Automated generation of personalized trajectories of aging phenotypes with DyViA-GAN

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Abstract

With a general increase in human lifespan, the need for technological advances to develop strategies for healthy aging has assumed great importance. In the present study, our goal is to predict the progression of selected aging phenotypes in a given healthy individual as one continues aging past 65 years. Therefore, we developed a novel framework called Dynamic Views of Aging with conditional Generative Adversarial Networks (or DyViA-GAN) which is capable of predicting the plausible personalized trajectories of a selected aging phenotype conditioned on the available measurements of the phenotype at a few initial time instances, and additional covariates. Given the prevalence of osteoporosis in the aging population, we selected femoral neck Bone Mineral Density (BMD) of a healthy individual as the phenotype of interest, and baseline individual Body Mass Index (BMI) as covariate. We trained DyViA-GAN on a publicly available longitudinal dataset of a large cohort of mostly white women in the United States of age 65 years or above. Thus, it generated, for each individual, continuous phenotype trajectories, along with a corresponding region of acceptable predictions, for an age range of 66 to 98 years, for eight different combinations both with and without involving the covariate. Our results clearly demonstrate the potential of generative deep learning frameworks in healthspan research.

Keywords: GAN, Deep Learning, BMD, trajectory prediction, aging phenotype, osteoporosis

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1 Introduction

Forecasting the trajectories of diseases has been a cornerstone of the field of epidemiology involving numerous approaches ranging from the classical such as SIR and related models to more recent ones based on time series and predictive analytics, genomics, etc. [33]. In fact, modeling and prediction of infectious diseases have been among the key drivers of methodological advances in biostatistics and public health over the past century [35, 36]. Since the COVID-19 pandemic, novel approaches have emerged for outbreak forecasting including AI-driven deep learning of spatio-temporal patterns, prediction by real and synthetic data fusion, e.g., [45, 13]. However, with a general increase in human lifespan over the past decades, some researchers in the field of disease prediction have now shifted their attention from the modeling of infectious disease outbreaks in a population to that of different chronic conditions and their progression in individuals in the form of personalized trajectories.

In the present study, our goal is to predict the progression of selected aging phenotypes in a given healthy individual as one continues aging past 65 years. Initial measurements of such phenotypes may be taken annually. With data from these initial time points as input, in combination with her other static or dynamic risk factors as covariates, we aim to build a reliable generative AI model that is capable of forecasting future values of the same phenotypes for this individual. Thus, our model will produce a set of plausible trajectories (univariate or multivariate depending on the selection of phenotypes), which could provide timely insights to inform and aid clinical decision-making that might extend her *healthspan*. For example, trajectories of aging phenotypes associated with one's cognition or bone health can help one strategically build preparedness or adopt preventive measures against any future onset of dementia or possible fractures.

In particular, we focus on osteoporosis, which accounts for approximately 1.5 million fractures just in the U.S. each year [7]. According to its National Institute of Aging (NIA)*, osteoporosis is a "silent disease" since it does not have any markers of progression until a bone breaks – usually in the hip, spine. or wrist. In severe osteoporosis cases, a simple movement such as a cough or minor bump can result in a broken bone, i.e., a fracture. Additionally, individuals with osteoporosis may also have a longer duration of recovery and may experience chronic pain. In older adults, hip and spine fractures, in particular, can have serious consequences such as loss of mobility and independence. In a single typical year (2019), there were 318,797 emergency department visits, 290,130 hospitalizations, and 7,731 deaths related to hip fractures alone among adults of age 65 years or older in the U.S. [29]. Thus, osteoporosis acts as a key determinant of one's (bone) healthspan over the course of aging.

Osteoporosis is defined as a systemic skeletal disease that has both the following characteristics: low bone mass and microarchitectural deterioration of bone tissues [31]. In clinical practice, osteoporosis is generally diagnosed when the measure of bone mineral density (BMD) of an individual is below the mean BMD of a reference population by at least 2.5 times the standard deviation, i.e., T-score ≤ -2.5 [21]. Low BMD or osteopenia is determined by a T-score between -1 and -2.5. As individuals age, BMD decreases and, consequently, osteoporosis becomes more prevalent in older adults [16, 37, 22]. A study of BMD of the femoral neck or lumbar spine estimated 43.4 and 10.2 million U.S. adults of age 50 years and above as having low bone mass and osteoporosis respectively.[43] While several factors may be involved in the etiology of osteoporosis, historically, the body mass index (BMI) has been linked to bone health as a protective factor

*https://www.nia.nih.gov/health/osteoporosis/osteoporosis

[15, 37]. Paganini-Hill et al. using data from 8600 postmenopausal women reported that high BMI was associated with a significant reduction in hip fracture risk independently of other potential confounders [32]. Their findings were later corroborated by other studies [8, 11].

The longest running cohort study in the U.S. on this topic is the NIH-NIA sponsored Study of Osteoporotic Fractures (SOF), a multi-site study that ran from 1986 to 2017 and recruited over 10,000 participants at 4 different sites While initially the study enrolled white women, beginning in 1997, the study began to recruit African American women. Exclusion criteria included bilateral hip prostheses or inability to walk without assistance. Study participants attended a series of clinical visits with physical and mental evaluations including imaging to measure bone density, physical examinations, and questionnaires. In addition to clinical visits, participants were contacted via telephone or mail every four months to complete follow-up assessments for information on any falls, fractures, and vital status [1].

In a seminal paper in 1995, the SOF researchers established the dual energy X-ray absorptiometry (DEXA) scan as a non-invasive, painless, safe, and accurate measurement of BMD [8]. Subsequently, the U.S. Preventive Services Task Force osteoporosis management guidelines recommended routine BMD screening DEXA scans for women 65 years of age or older [30, 20]. The SOF study also showed that women who fell and broke their hip were five times more likely to die in their first year of fracture than those who did not break their hip [1]. Notably, beyond screening, DEXA scans can also serve to monitor osteoporosis progression, leading to opportunities for intervention and prevention of fractures. Therefore, femoral neck BMD data, as measured by DEXA, is an ideal initial choice of an aging phenotype to build a model for automated generation of personalized trajectories using a suitable computational framework.

Deep learning frameworks, such as Long Short-Term Memory Networks (LSTMs), Gated Recurrent Units (GRUs) and transformers networks, have been successful in applications involving time series forecasting [14, 40, 46]. The training and forecasting accuracy of these models typically usually rely on access to training data recorded over many time-points. Many of the previous studies that applied deep learning for producing disease trajectories used one or more recurrent neural networks (RNN) for predicting the ICD code for an individual's next visit to the clinic [5, 6, 38]. Some have used GANs to predict such codes for multiple subsequent visits but not for tracking any actual phenotype of an individual [39]. Other deep learning applications have focused on specific health conditions or diseases, e.g., cystic fibrosis [23], Alzheimer's disease [12]. Measures of DNA methylation biomarkers that estimate epigenetic aging serve a somewhat distinct purpose [18, 3]. Yet other platforms such as the Danish Disease Trajectory Browser (DTB) use statistical analysis of population-scale medical data to produce disease trajectories but these are not personalized predictions [41].

To address such issues, we work with (a) individual longitudinal measurements of the selected phenotype that are available (b) only at a few (typically, 3-4) time-points. The aforementioned deep learning models are not appropriate to predict the phenotype trajectories under such conditions. We instead appeal to deep generative models which are suitable for solving probabilistic problems. Among existing generative frameworks, conditional Generative Adversarial Networks (cGANs) are popular in learning the underlying probability distribution of data conditioned on known values of other associated variables or parameters [26]. cGANs have been successfully designed to impute corrupted images in dynamic contrast enhanced computed tomography [34] and probabilistic brain segmentation from magnetic resonance images [27].

In this study, we proposed a novel cGAN framework called Dynamic Views of Aging with GAN (or DyViA-GAN) which is capable of predicting the plausible personalized trajectories of a selected aging phenotype conditioned on the available measurements of the phenotype at a few initial time instances, and additional covariates. For this purpose, we selected femoral neck BMD of a healthy individual as the phenotype of interest and baseline individual BMI as the covariate. We used DyViA-GAN to generate personalized trajectories, for eight different combinations both with and without involving the covariate. The publicly available dataset used for training our model, due to the SOF study, is described in the Dataset section. Then we provided the details of the cGAN framework including the network architectures, and its model nomenclature for different data and covariate combinations in the Methods section. The Results illustrate the corresponding cGAN-based generation of personalized trajectories of the selected phenotype. We end with Discussion on some of the limitations of our study and the scope for future work.

2 Methods

2.1 Dataset

We worked with an anonymized dataset for 9,704 mostly Caucasian women participants in the now concluded Study of Osteoporotic Fractures (SOF) study. The dataset is publicly available from the 'SOF Online' website (`https://sofonline.ucsf.edu/`). Attendance during the study varied as not all participant were available for all the visits, leading to significant gaps in the dataset. To ensure maximal number of participants in the training set, we considered participant data from Visit 2 (1989-90), Visit 4 (1992-94), Visit 5 (1995-96) and Visit 8 (2002-04), and considered the femoral neck BMD (denoted by FND) as measured by DEXA scans using Hologic QDR 1000 workstations. In accordance with best practices we exclude observations for patients over the age of 90 years to preserve patient anonymity [28]. We used longitudinally-adjusted scan measurements obtained by re-analyzing the previous scans and adjusting the regions-of-interest or deleting bone segments to match later scans. The T-scores of BMD were based on the parameters of a healthy reference population recommended by the International Society for Clinical Densitometry (ISCD) [24, 42].

In total, we have 2,113 de-identified participant records which were stratified based on the individual BMI values measured during Visit 1 (1986-87). We considered three strata: underweight and healthy participants (UWH) with BMI < 25, overweight participants (OW) with $25 \leq$ BMI < 30, and obese participants (OB) with BMI ≥ 30. Details of the samples and stratification can be found in Table 1. We also used the recorded age of the various participants during each of the four visits, with the ages rounded down to half years.

Moving forward, we use the following notations to denote the variables serving as input or predicted outputs of our deep learning model: FND_i is the FND value of a participant at visit $i \in 2, 4, 5, 8$, t_i is the (scaled) age of the participant during the i-th visit, and $Q \in \mathbb{R}^q$ is a vector of q baseline parameters or risk factors of the participant. For the present study, we chose the BMI (scaled by 100) to represent Q, with $q = 1$. We note that the age of the participants is scaled according to

$$t \to \frac{t - t_{\min}}{t_{\max} - t_{\min}}, \quad t_{\min} = 66, \; t_{\max} = 98, \tag{1}$$

where $[t_{\min}, t_{\max}]$ serves as the maximal age range (in years). These age limits were chosen based on the data available in the SOF dataset. The above scaling (1) ensures that $t \in [0, 1]$. We also remark here that the ages $\{t_2, t_4, t_5, t_8\}$ differ across participants in the dataset, thus adding an additional layer of complexity to the

trajectory prediction problem.

Table 1: Description of data (FND T-scores) used for training and testing. Stratification based on underweight and healthy participants (UWH), overweight participants (OW), and obese participants (OB).

	Strata	Number of Participants	Min. FND	Max. FND	Mean FND (± SD)
Training	UWH	800	-4.63	4.94	-2.02 (± 0.87)
	OW	720	-5.07	2.51	-1.69 (± 0.87)
	OB	360	-3.97	1.70	-1.35 (± 0.92)
Test	UWH	98	-4.28	1.58	-2.04 (± 0.94)
	OW	95	-4.03	5.42	-1.70 (± 1.10)
	OB	40	-3.09	1.42	-1.44 (± 0.96)

2.2 DyViA-GAN

The proposed DyViA-GAN to predict personalized plausible trajectories of the selected phenotype comprises two neural networks, namely the generator $\mathcal{G}$ and the discriminator $\mathcal{D}$. The generator is fed as input the vector $Y = (\text{FND}_2, \text{FND}_4, t_2, t_4, Q) \in \mathbb{R}^{4+q}$, and a variable $t \in [0,1]$ denoting the (scaled) age at which we want to predict the value of FND given Y. We denote the predicted value as $\widehat{\text{FND}}(t, Y, Z)$. In addition, we feed as input a random latent variable $Z \in \mathbb{R}^{N_z}$ which is sampled from an uncorrelated standard Gaussian distribution. Thus, the generator is mapping of the form $\mathcal{G} : (t, Y, Z) \in \mathbb{R}^{4+q+N_z} \times [0,1] \times \mathbb{R}^{N_z} \mapsto \mathbb{R}$.

The discriminator $\mathcal{D}$ is a scalar-valued network that is fed as input either a "true" data tuple (X, Y, t_5, t_8) where $X = (\text{FND}_5, \text{FND}_8) \in \mathbb{R}^2$ or a "fake" tuple $(\widehat{X}, Y, t_5, t_8)$ where $\widehat{X} = \big(\widehat{\text{FND}}(t_5, Y, Z), \widehat{\text{FND}}(t_8, Y, Z)\big) \in \mathbb{R}^2$ is generated using $\mathcal{G}$. Thus, the discriminator is a mapping of the form $\mathcal{D} : (X, Y, t_5, t_8) \in \mathbb{R}^2 \times \mathbb{R}^{4+q} \times [0,1]^2 \mapsto \mathbb{R}$. The role of the $\mathcal{D}$ is to distinguish between true and fake tuples, while the role of the $\mathcal{G}$ is to generate samples indistinguishable from those drawn from the true (unknown) conditional probability distribution of X given (Y, t_5, t_8), i.e., $P_{X|(Y,t_5,t_8)}$.

The two network are trained in an adversarial fashion by solving the following optimization problem associated with a least-squares GAN [25]

$$\begin{aligned} \mathcal{D}^* &= \arg\min_{\mathcal{D}} \; \mathop{\mathbb{E}}_{P_{X,Y,t_5,t_8}} \Big[\big(\mathcal{D}(X, Y, t_5, t_8) - 1\big)^2\Big] + \mathop{\mathbb{E}}_{P_{\widehat{X},Y,t_5,t_8}} \Big[\big(\mathcal{D}(\widehat{X}, Y, t_5, t_8)\big)^2\Big] \\ \mathcal{G}^* &= \arg\min_{\mathcal{G}} \; \mathop{\mathbb{E}}_{P_{\widehat{X},Y,t_5,t_8}} \Big[\big(\mathcal{D}(\widehat{X}, Y, t_5, t_8) - 1\big)^2\Big] \end{aligned} \tag{2}$$

where P_{X,Y,t_5,t_8} is the joint probability distribution of the true data, while $P_{\widehat{X},Y,t_5,t_8}$ is joint probability distribution for the same data but with $\widehat{X}$ generated by $\mathcal{G}$.

Once the DyViA-GAN is trained, the optimized generator $\mathcal{G}^*$ is used to generate an ensemble of possible values of FND at any point t given Y for an individual. This is achieved by drawing K random samples $\{Z^{(k)}\}_{k=1}^K$ of the latent variable and evaluating $\mathcal{G}^*(t, Y, Z^{(k)})$ for $1 \leq k \leq K$. By allowing t to vary in $[0,1]$,

we can generate an ensemble of plausible trajectories of the temporal values of FND for an individual. We can then compute the point-wise empirical mean and variance of the predicted trajectories (given a Y) for any $t \in [0, 1]$ as

$$\overline{\mathcal{G}}^*(t, Y, Z) = \frac{1}{K}\sum_{k=1}^{K} \mathcal{G}^*(t, Y, Z^{(k)}), \quad \mathrm{Var}[\mathcal{G}^*](t, Y, Z) = \frac{1}{K}\sum_{k=1}^{K} \left(\mathcal{G}^*(t, Y, Z^{(k)}) - \overline{\mathcal{G}}^*(t, Y, Z)\right)^2 \tag{3}$$

A schematic of the training and evaluation of DyViA-GAN is shown in Figure 1.

2.3 Network architectures

The generator $\mathcal{G}$ is taken to be a fully-connected network with input dimension $4 + N_z + 1$ (or $4 + N_z + q$ if covariates Q are used) with a scalar-valued output. We used four hidden layers of width 50 each with the hat activation function [17, 44]. To to ensure that the generator's prediction is constrained to be close to the given initial measurements at t_2 and t_4, the output of the generator is transformed as follows

$$\mathcal{G}(t, Y, Z) \to \mathcal{G}(t, Y, Z) \times (1 - \phi(t; t_2) - \phi(t; t_4)) + \phi(t; t_2) \times \mathrm{FND}_2 + \phi(t; t_2) \times \mathrm{FND}_4 \tag{4}$$

where $\phi(t; \tilde{t}) = \exp(-(t-\tilde{t})^2/(2\sigma))$ is a smooth function that takes takes the value 1 at $t = \tilde{t}$ and exponentially decays to 0 away from $\tilde{t}$, with the rate of decay controlled by σ. Thus, with the transformation Equation 4, the output of the generator is forced to be close to FND_2 and FND_4 when $t = t_2$ and $t = t_4$, respectively. In this work, we choose $\sigma = 10^{-3}$.

The discriminator $\mathcal{D}$ is a also taken to be fully-connected network with input dimension 8 (or $8+q$ if covariates Q are used) with a scalar-valued output. We used four hidden layers of width 50 with the hat activation function. Other hyperparameter values for DyViA-GAN are listed in Table 2.

Table 2: Common hyperparameter values used for the DyViA-GAN models.

Hyperparameter	Value/Choice
Latent Dimension N_z	20
Optimizer	Adam
Learning rate for $\mathcal{G}$	10^{-3}
Learning rate for $\mathcal{D}$	10^{-3}
Number of $\mathcal{D}$ updates per $\mathcal{G}$ update	4
ℓ^2 regularization parameter	10^{-7}
Batch size	ALL: 200, OWH: 200, OW: 180, OB: 90
Total epochs	2000

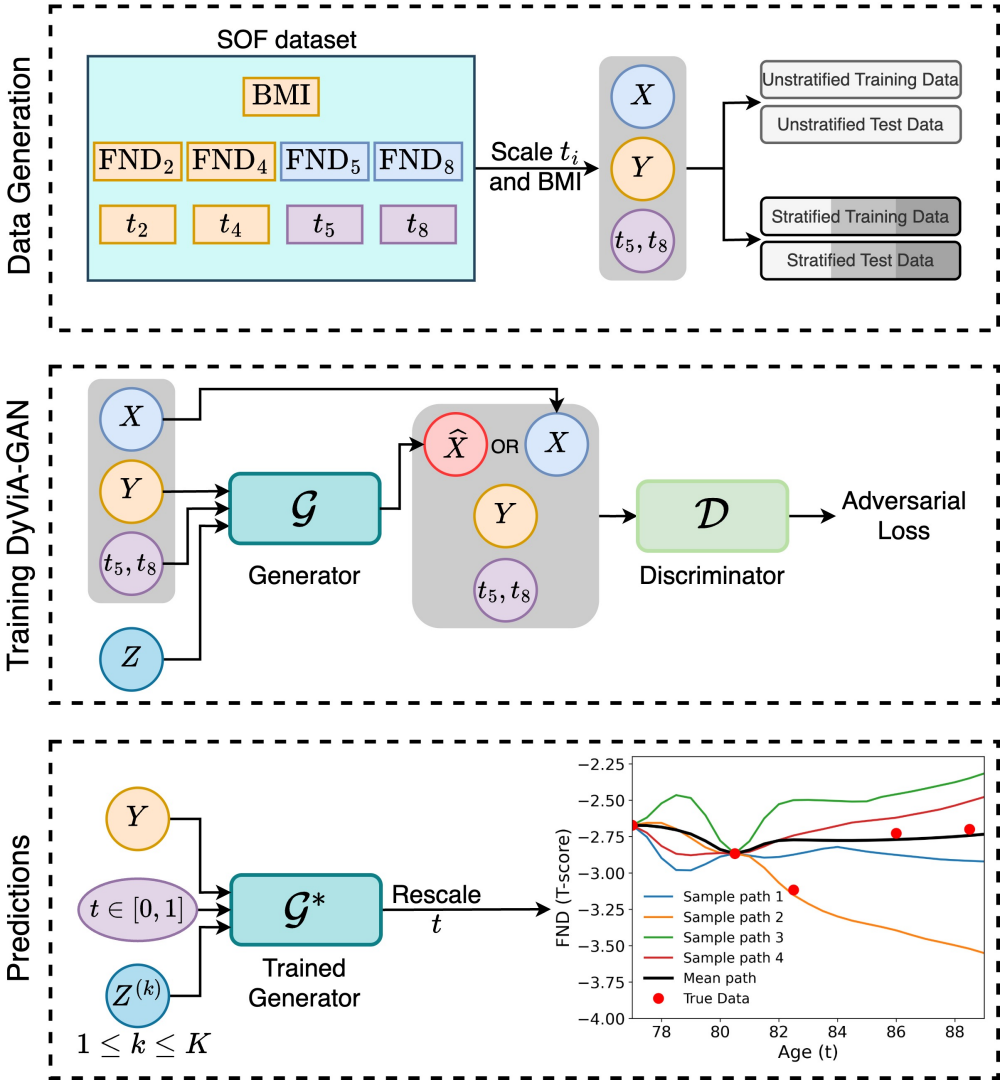

Figure 1: Schematic depicting the construction of the datasets, the inputs and outputs of $\mathcal{G}$ and $\mathcal{D}$ when training the DyViA-GAN, and how the trained generator $\mathcal{G}^*$ is used to predict plausible phenotype trajectories. **Top Panel:** From the SOF dataset, the FND and ages at during visits 2,4,5,8, along with the BMI measured at visit 1, are extracted for all participants without gaps in the data. After scaling the ages and BMI, unstratified as well as stratified training/test data tuples of the form (X, Y, t_5, t_8) are created. **Middle Panel:** During training phase, Y, Z and the scaled ages t_5, t_8 are fed to $\mathcal{G}$ to obtain the prediction vector $\widehat{X}$ at t_5, t_8. The discriminator $\mathcal{D}$ is fed either a true tuple (X, Y, t_5, t_8) or a fake tuple $(\widehat{X}, Y, t_5, t_8)$. Both network are trained simultaneously according to Equation 2. **Bottom Panel:** The trained generator $\mathcal{G}^*$ is fed the conditional data Y for a participant, any $t \in [0, 1]$, and K samples of the latent variable. The output is an ensemble of K personalized trajectories (4 sample trajectories are shown) and the mean trajectory (black curve), which can be compared to the known phenotype measurements (red dots). We observe that all predicted trajectories pass through the true data at t_2, t_4 (due to the Equation 4).

2.4 DyViA-GAN model nomenclature

We trained multiple version of DyViA-GAN on different data and covariate combinations. For easier reference, we use the nomenclature Model-$\langle$DT$\rangle$ for the models trained on different data types determined by tag $\langle$DT$\rangle$. The tag value $\langle$DT$\rangle$ = ALL implies that the model is trained on unstratified training data with 2100 samples (see Table 1), $\langle$DT$\rangle$ = UWH implies the networks are trained on the UWH strata samples with 900 samples, $\langle$DT$\rangle$ = OW implies training on the OW strata with 800 training samples, while $\langle$DT$\rangle$ = OB implies training on the OB strata with 400 training samples. Furthermore, the model name ends with an additional tag -Q if the covariate Q is fed as input to the generator. For example, Model-OWH denotes the model trained (and tested) on the OWH strata, while Model-OB-Q denotes the model trained (and tested) on OB strata with Q used as an input for the generator. In all, we consider 8 DyViA-GAN models: 1) Model-ALL, 2) Model-ALL-Q, 3) Model-UWH, 4) Model-UWH-Q, 5) Model-OW, 6) Model-OW-Q, 7) Model-OB, and 8) Model-OB-Q.

2.5 Evaluation of model performance

Using the trained generator $\mathcal{G}^*$, we quantify the performance of the various models by considering the score $\mathcal{S}$ for each training/test tuple (X, Y, t_5, t_8), which is defined as follows using empirical statistics (see Equation 3)

$$\mathcal{S}(X, Y, t_5, t_8) = \max \left\{ \frac{\left|\mathrm{FND}_5 - \overline{\mathcal{G}}^*(t_5, Y, Z)\right|}{\mathrm{Var}[\mathcal{G}^*](t_5, Y, Z)} \ , \ \frac{\left|\mathrm{FND}_8 - \overline{\mathcal{G}}^*(t_8, Y, Z)\right|}{\mathrm{Var}[\mathcal{G}^*](t_8, Y, Z)} \right\} \tag{5}$$

with the empirical statistics computed using $K = 1000$ random samples of Z. The score evaluates the normalized distance of the true values of the phenotype at $t = t_5, t_8$ from the mean predicted values. Thus, predictions with lower scores are preferable. We say that the *score is acceptable* for a sample if $\mathcal{S} \leq 1.5$.

3 Results

We ran DyViA-GAN on the individual samples of available (or "true") FND measurements from the described dataset to generate their respective personalized continuous trajectories of FND based on the stated models.

Using the above-mentioned criterion (Equation 5), we evaluated the percentage of training and test samples with acceptable scores, which are listed in Table 3. Although Model-ALL and Model-ALL-Q are trained on unstratified data, we also evaluate the trained generators on stratified data for a more fine-grained analysis. The scores of the other models trained on stratified data are only evaluated on the corresponding strata. We make the following observations based on the values listed in Table 3:

- Models trained on the stratified data perform better than models trained on unstratified data. Model-ALL and Model-ALL-Q have significantly lower percentages of training and test samples with acceptable scores ($\mathcal{S} \leq 1.5$) when compared to the other stratified models. This is perhaps not very surprising as the stratified models are trained on more homogeneous data, even though these datasets are smaller in size compared to the unstratified (but heterogeneous) datasets.
- Feeding the covariate Q (i.e., the BMI) as a generator input improves the performance of the models trained on unstratified data (compare the first two data rows of Table 3). The percentage of training samples with acceptable scores rises from 69% to 77%, while the percentage of test samples with

Table 3: Percentage (%) of samples with acceptable scores ($\mathcal{S} \leq 1.5$) for 8 different DyViA-GAN models. The percentages are also listed for each data strata for models trained on unstratified samples. For models trained on stratified data, the percentages are listed only for the corresponding strata. The notation - indicates no scores are evaluated for a particular strata with a given model.

	Training				Test			
Strata / Model	UWH	OW	OB	ALL	UWH	OW	OB	ALL
Model-ALL	71.62	68.33	66.39	69.36	68.37	71.58	67.50	69.53
Model-ALL-Q	79.75	76.25	74.17	77.34	73.47	75.79	75.00	74.68
Model-UWH	91.25	-	-	-	87.76	-	-	-
Model-UWH-Q	78.88	-	-	-	69.39	-	-	-
Model-OW	-	85.69	-	-	-	81.05	-	-
Model-OW-Q	-	79.31	-	-	-	75.79	-	-
Model-OB	-	-	91.11	-	-	-	90.00	-
Model-OB-Q	-	-	88.61	-	-	-	90.00	-

acceptable scores rises from 69.5% to 75%.

- Feeding the BMI as a generator input appears to deteriorate the performance of the models trained on stratified data.
- Although not presented here, we observed that in general the predictions at t_8 (as compared to t_5) have larger contributions towards samples having a score $\mathcal{S} > 1.5$, i.e., having unacceptable scores.

We also demonstrate the qualitative performance of the trained models on four test participants chosen from each strata UWH, OW and OB. The predicted personalized mean trajectory (with $K = 1000$) are shown for in Figure 2 (OWH), Figure 3 (OW) and Figure 4 (OB). For each test sample, we also plot the true measurements $\text{FND}_2, \text{FND}_4, \text{FND}_5, \text{FND}_8$ (red dots), and the region with acceptable scores (gray shading). In addition, we have access to the adjusted phenotype value at Visit 7 (1999) for these six test participants, which is depict in the plots (blue triangle). Note that the generator and discriminators never see the phenotype value for this visit during the training phase of DyViA-GAN. We make the following observations from the plots in Figure 2, Figure 3 and Figure 4:

- The mean trajectories pass through the data at t_2, t_4 with almost zero width of the acceptable regions at these time points. This demonstrates the effect of the constraint Equation 4 applied on the generator output, indicating the high certainty of the trajectory at the initial measurements.
- With the exception of Model-ALL and Model-ALL-Q (see Figure 3), the new unseen data at future time point t_7 (blue triangle) falls within the region of acceptable score with all other models. In other words, the mean trajectory value is close enough to this data point.

- For models trained on stratified data, acceptable score region in gray are generally wider and does a better job at enveloping the true phenotype measurements at future time points t_5, t_7, t_8. The only outlier seems to be the first test sample shown from the OW strata (row 1 of Figure 3) for which all models struggle to properly capture the true value at t_8.

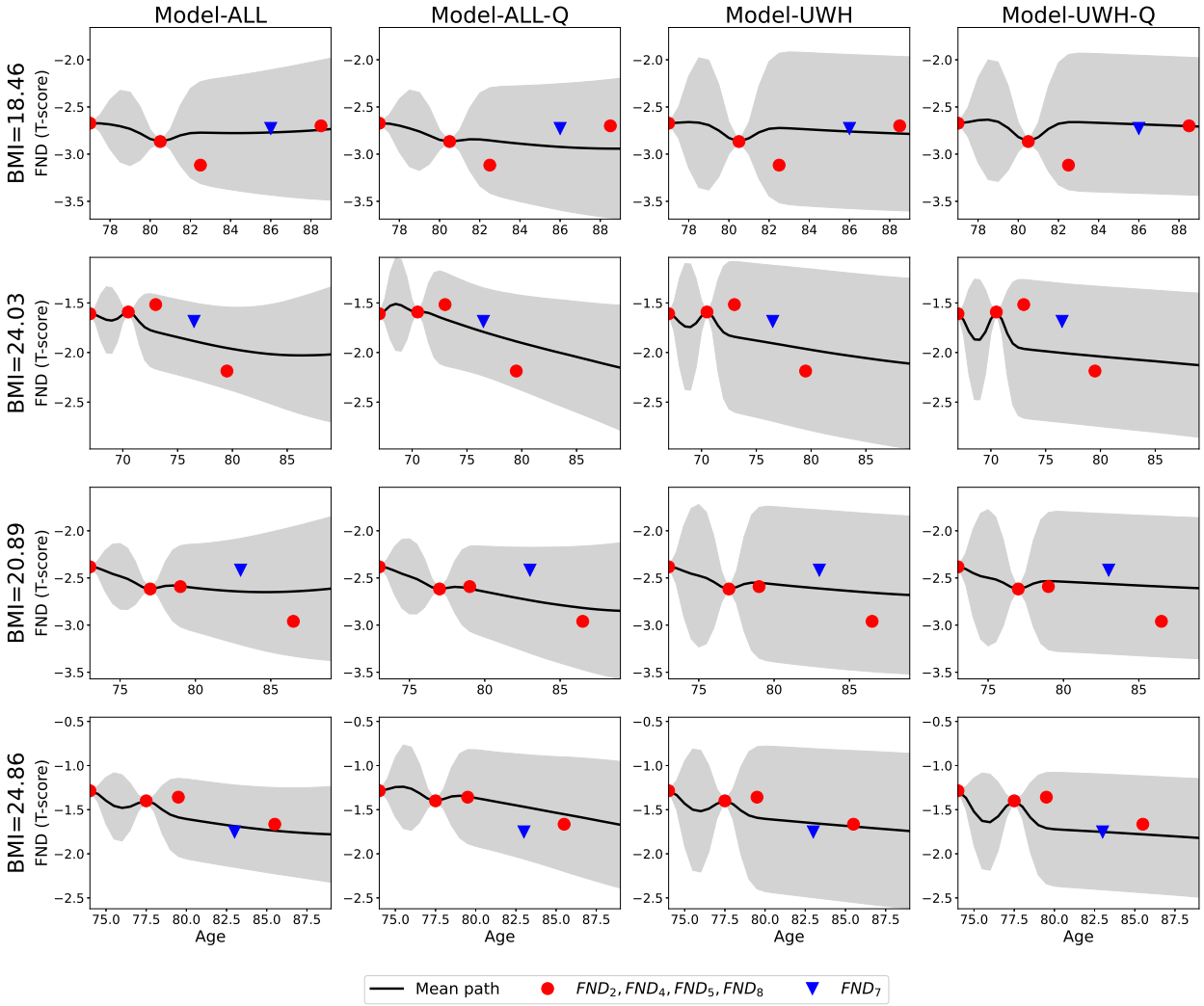

Figure 2: Predictions with various models for four test participants from strata UWH. Each plot depicts the mean personalized phenotype trajectory (black curve), the region of acceptable scores (gray shading), the phenotype measurements at times t_2, t_4, t_5, t_8) (red dots), and an additional measurement at t_7 (blue triangle) which was never seen during the training phase of DyViA-GAN. The BMI of the participant is listed on the left of each row.

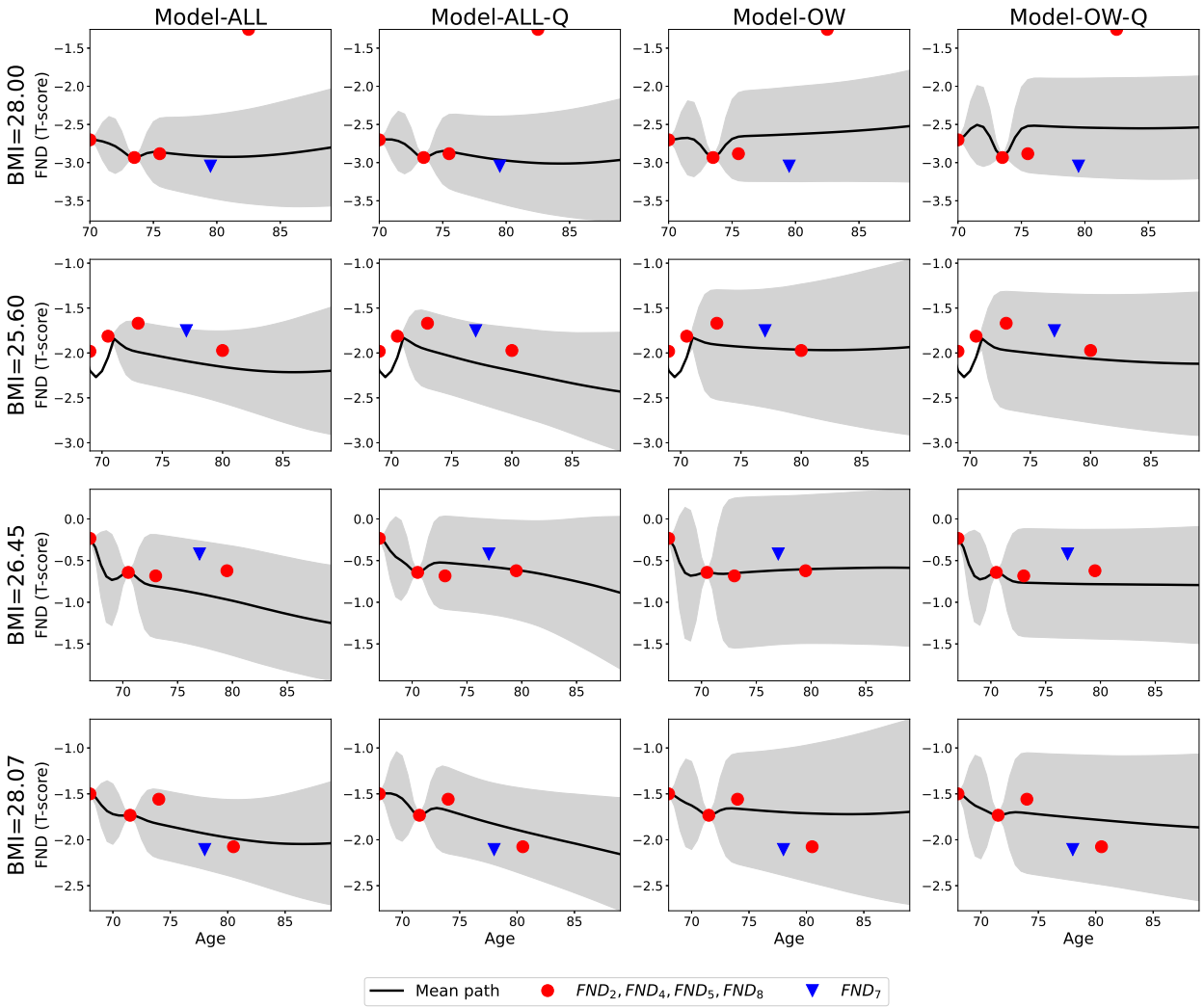

Figure 3: Predictions with various models for four test participants from strata OW. Each plot depicts the mean personalized phenotype trajectory (black curve), the region of acceptable scores (gray shading), the phenotype measurements at times t_2, t_4, t_5, t_8) (red dots), and an additional measurement at t_7 (blue triangle) which was never seen during the training phase of DyViA-GAN. The BMI of the participant is listed on the left of each row.

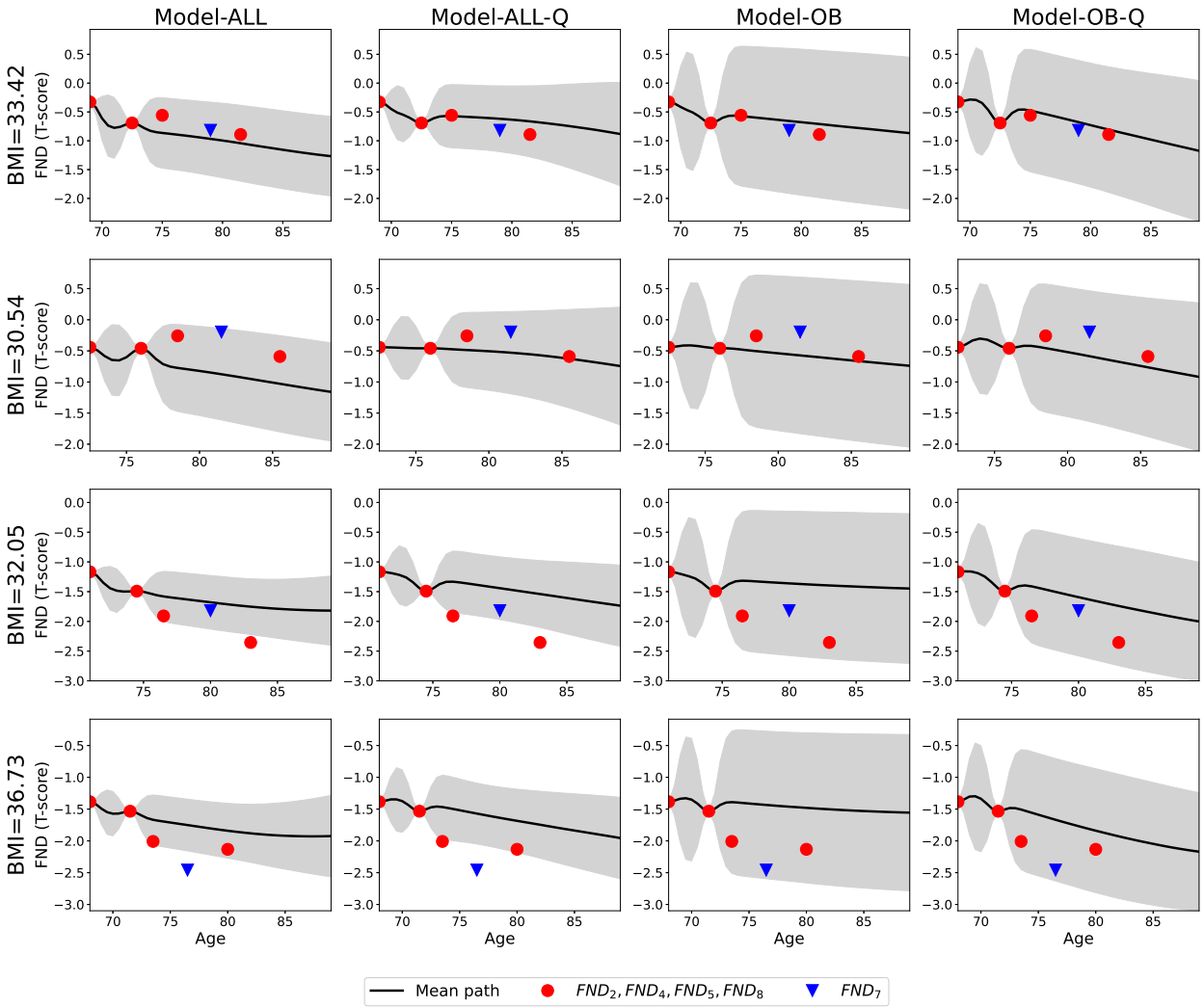

Figure 4: Predictions with various models for four test participants from strata OB. Each plot depicts the mean personalized phenotype trajectory (black curve), the region of acceptable scores (gray shading), the phenotype measurements at times t_2, t_4, t_5, t_8) (red dots), and an additional measurement at t_7 (blue triangle) which was never seen during the training phase of DyViA-GAN. The BMI of the participant is listed on the left of each row.

4 Discussion

While noting that the concept of *healthspan* is relatively new in geroscience research [4] and there is no universal agreement yet on its definition, the author of a perspective paper in *GeroScience* made two key observations: (ii) "health itself may be better considered as a continuous variable that changes in a dynamic way throughout life" and (2) "The health trajectory will be different in different individuals, but will generally trend downward with age".[19] However, understanding and prolonging individual-specific healthspan is challenging for many reasons, including not being timely aware of the trajectories of the different aging phenotypes. Advance knowledge of progression of such an outcome as osteopenia, the precursor of osteoporosis, is crucial, as it can lead to an accelerated reduction in one's bone healthspan, and DyViA-GAN provides precisely that capability.

The present study has, in fact, some distinct advantages. Using only very few initial observations as input, it demonstrated the capability of cGAN-type models to predict the personalized trajectory of a single phenotype – femoral neck BMD – that is particularly relevant to one's healthspan, and increasingly so as one continues to age. The generators of the proposed DyViA-GAN takes as input the (scaled) age variable t and the output generated is a *continuous* trajectory for the entire age-span, and not just for some discrete time points at which data is available during training/testing. The continuous representation also allows for easy calculation of the gradient (and higher derivatives) of each trajectory using automatic differentiation on neural nets.

Notably, there are several key findings from the results presented in section 3. First, the quality of the model predictions measured in terms of the score $\mathcal{S} \leq 1.5$, i.e., the proximity of the personalized mean trajectory to true phenotype measurements, are better if more samples are considered to train the model. Second, the inclusion of additional risk factors, such as BMI, may lead to better personalized predictions in situations where training data is stratified. However, such an inclusion may have a negative effect on the performance on test data if unstratified training data is used. Third, the mean trajectory with all eight versions of the DyViA-GAN considered in this study are close (in terms of the score function) to the true measurement of the phenotype from visit 7, which was never shown to the model during training.

According to the U.S. Census Bureau's 2017 National Population Projections, the year 2030 will mark an important demographic turning point in U.S. history when one in five Americans will be 65 years or older. Clearly, planning for and achieving individual healthspan goals will assume increasing importance in the society. Towards this, a variety of new sources of rich, high-resolution data such as genomics, epigenetics, wearable monitoring devices, etc., is making healthcare more preventive and personalized. Such data also allows for complex interplays among the factors of healthy aging – ranging from static to dynamic, and both internal and external – to inform the models for predicting a wider and more insightful set of outcomes. For instance, a better understanding of the non-linear relationship between one's BMI and BMD, over the course of aging, could emerge [8].

We understand that there are certain limitations of our study. As future work, our approach could be extended to predict simultaneously the trajectories of multiple phenotypes, say, BMD values of multiple regions of the body. Moreover, DyViA-GAN has the flexibility to include, in addition to static baseline risk factors, also dynamic covariates such as a participant's physical activity level or chronic inflammation or epigenetic changes. The fact that the presently generated trajectories are not dynamically updated could be revised in the future to allow for intermediate events, lifestyle alterations, and medical interventions. Further,

we plan to extend the application to alternative deep generative frameworks (e.g., [2, 10]), as well as other similar longitudinal datasets on aging phenotypes and groups to train our generative models (e.g., [9]).

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