure 1. Flow diagram of the literature search and selection process

Regression Model Building:

R, version 3.6.1 [93], was used to conduct the data analysis. For building regression models using the original aggregate literature data (Model-O), the Linear, Partial Least Squares, Elastic-Net, Multivariate Adaptive Regression Splines, and Support Vector Machines multivariable

regression models were used as per the recommendations from Kuhn et al. [94] Since the predictors which represent body size (height, weight, BSA, and BMI) are correlated, if the articles did not report all of the body size predictors, we impute the missing values using the Mosteller formula [90] and BMI formula as applicable. Since correlated variables should not be used together while building regression models [95], the models used specific combinations of body-size predictors (height and weight, BSA and BMI, or height, weight, BSA, or BMI only) for the regression models. We chose the best combination among the body size predictors by comparing the Root Mean Squared Error (RMSE) of the regression results.

For building Model-O, we centered and scaled the predictor values, used the sample size for weighing each data point, and tuned the hyperparameters associated with each of the regression algorithms by using five-fold cross-validation repeated three times. The Model-O cross-validation RMSE ($RMSE_{Mod\text{-}O\text{-}CV}$) provided an estimate of the error for predicting aggregate data using models built on aggregate data (**Fig. 2**).

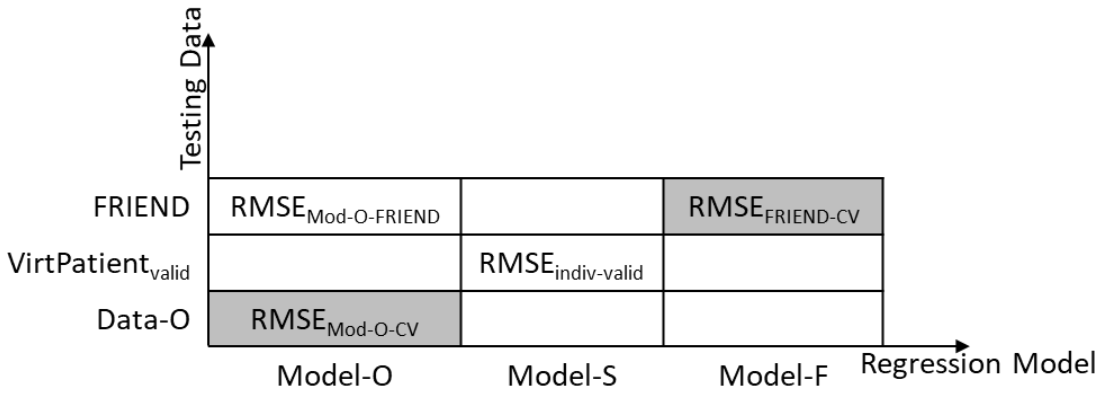

Figure 2. Descriptions of the RMSEs reported and their method of calculation with respect to the regression model and the testing data. The shaded entries are cross-validation RMSEs and the others are validation RMSEs for regression models built on aggregate data against subject data.

Simulation Studies:

Overview:

As this study compiled data from a systematic review, we did not have access to subject-level data. In order to evaluate the impact of the ecological fallacy [96], we performed simulation studies to determine whether inferences on individuals can be made from the aggregate group data in our regression analyses. The simulation studies procedure aimed to generate (simulate) multiple instances of subject-level data (30 instances) from the aggregate data and then check the performance of Model-O against the simulated subject-level data. In other words, simulation studies (**Fig. 3**) estimated the validity of using regression models built on aggregate data for subject-level predictions.

We generated the subject-level data for model training and validation based on the mean and SD of Data-O. The training dataset that consisted of these simulated subjects was randomly aggregated into groups so that each group had the same structure as Sample-O_{aggr}, and regression models (Model-S) were trained using this simulated aggregate data. This procedure imitated how

Model-O was built from Data-O which contains aggregate data from the literature. This random grouping was repeated 20 times for each simulated dataset. The simulated validation dataset was left as subject-level data points which we used to evaluate the performance of Model-S for making subject-level predictions. Thus, the RMSEs ($RMSE_{indiv\text{-}valid}$) of this simulated validation set against Models-S represented the error associated with predicting subject-level data using regression models built on aggregate data (**Fig. 2**); whereas $RMSE_{Mod\text{-}O\text{-}CV}$ represented the error associated with predicting aggregate data using regression models built on aggregate data (**Fig. 2**).

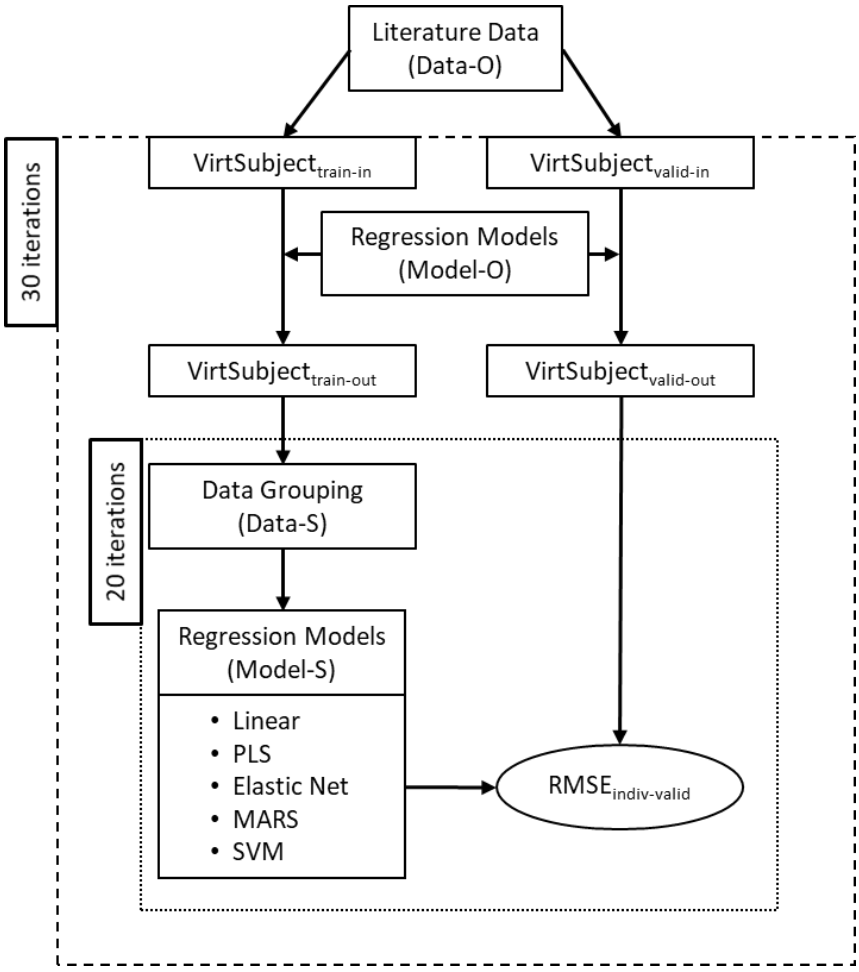

Figure. 3. Procedure for simulation studies with 20 iterations for the different ways of data aggregation and 30 iterations for the different ways of data generation. The left column describes the simulation of the aggregate training set (Data-S) and the right column describes the simulation of the subject-level testing sets. Details of generating the predictor and output values are provided in the 'Simulated Predictor Values' and 'Simulated Cardiovascular Parameter Values' sections. $VirtSubject_{train\text{-}in}$ and $VirtSubject_{train\text{-}out}$: the simulated set of predictors and cardiovascular parameter values describing virtual subjects in Data-S (these subjects are used to train Model-S), $VirtSubject_{valid\text{-}in}$ and $VirtSubject_{valid\text{-}out}$: the simulated set of predictors and cardiovascular parameter values describing virtual subjects in the validation group (these subjects are used to validate Model-S for subject-level predictions), PLS: Partial Least Squares, MARS: Multivariate Adaptive Regression Splines, SVM: Support Vector Machines.

Simulated Predictor Values:

In order to generate the training set for building Model-S, we assumed the predictors follow a multivariate normal distribution, where the means and SD of the predictors were as reported in Data-O. We approximated the correlation coefficients between the predictors from Data-O, set the coefficients of age vs. body size parameters to 0 to represent no growth for adults, and set the coefficient of MET versus all other parameters to 0 to indicate that during exercise, the control variable MET, was not dependent on any other predictors.

In order to ensure that enough virtual subjects were generated which adequately represented every Sample-O_{aggr}, we simulated an initial dataset with the sample size equal to the square of the original sample size and applied a range constraint that removed subjects from this initial dataset with characteristics that did not represent the literature data. The range constraints were chosen such that they included the subjects with feature values approximately in the mean ± 2SD (95% confidence) interval for all Sample-O_{aggr}. This corresponds to subjects with age from 16 - 80 years, height from 150 - 200 cm, weight from 50 - 120 kg, BSA from 1.2 - 2.6 m^2, BMI from 18 - 35 kg/m^2, and MET from 0.9 - 20. From this constrained dataset, a subset of size equal to the sample size of the Sample-O_{aggr} was randomly selected for further analysis. This was done for every Sample-O_{aggr} and therefore, the total number of subjects represented in this simulated training dataset was equal to that in Data-O. This dataset ($VirtSubject_{train\text{-}in}$ in **Fig. 3)** represented a possible set of the predictor values which described all the subjects in Data-O.

We simulated the validation dataset (for the purpose of evaluating Model-S) using a similar procedure. To generate at most five realistic datapoints for each Sample-$O_{aggr,}$ the same range constraint filtered an initial dataset size of 25, and five datapoints were randomly selected from this filtered dataset. If the sample size of Sample-O_{aggr} was less than five, then we added only one datapoint to the validation set to avoid generating pseudoreplicates [97]. This simulated dataset ($VirtSubject_{valid\text{-}in}$ in **Fig. 3**) represented a possible set of predictor values that described a subset of subjects from Data-O.

Simulated Cardiovascular Parameter Values:

The values of the simulated cardiovascular parameters for each subject in the simulated training and validation datasets were generated in three steps. We first fed the simulated predictor values into Model-O to generate the initial value of the cardiovascular parameter (Step 1). For a regression model, the residual is the difference in the predicted and observed values. To ensure that the simulated parameter values account for the error in Model-O predictions, the Sample-O_{aggr} versus Model-O residual was added to the value obtained in step 1 (Step 2). Finally, we randomly added a normally distributed error, with mean equals to 0 and SD equals to the SD of the cardiovascular parameter as reported in Data-O, to each cardiovascular parameter value associated with the Sample-O_{aggr} to account for the noise in Data-O (Step 3).

Regression Modeling of the Simulated Data:

The purpose of the simulated training dataset was to train the Model-S regressions and the simulated validation dataset was used to evaluate the performance of Model-S for subject-level predictions. To capture the numerous possibilities of the subject-level data distributions, we repeated the procedure of creating the simulated training and validation datasets six times using each of the five Models-O (Linear, Partial Least Squares, Elastic-Net, Multivariate Adaptive Regression Splines, and Support Vector Machines), resulting in the creation of a total of 30 sets of simulated data (**Fig. 3**).

The set of virtual subjects in the simulated training dataset was shuffled and then divided into groups with the size of each group equal to the sample size of each Sample-O_{aggr} in Data-O.

We calculated the mean values of predictors and the corresponding cardiovascular parameters for each group and therefore, aggregated the simulated subject-level training dataset to form Data-S. For every simulated training dataset generated, we repeated this grouping 20 times to capture the multiple grouping possibilities from the subject-level data (Data Grouping cell in **Fig. 3**).

In summary, 30 different simulated subject-level datasets grouped in 20 random ways generated 600 possibilities of Data-S. Each of the five regression algorithms was used to fit each of the 600 Data-S sets to create a total of 3000 Models-S (Regression Models cell in **Fig. 3**).

Model Comparison:

$RMSE_{indiv\text{-}valid}$ is the RMSE of the Models-S predictions on the simulated validation dataset. (**Fig. 2**). Therefore, for every regression algorithm, we obtained 600 $RMSE_{indiv\text{-}valid}$ values representing the goodness of fit of the predicted cardiovascular parameters (simulated) from subject features (simulated). The means of these 600 $RMSE_{indiv\text{-}valid}$ values provided an estimate of the error in subject-level predictions for each regression algorithm [98].

We compared the magnitude of the correlation of each predictor by using a dimensionless value of the regression coefficients. The regression coefficients describe the change of the cardiovascular parameter value per unit increment of each predictor (i.e. age by one year, height by one cm, etc.). Since comparing these coefficient values directly would not provide meaningful results, we multiplied the regression coefficients by the SD of the predictor values in Data-O and then normalized them with respect to the SD of the cardiovascular parameter to obtain a non-dimensional percentage value according to previous work on the standardization of coefficients [99]. We classified the correlation as weak if this value was <30% and strong if it was >60%.

Validation against real-world subject-level data:

Simulation studies used generated data as subject-level data was not accessible for all cardiovascular parameters. For real-world validation, data from cardiopulmonary exercise tests from the Fitness Registry and the Importance of Exercise National Database (FRIEND) [50–52] was used. The data included the systolic pressure, diastolic pressure, and heart rate at rest and at peak exercise. Information on whether the subject was hypertensive, diabetic, etc. was also provided. After excluding the hypertensive and diabetic subjects, this study used 1831 healthy subjects from FRIEND for analysis.

In contrast to $RMSE_{indiv\text{-}valid}$, which was obtained using simulated data, the RMSE of Model-O predictions against FRIEND data ($RMSE_{Mod\text{-}O\text{-}FRIEND}$) represented the error of the aggregate regression model for subject-level predictions using real-world data (**Fig. 2**). Thus, we can assess whether real-world data produced similar outcomes as compared to simulated data to validate the simulation studies procedure. This helped provide confidence to the simulation study procedure which we used to appraise the models where no real subject data was available for validation. Since FRIEND did not include ventricular volume and cardiac output data, we were able to evaluate only some of the models using this method. Further, we used the same five regression algorithms to build models for systolic pressure, diastolic pressure, and heart rate based on the real-world FRIEND data (Model-F) for comparison against the models built on aggregate data (Model-O).

We calculated the left and right ventricular EDV and ESV for the FRIEND subjects using Model-O for left and right ventricular volumes. The difference between the EDV and ESV gave the stroke volumes of the left and right sides for each subject. The stroke volume for the left and right side of the heart should be equal [100]. We used this difference in the left and right stroke volume to check the performance of the ventricular volume models because no subject-level databases were available to validate these models.

Results:

Systolic and Diastolic Pressure:

The Elastic-Net model, with age, height, weight, and MET as predictors, gave the lowest $RMSEs_{indiv\text{-}valid}$ and was the model chosen for further analysis for systolic and diastolic pressure. The difference between $NRMSE_{Mod\text{-}O\text{-}CV}$ and $NRMSE_{indiv\text{-}valid}$ was less than 1% for systolic pressure and 2.1% for diastolic pressure(**Table 3**). The Model-O coefficients (**Table 4**) showed that systolic and diastolic pressures correlated positively but weakly to age, height, and weight, and positively and strongly to MET.

The $NRMSE_{indiv\text{-}valid}$ was 0.9% and 2.5% higher than $NRMSE_{Mod\text{-}O\text{-}FRIEND}$ (**Table 5**) for systolic and diastolic pressures, respectively. For Model-F, the coefficients for age, weight, and METs (**Table 4**) were similar to those from Model-O. However, for height, Models-F provided a weak and negative correlation to both blood pressures.

The Elastic-Net algorithm gave the best results for fitting subject-level data (lowest $NRMSE_{indiv\text{-}valid}$). We also noted that $NRMSE_{FRIEND\text{-}CV}$ (**Table 5**) was lower than $NRMSE_{Mod\text{-}O\text{-}FRIEND}$. The Data-O vs. predicted plot for Elastic-Net Models-F (**Fig. 4**) showed that the models tend to under-predict higher values of systolic and diastolic pressures (which mostly correspond to higher MET levels).

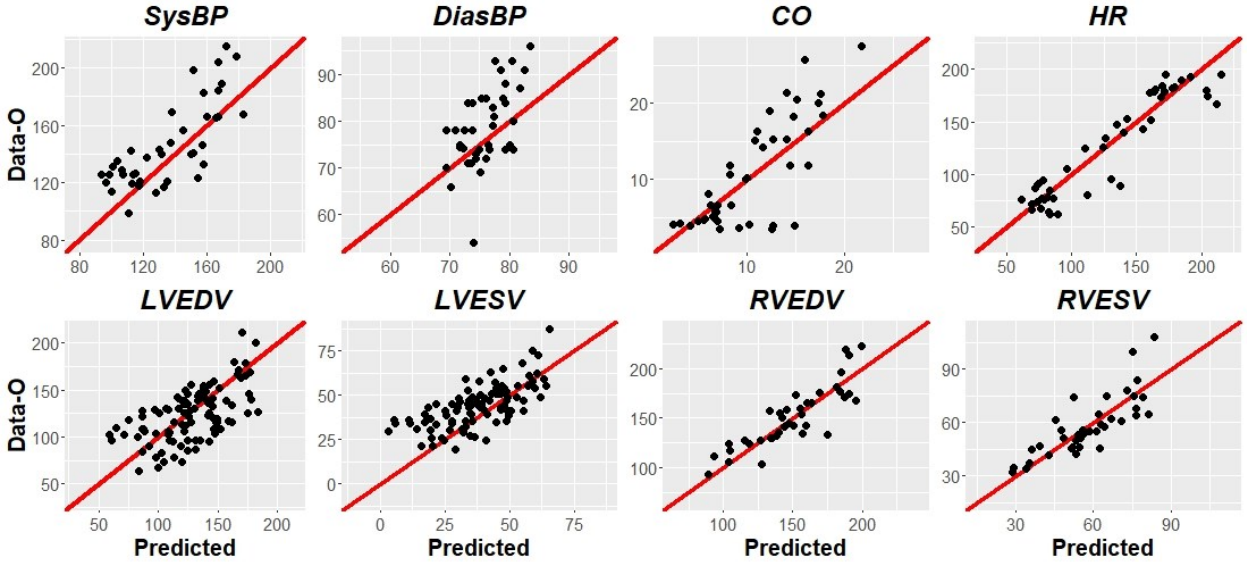

Figure 4. The actual (Data-O) vs. predicted cardiovascular parameter value using the regression models with the lowest NRMSEs. The 45° line (red) corresponds to where the predicted and actual values are equal. Note that the left ventricle predictions here are performed based on the right ventricle models plus a bias offset as discussed in the "Recommended Regression Models" section of the manuscript. SysBP: systolic blood pressure, DiasBP: diastolic blood pressure, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, RVEDV: right ventricular end-diastolic volume, RVESV: right ventricular end-systolic volume, CO: cardiac output, HR: heart rate.

Ventricular Volumes:

For all the ventricular volume models, the Linear models with age, height, and weight as predictors provided the lowest $NRMSEs_{indiv\text{-}valid}$ and were the models chosen for further analysis.

The difference in $NRMSE_{Mod\text{-}O\text{-}CV}$ and $NRMSE_{indiv\text{-}valid}$ was 9.3%, 20.5%, 7.96%, and 11.7% for Left Ventricular EDV, ESV, and Right Ventricular EDV, and ESV, respectively (**Table 3**). The Linear Model-O coefficients (**Table 4**) showed that all ventricular volumes correlated negatively to age, positively to weight, and positively to height.

Even though the amount of data for left and right ventricular volumes that we obtained through the literature search were quite different (**Table 2**), there was no skewness (due to the much smaller data size) in the right ventricular predictor data as the histograms for all the predictors were similar for both the ventricles.

The means of the stroke volumes in Data-O for the left and right sides were 70.1 ml and 87.4 ml, respectively. The means of the predictions of stroke volumes from the 1831 subjects from FRIEND were 78.2ml and 94.5ml for the left and right side, respectively, and the RMSE of the difference between the left and right stroke volumes for the same subjects from FRIEND was 17.7 ml. We also note that the mean of the resting ejection fraction in Data-O for the right ventricle was 62%, which is higher compared to some previously reported values of resting ejection fraction [101–103].

Heart Rate:

The heart rate model used the combination of age, height, weight, and METs as predictors. The Linear model provided the lowest $NRMSE_{indiv\text{-}valid}$ and was the model chosen for further analysis. The difference in the $NRMSE_{Mod\text{-}O\text{-}CV}$ and $NRMSE_{indiv\text{-}valid}$ was about 5% (**Table 3**). The Model-O coefficients (**Table 4**) showed that heart rate correlated negatively but weakly to age, positively and weakly to height and weight, and positively and strongly to METs.

The $NRMSE_{Mod\text{-}O\text{-}FRIEND}$ was 8.4% higher than $NRMSE_{indiv\text{-}valid}$ (**Table 5**). For Model-F, the coefficients for weight and METs (**Table 4**) were similar to those from Model-O but the coefficients for age and height showed an opposite trend with respect to Model-O. Also, the intercept value for the Model-F was significantly different as compared to Model-O. We observed reasonable agreements between model predictions and Data-O for Linear Model-F (**Fig. 4**).

Cardiac Output:

The Linear model with age, weight, and MET as predictors yielded the minimum $NRMSE_{indiv\text{-}valid}$ and was the model chosen for further analysis for cardiac output. The difference in the $NRMSE_{Mod\text{-}O\text{-}CV}$ and $NRMSE_{indiv\text{-}valid}$ was less than 2% (**Table 3**). The Model-O coefficients (**Table 4**) showed that cardiac output correlates negatively and weakly to age, positively and weakly to weight, and positively and strongly to METs. **Fig. 4** showed that for higher values (which mostly correspond to higher MET levels), the Linear Model-O tended to under-predict cardiac output.

TABLE 3

$NRMSE_{INDIV\text{-}VALID}$ AND $NRMSE_{MOD\text{-}O\text{-}CV}$ COMPARISON

	NRMSE values (%)				
	Linear	**PLS**	**E-Net**	**MARS**	**SVM**
Systolic Pressure	17.24	12.35	**15.17**	13.50	11.57
	16.07	17.50	**15.83**	18.99	22.01
Diastolic Pressure	14.71	14.17	**14.41**	16.04	13.96
	16.68	17.57	**16.48**	18.97	17.66
Heart Rate	**11.56**	11.04	11.40	12.45	11.17
	16.45	18.91	16.80	19.08	38.04
Left Ventricular EDV	**22.96**	20.61	22.71	22.41	22.62
	32.30	32.42	32.34	40.00	37.86
Left Ventricular ESV	**23.44**	22.10	23.59	23.24	24.07
	43.96	44.38	44.08	52.01	53.35
Right Ventricular EDV	**12.24**	9.88	11.01	13.29	14.01
	20.20	20.36	20.40	43.56	58.71
Right Ventricular ESV	**19.71**	17.92	18.35	20.04	21.57
	31.41	31.71	31.85	51.79	66.78
Cardiac Output	**52.69**	50.90	55.50	59.68	53.84
	54.33	55.79	55.63	64.75	82.42

$NRMSE_{Mod\text{-}O\text{-}CV}$

$NRMSE_{indiv\text{-}valid}$

EDV: end-diastolic volume; ESV: end-systolic volume, PLS: Partial Least Squares, E-Net: Elastic-Net; MARS: Multivariate Adaptive Regression Splines, SVM: Support Vector Machines.

TABLE 4

REGRESSION COEFFICIENTS

		Coefficients					Expected Error (95% probability)	
		Intercept	**Age (yrs.)**	**Height (cm.)**	**Weight (kg.)**	**MET**		
Systolic Pressure	Model-O	25.45	0.09	0.4	0.24	5.57	±48.2	mmHg
	Model-F*	**94.89**	**0.72**	**-0.28**	**0.46**	**6.01**	**±40.3**	**mmHg**
Diastolic Pressure	Model-O	29.23	0.18	0.15	0.18	1.02	±26.8	mmHg
	Model-F*	**63.13**	**0.14**	**-0.04**	**0.16**	**0.53**	**±19.9**	**mmHg**
Heart Rate	Model-O	-32.25	-0.36	0.62	0.13	9.27	±36.9	bpm
	Model-F*	**204.2**	**0.11**	**-1.07**	**0.49**	**11.73**	**±43.6**	**bpm**
LVEDV	Model-O	-134.73	-0.42	1.04	1.25	NA	±70.8	ml
LVESV	Model-O	-91.21	-0.21	0.68	0.36	NA	±34.8	ml
RVEDV	**Model-O***	**-269.62**	**-1.03**	**2.44**	**0.63**	**NA**	**±56.0**	**ml**
RVESV	**Model-O***	**-179.77**	**-0.47**	**1.5**	**0.01**	**NA**	**±32.3**	**ml**
Cardiac Output	**Model-O***	**0.71**	**-0.06**	**NA**	**0.08**	**0.95**	**±9.4**	**l/min**

*(and bolded) recommended regression models, LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume, RVEDV: right ventricular end-diastolic volume; RVESV: right ventricular end-systolic volume.

TABLE 5

NRMSE COMPARISON FOR ASSESSMENT OF SIMULATION STUDIES

	Regression Algorithms	$NRMSE_{indiv\text{-}valid}$ (%)	$NRMSE_{Mod\text{-}O\text{-}FRIEND}$ (%)	$NRMSE_{FRIEND\text{-}CV}$ (%)
Systolic Pressure	**Elastic-Net**	15.83	14.92	13.23
Diastolic Pressure	**Elastic-Net**	16.48	13.90	12.27
Heart Rate	**Linear**	16.45	25.85	19.45

Discussion:

Systolic and Diastolic Pressures:

The Elastic-Net Model-O gave the best results for systolic and diastolic pressures for subject-level predictions. The similar error magnitudes from the comparison against simulated ($NRMSE_{indiv\text{-}valid}$) and real-world subject data ($NRMSE_{Mod\text{-}O\text{-}FRIEND}$) (**Table 5**) showed that the simulation procedure was effective, validating the simulation studies procedure for systolic and diastolic pressure models. Even though this showed that Model-O was not affected by the ecological fallacy, the fact that $RMSE_{FRIEND\text{-}CV}$ was lower than $RMSE_{indiv\text{-}valid}$ indicated that Model-F, which was directly built on subject data, still outperformed Model-O.

Our findings regarding correlations between predictors and blood pressure compared to those from previous studies were as follows. Positive correlations for blood pressures versus age [1,2,46,63,104] agreed with the results of our study. A negative correlation [3] and a positive correlation [104] with height agreed with Model-F and Model-O, respectively. Chen et al. [1] also reported a weak positive correlation with weight which was consistent with our results. Finally, a previously identified linear increase in blood pressures to MET [105–107] agreed with both Model-O and Model-F results.

Previous literature reported a weak positive or zero correlation with respect to BMI [1,35,108]. For constant height, BMI increases with increasing weight. Thus, because of the positive correlation with weight in Model-O, we observed an increase in systolic and diastolic pressures with increasing BMI. However, for constant weight, BMI decreases with increasing height which yielded a decrease in systolic and diastolic pressures due to their positive correlation with height. Therefore, with respect to BMI, Model-O provided no clear association, whereas Model-F on the other hand, having a negative correlation with height, resulted in a positive correlation with BMI agreeing with previous studies [1,35,108].

Ventricular Volumes:

The Linear Model-O provided the best subject-level predictions for the ventricular volumes. Similar to the results of this study, previous studies observed a negative correlation with age [10,11,31,40,63,79,80,109] and a positive correlation with respect to height and weight [40]. Model-O coefficients were comparable to the age-BSA-sex model correlation coefficients in reference [34]. As compared to the Left Ventricular EDV Model-O, the coefficients for the age-height-weight-sex linear models in reference [40] yielded a stronger positive correlation for height and weight and a comparable negative correlation to age. The RMSE was 18.7ml in reference [40] for subject data as compared to 35.4ml for the Left Ventricular EDV Model-O which used simulated subject data. Non-linear relationships of ventricular volumes against body size [31,40]

have also been reported. The best performing models in this study were linear and thus did not capture non-linear behaviors, potentially explaining the high $RMSE_{Mod\text{-}O\text{-}CV}$ and $RMSE_{indiv\text{-}valid}$ values.

Comparing to data from previous literature [26,27], Model-O predictions of ventricular volumes for the subjects in FRIEND resulted in some discrepancies in terms of stroke volumes. The predictions of the left ventricular stroke volumes for FRIEND subjects were biased towards lower values while the right ventricular volume predictions agreed with the observed ranges for healthy subjects in references [26,27]. Even though the predictor values and other physical descriptions of the subjects were all very similar among the 10 common articles selected for ventricular volume analyses, three articles [78–80] reported 10 - 30 ml lower left ventricular volumes (EDV, ESV, and stroke volumes) than the others. There was no skewness in the predictor data in these three studies which this bias can be attributed to. These three articles [78–80] seemed to be the only source for the left ventricular volumes bias. In conclusion, the predictions of the right ventricular volume models were more reliable as compared to the left ventricular volume models.

Heart Rate:

The Linear Model-F yielded the best results for heart rate for subject-level predictions. Model-O predictions compared using simulated ($RMSE_{indiv\text{-}valid}$) and real-world subject data ($RMSE_{Mod\text{-}O\text{-}FRIEND}$) showed that the simulation studies procedure underestimated the error in subject-level prediction. However, for the Linear Model-F, the $RMSE_{FRIEND\text{-}CV}$ was lower than $RMSE_{indiv\text{-}valid}$ which suggested that the subject data from FRIEND yielded the best model.

Model-F's linear, positive correlation to MET was consistent with previous literature [110], implying that peak HR corresponds to peak MET. The decreasing trend of peak MET with age identified in previous literature [111] interacting with the weakly increasing trend of heart rate with age in Model-F yielded a decreasing trend of peak heart rate with age, also consistent with a previous report [112]. Indeed, Model-F's intercept of 204 bpm (**Table 4**) was comparable to the intercept of the peak heart rate equation reported by Tanaka et al. [112] (208 – 0.7 Age), providing confidence for the ability of Model-F to predict peak heart rate.

Cardiac Output:

$NRMSE_{Mod\text{-}O\text{-}CV}$ and $NRMSE_{indiv\text{-}valid}$ were around 50% which was much higher as compared to the models for other cardiovascular parameters. However, the difference between the $NRMSE_{indiv\text{-}valid}$ and the $NRMSE_{Mod\text{-}O\text{-}CV}$ was less than 2% (**Table 3**) which suggested that the effect of data aggregation on building the regression model was small. For subject-level predictions, the Linear regression model provided a 95% confidence interval of ±9.4 l/min. The range of cardiac output for healthy adults is 4 to 8 l/min [113] which was smaller than Model-O's confidence interval.

In a review paper [114], Vella et al. concluded that the stroke volume plateaus at 60% of the maximum exercise intensity for healthy untrained adults. We calculated cardiac output by assuming this trend for stroke volume, using predictions from the right ventricular Model-O (**Table 4**), and using the heart rate Model-F in the equation CO = HR x SV. The values for cardiac output obtained using this method were very similar to the values predicted by the cardiac output Model-O. The differences in the predicted cardiac output values were high (20-30%) for MET values lower than 3. However, for higher METs, i.e. 3 - 12 MET, the errors in the predictions were less than 10%. This provided support that the Linear cardiac output Model-O may be effective for predictions for higher values of MET.

Recommended Regression Models:

Table 4 summarizes the recommended model details and the prediction errors for these cardiovascular parameters. For systolic and diastolic pressures, the Elastic-Net Model-F provided the smallest prediction error and is the recommended model from this study. While the Linear regression algorithm performed the best for all ventricular volumes, due to the discrepancy of the left ventricular volume predictions as discussed above, we recommend that the left ventricular volumes at rest be predicted by subtracting the average bias (17.7ml) from the Linear right ventricular Models-O. For heart rate, the Linear Model-F provided the lowest prediction error and is the recommended model from this study. We recommend using the Linear Model-O for cardiac output predictions. To obtain the stroke volume during exercise, we recommend using the Linear cardiac output Model-O and the Linear heart rate Model-F together.

Limitations:

The predictors used did not capture all the covariates mentioned in literature as many factors beyond age, body size, and exercise influence cardiovascular parameters. For example, for aortic blood pressure, resting heart rate [115], posture [116], type of exercise [117], exercise training [118,119], race [42], diet [120], smoking [121], and menopausal status [122] have all been shown to be contributory. Likewise, for ventricular volumes, sex [41], fitness level [123,124], exercise intervention [125], altitude [126], and pulmonary artery systolic pressure [44] may be important influential factors. More data and a provision to include categorical variables in the regression algorithms are necessary to add sex, race, and some of the aforementioned factors as predictors. While including more predictors in the analysis may reduce the prediction error (**Table 4**), data was not abundantly available for such analysis.

To improve the regression approach, there is evidence that allometric scaling [30,127] for body size variables, especially for cardiac output, heart rate, and ventricular volumes can be more effective. However, allometrically indexed predictors cannot be used on aggregate data since the index of the mean of the subject data is not the same as the mean of the indexed subject data.

Due to the non-linear trends reported for these cardiovascular parameters, we expected the Multivariate Adaptive Regression Splines and Support Vector Machines models to perform better than the linear algorithms. However, the non-linear regression algorithms used for fitting the data showed signs of overfitting and performed very poorly when comparing the $RMSE_{indiv\text{-}valid}$ with the linear models. More complicated models such as neural networks or random forest are likely to produce similar results, but more analysis is necessary before making any definitive conclusions about these nonlinear models.

The data extracted from the systematic review (**Table 1**) were not specifically reported for the purpose of regression modeling. The systolic and diastolic pressures Models-F yielded lower RMSEs than the corresponding Models-O. For heart rate, while Model-F had a higher RMSE compared to Model-O, it exhibited better agreement with literature trends. These findings suggest that using subject-level data for regression modeling tends to give better results than the aggregate data models (Models-O). With access to more subject-level data, it may be possible to build regression models with higher fidelity.

Conclusion

This work systematically reviewed prior studies that measured ventricular volumes, blood pressures, and cardiac output during resting and exercise conditions. It aims to provide a valuable resource by delineating regression equations for these cardiovascular parameters with respect to age, body size, and exercise intensity, providing both reference values and overall trends.

In this study regression models were formulated using aggregate data, therefore, to evaluate the impact of the ecological fallacy, we used a simulation-based procedure to estimate the subject-

level prediction error for the regression models. If the $RMSE_{Mod\text{-}O\text{-}CV}$ and the $RMSE_{indiv\text{-}valid}$ were comparable, then it suggested that the models built on aggregate data provided a good subject-level prediction.

The current clinical setting compares the cardiovascular parameters to ranges of values that are common for all healthy adults. This study aims to encourage a more personalized approach to obtain reference parameter values by specifying the subject's age, body size, and exercise intensity as inputs. Furthermore, the models developed in this study can be useful to researchers for initializing and tuning computational models.

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