Distributional data analysis with accelerometer data in a NHANES database with nonparametric survey regression models

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Abstract

Accelerometers enable an objective measurement of physical activity levels among groups of individuals in free-living environments, providing high-resolution detail about physical activity changes at different time scales. Current approaches used in the literature for analyzing such data typically employ summary measures such as total inactivity time or compositional metrics. However, at the conceptual level, these methods have the potential disadvantage of discarding important information from recorded data when calculating these summaries and metrics since these typically depend on cut-offs related to intensity exercise zones that are chosen subjectively or even arbitrarily. Much of the data collected in these studies follow complex survey designs, making application of standard statistical tools such as non-parametric regression models inappropriate and the requirement of specific estimation procedures according to particular sampling-design is mandatory. With functional data or other complex objects, barely literature exist that handles complex sampling designs in the statistical analysis. This paper aims two-fold; first, we introduce a new functional representation of accelerometer data of a distributional nature to build a complete individualized profile of each subject's physical activity levels. Second, using the NHANES accelerometer data (2003-2006), we show the potential advantages of this new representation to predict patients' outcomes over 68 years of age. A critical component in our statistical modeling is that we extend non-parametric functional models used: kernel smoother and kernel ridge regression, to handle the specific effect of complex sampling design in order to provide reliable conclusions about the influence of physical activity in distinct analysis performed.

1 Introduction

A patient's physical activity levels are an influential causal factor associated with the development of chronic diseases, mortality, life-span, and increased

medical costs [Pedersen and Saltin, 2006, Almeida et al., 2014, Bolin, 2018]. At the same time, regular physical exercise is one of the most effective interventions to control glucose values in diabetic patients [Mendes et al., 2016], reduce weight [Franks and Atabaki-Pasdar, 2017], minimize the effects of aging [Sattler et al., 2020], and improve health in general [Friedenreich et al., 2021, Burtscher and Burtscher, 2020], often without introducing pharmacological treatment. Most medical guidelines recommend 150 minutes per week of aerobic exercise for the general population [Mendes et al., 2016]. However, to ensure the intervention's success, a personalized training prescription and evaluation are required [Matabuena et al., 2019, Buford et al., 2013].

Traditionally, in epidemiological studies, physical activity levels in the general population have been measured using methods that introduce subjectivity, such as surveys, sleep-logs, and daily diaries [Sirard and Pate, 2001]. In a similar sense, in professional sports, subjective assessment metrics such as the rating of perceived exertion (RPE) [Eston, 2012] have been widely used. With the boom of digital medicine [Kvedar et al., 2016] and the possibilities of monitoring patients in real-time through biosensors, the objective measurement of physical activity levels with these technologies is becoming increasingly common [Matabuena and Rodríguez-López, 2019]. The estimation of energy expenditure using accelerometers is probably the most general and reliable procedure for this purpose at the moment.

Accelerometer data provides a vast source of information that quantifies the intensity, volume, and direction of physical activity in real-time in the period in which the device is worn. For the last 15 years, multiple epidemiological studies have used these devices to infer physical activity patterns in various cohorts. For example, in [Troiano et al., 2008], the authors describe the physical activity patterns in the American population using simple summary measures by age-groups; in [Goldsmith et al., 2016], the authors analyze how physical activity patterns vary minute-to-minute through functional data analysis techniques with children from New York. Other studies use accelerometers to resolve complex questions such as the relationships between physical activity levels and short-term mortality or life-span [Lynch et al., 2010, Ekelund et al., 2019, Tarp et al., 2020. Precisely in this domain, a remarkable recent study [Smirnova et al., 2019] showed that physical activity patterns may predict mortality more accurately than well-established epidemiological variables such as age, smoking, and the presence of cancer. Answering these questions with precision is essential to guide public health policies and design physical activity routines that optimize the population's health [Raichlen et al., 2020, Ding et al., 2020l. The National Health and Nutrition Examination Survey (NHANES) is a public database that collects information on the American population's physical activity levels during the period 2003-2006, and is the bestknown database of accelerometers. Other cohorts with available accelerometer data include the Baltimore longitudinal study [Nastasi et al., 2018], and more recent studies with the UK Biobank [Strain et al., 2020] or the International Children's accelerometer Database [Sherar et al., 2011], and have provided new clinical knowledge with different study populations and other or similar sampling designs.

In the current era of precision medicine [Kosorok and Laber, 2019], these devices are also beneficial for individualized prescription of physical exercise, given that the data obtained is vital for the control and measurement of exercise

performed in general and sports populations. For these reasons, accelerometer technology has also been gradually used to evaluate interventions and more beneficial physical activity therapies in clinical trials [Napolitano et al., 2010].

From a statistical point of view, the analysis of this data is usually complicated, and summary measurements must be used to compress the information recorded by the curves obtained with these devices. One of the main methodological obstacles that must be overcome is that the curves can have different lengths, and the subjects are not in standardized conditions, so a direct time series or functional data analysis is not usually workable. Given the inherent difficulty of direct examination of this data, practitioners often define several target zones and quantify the proportion of time (or total time) that the individual spends in each target zone when the device is worn. In many domains, such as diabetes, these metrics are commonly referred to as time in range metrics [Beck et al., 2019, Biagi et al., 2019a, Dumuid et al., 2018]. When the characteristic vector obtained is a ratio-vector, several papers have recently been suggested to use specific compositional data analysis techniques [Dumuid et al., 2018, Dumuid et al., 2019, Biagi et al., 2019b]. Naturally, timein-range metrics suffer from a loss of information, as the information is discrete in intervals. In addition, the cut-off points chosen may be arbitrary and dependent on the characteristics of the population under study.

In a recent work [Matabuena et al., 2021], the limitation of time in range metrics in diabetes with continuous glucose monitoring data (CGM) was overcome by a more comprehensive distributional representation of the data. Specifically, a generalization of the time in range metric approach was introduced and consisted of constructing a functional profile called a glucodensity that can be used to extract (through integration) the proportion of time spent in any interval of glucose concentration levels. In addition, a framework of non-parametric statistical techniques was proposed based on the Wasserstein distance between glucodensities. The results obtained in diabetes showed better clinical sensitivity compared to traditional approaches that include time in range metrics with American Diabetes association recommendation cut-offs [Battelino et al., 2019].

In this paper, a similar strategy to that of glucodensities is applied, exploiting the connection between the Wasserstein geometry and quantile functions, with the dynamic accelerometer data being represented as probability distributions. Here, the induced probability distribution differs from the glucodensity extracted from CGM data in that it is a mixed distribution containing an atom at zero representing the proportion of inactive time. With the intended purpose of drawing more representative conclusions of physical activity levels at the population level than can typically be achieved with observational studies, many of the main cohorts' physical activity studies are designed with a complex survey structure including demographical characteristics in sample selection, as is notably the case in the NHANES database. In order to handle these sampling characteristics in our analysis, we propose adaptations of well-known estimators, such as kernel smoothing [Wand and Jones, 1994] or machine learning approaches such as kernel ridge regression [Vovk, 2013], that accommodate the survey design structure as well as complex objects like the proposed physical activity distribution representation of accelerometer data. Including these nonparametric regression models can be a valuable option for practitioners to utilize their data more effectively by considering the study design's specific nature. Although there does not exist a vast amount of literature on estimation of nonparametric regression using survey data [Harms and Duchesne, 2010, Lumley and Scott, 2017], such techniques have the potential to contribute to obtain new clinical findings by modeling complex data relations that are usual in biology and related fields. Since survey data can lead to more reliable conclusions than observational data [Lumley, 2011, Ackerman et al., 2021], the development of these tools for more complex data objects such as physical activity distributions has a high potential impact. We must note that it is increasingly frequent in standard clinical practice to use medical devices that monitor high-resolution level patient conditions and return these complex statistical objects that can be analyzed with the new techniques proposed in this paper.

1.1 Contributions

We summarize the main contributions of the paper below.

- 1. A new representation of accelerometer data is proposed that extends compositional data metrics in this domain to a functional context. The continuous gait component is modeled through a density function, while inactivity time is modeled as a proportion. Importantly, this representation automatically captures compositional metrics and other summary measures that are widely used, such as total activity or proportion of inactive time, without the need to introduce any prior expert knowledge to subjectively define summary metrics.
- 2. As the above representation is a constrained data due to its distributional nature, the Wasserstein geometry is utilized to compare probability distributions via distances between quantile functions, similar to the glucodensity approach of [Matabuena et al., 2021].
- 3. To obtain reliable conclusions from the NHANES database, the specific survey design is used to inform model fitting. To date, few if any techniques have been proposed to incorporate complex data objects such as probability distributions using survey methods. This paper expands general kernel smoothing and kernel ridge regression to estimate nonparametric regression models involving physical activity distributions with survey data.
- 4. In the public accelerometer database NHANES:
 - The proposed representation, together with the inclusion of the new nonparametric survey regression models, are able to capture relevant biomarkers associated with health, such as age, body mass index (BMI), and cholesterol, better than standard metrics widely used in accelerometer field.
 - The physical activity distributions are used in non-parametric models
 to predict five-year mortality, and this new representation is shown
 to provide additional insight compared to existing methods in terms
 of identifying risk patients and extreme physical inactivity profiles.
 - Using a clustering analysis of the physical activity distributions, five clinical phenotypes of physical activity behavior are identified that can be the basis of personalized medicine models. Utilizing patient

groups identified by the clustering algorithm as a categorical variable in a simple logistic regression and Kaplan-Meier survey models, we show that we obtain better results in predicting mortality and survival than well-established variables, such as total activity count (TAC).

1.2 Outline

The structure of the paper is summarized as follows. First, we describe the data analyzed in the NHANES database. Next, we introduce the new representation along with notions about statistics in metric spaces. Then, we present the approach for fitting nonparametric regression models based on survey data techniques in order to handle physical activity distributions computed from the NHANES database. Subsequently, we validate and illustrate our representation through its performance in different prediction tasks. Finally, we discuss the results obtained and the potential applications of the methodology proposed herein for other accelerometer and wearable device data.

2 NHANES-database

The National Health and Nutrition Examination Survey (NHANES) is an extensive, stratified, multistage survey conducted by the Centers for Disease Control (CDC) that collects health and nutrition data on the US population.

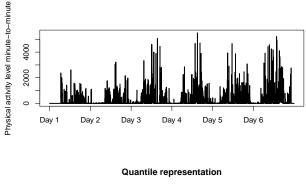
The NHANES data are publicly available from the CDC https://www.cdc.gov/nchs/nhanes/index.htm and are broadly categorized into six areas: demographics, dietary, examination, laboratory, questionnaires, and limited access. The accelerometer data for a Particular NHANES cohort can be downloaded from the "Physical Activity Monitor" subcategory under the "Examination data" tab.

As noted in [Leroux et al., 2019], data manipulation of the raw NHANES accelerometer-data can be complex mainly because of the large size of the data, the lack of software, the intricate patterns of heterogeneity of the missing data, and the need to adjust sampling-weights with specific statistical analysis.

Motivated by this problem, precisely in [Leroux et al., 2019], they create the R package *rnhanesdata* where: i) they organize the data of accelerometers and other essential variables of the patients like age, sex, comorbidities, life-styles, time of mortality, or other characteristic patient variables; ii) they introduce the function *reweightaccel* to calculate the sample survey weights. Besides, the authors upload to GitHub https://andrew-leroux.github.io/rnhanesdata/articles/vignette_prediction.html codes from their statistical analyses performed to predict five-year mortality from the physical activity patterns and other variables discussed above.

In this work, we use subset patients that are between 68 and 85 years old. This data subset is different that employs [Leroux et al., 2019] that involve patients more of a wider age range (50-85 years old). Two reasons justify our election: first, despite that the Area Under Curve (AUC) fitting was high in five years mortality prediction, the algorithm do not clasificate any dead individuals, as well as a remarkable imbalance problem. In this context, the classical sensitivity vs. specifity analysis that captures the ROC curve does not have

the optimal sense, and AUC may not be the best metric to assess the usefulness and capacity predicting clinical diagnostic model in this type of supervised modelling. Second, we think it is more clear to constraint the analysis a more specific target population that can show more reality the impact of physical inactivity than a more general and heterogeneous sample that involves lower-risk patients. In this sense, we must interpret physical activity's impact on mortality with caution and not make an automatic analysis with the use of standard model performance metrics. For example, in this domain, if the model predicts an death and finally they do not die, it may not have a negative impact, only identifying a high-risk individual who may be able to transform their lifestyle in five years, revoking their medical condition. We cannot hope to predict mortality using only physical activity levels, and we must use these tools as instruments to identify highly inactive patients phenotypes that demand with more urgency physical activity programs defined according to their specific characteristics. General models to predict mortality in five years also have a limited capacity prediction (see for example [Griffith et al., 2020, Ganna and Ingelsson, 2015]), and maybe it is necessary to use longitudinal models that capture realisticaly patient dynamic evolutions in this type of prediction tasks [Tsiatis, 2019].



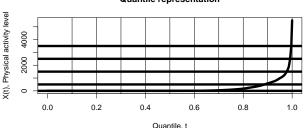


Figure 1: Example transformation of the raw accelerometer signal into the quantile representation of a randomly chosen individual from the analyzed data.

In order to explore the data, we estimate some basic patient characteristics of the patients examined using the survey weights for this target population estimated using R package *rnhanesdata* [Leroux et al., 2019]. Table 1 contains population characteristics of individuals according to their mortality status after five years. Furthermore, in Figure 2, we show the raw data during several days of one participant selected randomly from the database. For each individual, while the device is worn, accelerometer devices perform an estimate minute-by-

Variable	Survivors	Decedents
TAC	193735.4 (115239.8)	129456.5 (76978.72)
Age	72.3 (4.5)	75.5 (5.5)
MVPA	$12.3 \ (4.5)$ $12.3 \ (4.5)$	4.5 (9.6)
ASTP	0.3 (0.1)	0.37 (0.12)
Sedentary time	1126.7 (112.1)	1180 (110.5)
TLAC	2651.7 (764.3)	2328.7 (766.7)
Mobility problem	367 (37%)	129 (60.0%)
SATP	0.078(0.02)	$0.07\hat{5}$ (0.02)
Education	()	()
Less than high school	393 (39%)	81 (38%)
High school	262 (26%)	64 (30%)
More than high school	349 (35%)	71 (33%)
Drinking Status	,	,
Moderate Drinker	442 (44%)	75 (35%)
Non-Drinker	496 (49%)	118 (55)
Heavy Drinker	40 (3%)	15 (7%)
Missing alcohol	26 (2%)	8 (4%)
Smoking Status		
Never	460 (46%)	68 (13%)
Former	466 (46%)	110 (51%)
Current	78 (8%)	38 (18%)
CHF	115 (11%)	37 (17%)
Gender		
Male	519 (52%)	145 (67%)
Female	485 (48%)	$71\ 34\%$
Diabetes	$163 \ (18\%)$	48~(22%)
Cancer	$231\ 23\%$	$57\ 26\%$
BMI		
Normal	$283\ 28\%$	75 (35%)
Underweight	7 1%	7 (3%)
Overweight	$414\ 41\%$	76 (35%)
Obese	300 (29%)	58 (27%)
CHD	115 (11%)	37 (17%)
Stroke	71 (7%)	31 (14%)
Race		
White	648 (65%)	161 (74%)
Mexican American	172 (17%)	22 (18.8%)
Other Hispanic	17 (2%)	0 (0%)
Black	144 (14%)	28 (10%)
Other	23 (2%)	5 (2%)
Wear time	878.4 (161.0)	892.2 (164.98)

Table 1: Patients characteristic of sample considered in this work beetween live and deceased patients. The Table extracted show means (standard deviation) or n (%). In bold, multivariate categorical variables.

TAC total activity count (TAC); total log-transformed activity count (TLAC); total minutes of moderate/vigorous physical activity (MVPA); active to sedentary/sleep/non-wear transition probability (ASTP); sedentary/sleep/non-wear to active transition probability (SATP); Coronary heart disease CHD (CHD); Congestive heart failure (CHF)

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minute energy expenditure. However, given that the device is not worn all day, the recorded signal cannot be continuous, and there are intricate missing data patterns. Precisely with this same database, several works propose a method of

missing data to address this problem [Ae Lee and Gill, 2018]. In our particular setting, we rely on the pre-processing done in [Leroux et al., 2019].

3 Functional representation of accelerometer data and regression models

3.1 Definition of functional representation

First, we introduce the formal definition of the new representation. For a patient i, let n_i be the number of observations recorded in form of pairs (t_{ij}, X_{ij}) , $j = 1, \dots, n_i$, where the t_{ij} are the different temporal points in the interval $[0, T_i]$ where the accelerometer records activity information, and X_{ij} is the measurement of the accelerometer at time t_{ij} . Unlike continuous glucose monitoring data, accelerometer readings of exactly zero are quite frequent, representing physical inactivity. Thus, in our distributional representation, we will assign positive probability mass at zero equal to the fraction of total time that the individual is physically inactive. In addition, the range of values measured by the accelerometer varies widely between individuals and groups, which can present difficulties when trying to apply common distribution data analysis methods, for example functional transformations [Van den Boogaart et al., 2014, Petersen et al., 2016, Hron et al., 2016] that can be alternative strategy to handle the representation that we specify below.

In order to handle accelerometer data gathered over different monitoring periods in free-living environments, we propose to utilize a cumulative distribution function $F_i(x)$ for each individual. Formally, consider a latent process $Y_i(t)$ such that the accelerometer measures $X_{ij} = Y_i(t_{ij})$ $(j = 1, ..., n_i)$, and define F_i as

$$F_i(x) = \frac{1}{T_i} \int_0^{T_i} \mathbf{1}(Y_i(t) \le x) dt, \quad \text{for } x \ge 0.$$
 (1)

This definition corresponds to using x = 0 as a cutoff for inactivity; in the NHANES data set, it always holds that $F_i(0) > 0$. Thus, if U_i is a random variable uniformly distributed on $[0,T_i]$ that is independent of Y_i , F_i is the distribution function of $Y_i(U_i)$. In practice, one could use another reasonable cutoff for inactivity. For example, other studies have used accelerometer measures between 0-100 to quantify the inactive range. In this case, one would define F_i as the distribution of the censored random variable which takes the value 100 whenever $Y_i(U_i) \leq 100$ and $Y_i(U_i)$ otherwise. Analogously, we may be interested in truncating the latent process from above, for example to combine measurements representing high-intensity exercise, e.g., device observations greater than or equal to 3500. For instance, this idea can be exploited to establish high-intensity exercise benefits in the prediction of mortality or another relevant outcome. Practically speaking, an upper threshold of this type would lead to a simpler model that could be beneficial in the predictive task. Then F_i would be the distribution of the censored random variable taking values $Y_i(U_i)$ whenever this is at most 3500, and 3500 otherwise. Combination of lower and upper cutoffs would be treated in a similarly straightforward manner.

In the remainder of the paper, we define F_i as in (1), and denote $\mathbb{P}^i_{inactive} = F_i(0)$, $F^i_{active}(x) = F_i(x) - F_i(0)$ for x > 0, and $f^i_{active}(x) = [F^i_{active}]'(x)$. Hence,

 $F_i(x) = \mathbb{P}^i_{inactive} + \int_0^x f^i_{active}(s) \mathrm{d}s$, which more clearly demonstrates the mixed nature of the distribution. In real world settings, $\mathbb{P}^i_{inactive}$ and $f^i_{active}(\cdot)$ are not observed, but must estimated from the observed sample following, which we carry out using the following two-step strategy. First, we estimate the proportion of inactivity-time, that is

$$\hat{\mathbb{P}}_{inactive}^i = \frac{1}{n_i} \sum_{j=1}^{n_i} \mathbf{1}_{\{X_{ij} = 0\}}.$$

Second, we estimate the continuous physical activity profile as conditional smooth density-function. Letting \mathbb{K} denote a univariate probability density function and $h^i > 0$ the bandwidth parameter, define

$$\hat{f}_{active}^i(x) = (1 - \hat{\mathbb{P}}_{inactive}^i) \frac{1}{n_i^{active}h^i} \sum_{j=1}^{n_1} \mathbb{K}\left(\frac{X_{ij} - x}{h^i}\right) \mathbf{1}_{\{X_{ij} > 0\}}, \quad n_i^{active} = \sum_{i=1}^{n_1} \mathbf{1}_{\{X_{ij} > 0\}}.$$

In our experiments, the Gaussian kernel was used for \mathbb{K} and the smoothing parameter was selected through Silverman's "rule of thumb." More discussion about density estimation procedure and kernel bandwidth selection with biosensor data can be found in the glucodensity paper [Matabuena et al., 2021].

3.2 Statistical Framework for the Distributional Representation

While the representation of physical activity levels via the inactivity probability $\hat{\mathbb{P}}^{i}_{active}$ and activity density f^{i}_{active} provides a rich and fairly comprehensive representation of the accelerometer data, the mathematical constraints of these objects makes statistical analysis challenging. In particular, naive application of functional data analysis for the f_{active}^{i} is known to yield results that are often difficult to interpret, as these methods do not respect the inherent constraints. Thus, we will work under the same framework outlined in [Matabuena et al., 2021] based on the Wasserstein geometry of optimal transport [Villani, 2008, Ambrosio and Gigli, 2013]. This metric has theoretical appeal, has given intuitive results in a variety of applications, and possesses many computational advantages [Peyré et al., 2019] due to its connection to quantile functions, as will be seen below. In particular, while it is still helpful to compute the density estimates as in outlined previously in order to perform exploratory analysis and visualize results, these are not strictly necessary for the model fitting described in Section 3.3, where it suffices to obtain estimates of quantile functions. Moreover, due to the mixed nature of the physical activity level distributions, the Wasserstein geometry is even more attractive as it accommodates such distributions without any special adaptation.

Next, we define the space of the physical activity distributional representations. Let $A:=\{f:(0,\infty)\to\mathbb{R}^+:\int_0^\infty f(x)\mathrm{d}x<1\text{ and }\int_0^\infty x^2f(x)\mathrm{d}x<\infty\}$. Then the activity distributions constitute the set $\mathcal{D}\subset[0,1]\times A$, where $(c_f,f)\in\mathcal{D}$ if $f\in\mathcal{A}$ and $c_f=1-\int_0^\infty f(x)\mathrm{d}x$. Given two arbitrary inactive-active representations $\mathfrak{f}=(c_f,f)$ and $\mathfrak{g}=(c_g,g)\in\mathcal{D}$, the 2-Wasserstein (or simply Wasserstein) distance between them is

$$d_{W^2}(\mathfrak{f},\mathfrak{g}) = \sqrt{\int_0^1 (F^{-1}(t) - G^{-1}(t))^2} dt,$$
 (2)

where F^{-1} and G^{-1} are the quantile (inverse cumulative distribution) functions corresponding to the distributions represented by \mathfrak{f} and \mathfrak{g} , respectively.

Given a metric or distance d on \mathcal{D} , of which d_{W^2} is one example, and a random variable \mathfrak{f} defined on \mathcal{D} , the Fréchet mean of f [Fréchet, 1948] is

$$\mu_{\mathfrak{f}} = \arg\min_{g \in \mathcal{D}} E(d^2(\mathfrak{f}, g)).$$

The corresponding Fréchet variance of f is then

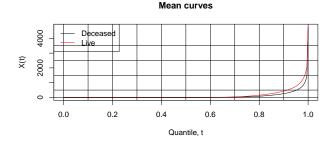
$$\sigma_{\mathfrak{f}}^2 = E(d^2(\mathfrak{f}, \mu_{\mathfrak{f}})).$$

With the particular choice $d = d_{W^2}$, we have

$$\mu_{\mathfrak{f}} = \arg\min_{\mathfrak{g}\in\mathcal{D}} E\left[\int_0^1 (F^{-1}(t) - G^{-1}(t))^2 dt\right],$$

and, with $Q_{\mathfrak{f}}$ denoting the quantile function corresponding to $\mu_{\mathfrak{f}},$

$$\sigma_{\mathfrak{f}}^2 = E\left[\int_0^1 (F^{-1}(t) - Q_{\mathfrak{f}}(t))^2 dt\right].$$



Deceased Live 0.0 0.2 0.4 0.6 0.8 1.0 Quantile, t

Standard deviation curve

Figure 2: Summary curves of physical activity distributions in Quantile space (mean and standard deviation) between life and deceased patients groups after five years

Given n samples of accelerometer measures belong n individals $\{X_{i,j}\}_{j=1}^{n_i}$, $i=1,\ldots,n$, we can form empirical quantile functions $\hat{Q}_i=\hat{F}_i^{-1}$. Then, due to the Euclidean nature of (2), the empirical Fréchet mean and variance, written

in terms of quantile functions, take the form of

$$\overline{Q}(t) = \hat{Q}_{\mathfrak{f}}(t) = \frac{1}{n} \sum_{i=1}^{n} \hat{Q}_{i}(t), \ t \in [0, 1], \text{ and}$$

$$\hat{\sigma}_{\mathfrak{f}}^2 = \frac{1}{n-1} \sum_{i=1}^n \int_0^t (\hat{Q}_i(t) - \overline{Q}(t))^2 dt.$$

In this case, also we can estimate the quantile variance curve as we denote $\tilde{\sigma}_f^2(t)$, for each $t \in [0,1]$. Figure 2 illustrates the process of transform raw data into our representation. In addition, in Figure 2, show the mean and variance curve of our representation in dead and deceased patients after 5-years.

3.3 Survey regression models

The individuals that we analyze from the NHANES database do not represent a random sample of a population. Instead, they are the result of a structured sample of a complex survey design from a finite population of N individuals. In order to perform inference correctly and obtain reliable results, one must account for the effects of the specific sample design when building a predictive model. Note that the information provided by this type of survey data is typically richer than those used in most medical studies that are of an observational nature [Lumley, 2011, Ackerman et al., 2021]. In the latter case, the research does not explicitly control the sampling mechanism, so that obtaining a representative population results can be challenging and would often demand colossal data volumes.

Suppose that observations $\{(Y_i, X_i); i \in S\}$ are available, where Y_i is a scalar response variable, and X_i a collection of covariates taking values in a metric space. The index set S represents a sample of n units from a finite population. To account for this sampling, each individual $i \in S$ will be associated with a positive weight w_i . In our analyses, these weights were taken to be the the inverse of the probability $\pi_i > 0$ of being selected into the sample [Kish, 1965], i.e. $w_i = 1/\pi_i$, although more general situations are available [Lumley and Scott, 2017]. When performing estimation with survey data, a common approach is to use the w_i to define weighted versions of usual estimates designed for random samples. For example, the normalization Horvitz-Thompson estimator [Horvitz and Thompson, 1952, Rabe-Hesketh and Skrondal, 2006] for the population average of the Y_i is the weighted sample average

$$\overline{Y}_w = \sum_{i \in S} \frac{\frac{1}{\pi_i} Y_i}{\sum_{i \in S} \frac{1}{\pi_i}} = \sum_{i \in S} \frac{w_i Y_i}{\sum_{i \in S} w_i}.$$
 (3)

Although simplistic in appearance, the researcher often controls the study and sampling design for survey data so that weights can be calculated easily without the need to resort to any data-driven approach. In particular, the sampling weights are calculated according to some demographics variables that are essential in describing population composition. These variables are used in the process of selecting a sample of elements from a population. In the NHANES cohort, we can download for each study participant their representative weight in the United States population. However, we must re-weight according to

variables (not all NHANES participants have accelerometer data) and specific patients that we introduce in the analysis (for example, subset of patients with more than 68 years).

In this paper, we propose to use a general kernel smoother [Wand and Jones, 1994, Chacón and Duong, 2018] for survey data with weights that are composed of both the sampling weights w_i as well as the usual local weights that appear in such kernel methods. One main advantage of this estimator is its flexibility, as it is valid for either regression or classification problems. In addition, we also extend kernel ridge-regression [Vovk, 2013], but this method is only appropriate for a continuous response variable. Theoretical properties such as asymptotic results and convergence rates, although interesting, will not be investigated here as the main goal to solve and model a real problem.

3.3.1 Kernel smoother for survey data

Suppose the following mean regression model holds:

$$Y = m(X) + \epsilon, \tag{4}$$

where ϵ is a random error term satisfying $E(\epsilon|X) = 0$. Hence, the value m(X) represents the conditional mean of Y given X, where m is assumed to be a smooth function. Given a sample $\{(Y_i, X_i, w_i); i \in S\}$ of size n from the finite population as described above, an estimate of m(x) for a generic input x may be obtained using the standard kernel estimator [Wand and Jones, 1994]

$$\hat{m}(x) = \sum_{i \in s} s(X_i, x) Y_i, \tag{5}$$

where $s(X_i,x)$ is an appropriate weight function that provides more weight for predictors X_i with smaller distance to x. Furthermore, the constraint $\sum_{i \in s} s(X_i,x) = 1$ must be satisfied for all x to obtain a coherent estimator. Typical choices for s include Nadayara-Watson weights, given by $s(X_i,x) = \frac{\mathbb{K}(\frac{d(X_i,x)}{h})}{\sum_{i \in s} \mathbb{K}(\frac{d(X_i,x)}{h})}$, where d is a metric on the set of predictors, for example the Wasserstein distance defined in (2) if the covariate X represents a physical activity level distribution, and h > 0 is the smoothing-parameter. The generalization of the standard Nadaraya-Watson estimator, which was originally proposed for scalar or vector predictors, to more abstract data types has been used to handle functional predictors [Ferraty and Vieu, 2006] as well as predictors and responses in more general spaces that possess a metric [Steinke et al., 2010]. Here, we will utilize the quantile functional representation of the accelerometer data along with the Wasserstein metric to incorporate these complex objects as predictors of relevant outcomes.

Due to the survey design, we make the necessary adjustment to the usual Nadaraya-Watson weights by scaling them according to the survey weights w_i . Specifically, we set $s(X_i, x) = \frac{\mathbb{K}(\frac{d(X_i, x)}{h})w_i}{\sum_{i \in s} \mathbb{K}(\frac{d(X_i, x)}{h})w_i}$. This definition reflects that an observation should be given higher weight when the probability of selection is lower (large values of w_i), consistent with the principles outlined in [Horvitz and Thompson, 1952], and when the observed input X_i is closer to the input x at which one desires an estimate of the conditional mean. In general,

the kernel smoother in (5) corresponds to a convex combination of the observed responses, a property that is not shared by similar smoothers, for example local linear regression estimators.

An important consequence of this convexity property is in the case of a binary response variable $Y \in \{0,1\}$. In this case, $m(x) \in [0,1]$ represents a probability, so that (5) yields an estimate $\hat{m}(x) \in [0,1]$ that can be used in classification tasks, for example, without any post hoc modification. When Y represents a categorical variable that can assume more than two values, a simple modification of (5) can still be used to produce valid estimates of the various probabilities.

3.3.2 Kernel ridge regression for survey data

Let $X \in \mathcal{D}$ be an object of complex type as our probability distribution of physical activity levels. The Reproducing Kernel Hilbert Space (RKHS) learning paradigm [Rakotomamonjy et al., 2005] provides a unique and rich framework to create new and more flexible predictive models that can handle abstract variables X as predictors by assuming that the regression function m in (4) is an element of a space of functions V on $\mathcal D$ that is an RKHS. This section focuses attention on a method known as kernel ridge regression that leverages the properties of an RKHS to produce estimates that can be viewed as generalizations of the usual ridge regression estimator for linear models. In the following, we summarize the necessary components of the RKHS-based model and its estimator, and then adapt the estimator to the case of survey data.

For each input value $x \in \mathcal{D}$, one way of defining an RKHS is to begin with a kernel $K: \mathcal{D} \times \mathcal{D} \to \mathbb{R}$ that is symmetric and positive definite. Beginning with functions of the type $\phi_x(\cdot) = K(x,\cdot)$ as basic elements, one can construct a Hilbert space of functions by taking linear combinations and, finally, by taking the usual metric completion. The constructed Hilbert space V can be shown to have the inner product $\langle \cdot, \cdot \rangle_V$ with the property that $\langle \phi(x), \phi(y) \rangle_V = K(x,y)$. Furthermore, for any $f \in V$, one has $f(x) = \langle \phi_x, f \rangle_V = \langle K(x,\cdot), f \rangle_V$, so that K is often referred to as a reproducing kernel, or the kernel that generates V. Observe that the use of the term kernel is distinct from that of the previous section. For clarity, a distinct notation has been introduced for the bivariate kernel of the current section.

Considering the model defined Equation 4, an alternative to the smoothing method of the previous section is to assume that the regression function $m(\cdot) \in V$. Given the infinite-dimensional nature of V, estimation of $m(\cdot)$ through the use of least squares, i.e.

$$\hat{m} = \arg\min_{m \in V} \sum_{i \in S} (Y_i - m(X_i))^2 + \lambda \|m\|^2$$
(6)

is ill-defined, where $\|\cdot\|$ is the Hilbertian norm on V. Specifically, there are many different solutions to (6) that attain zero empirical error. Naturally, overfitting the model in this way results in poor predictive capacity for new observations.

In the RKHS framework, it is common to introduce a norm-based penalty on m in the optimization procedure to induce regularization. The kernel ridge

regression estimator then becomes

$$\hat{m} = \arg\min_{m \in V} \sum_{i \in S} (Y_i - m(X_i))^2 + \lambda \|m\|^2,$$
(7)

where λ is the regularization parameter that controls the usual trade-off between bias and variance, which in turn determines the capacity of the model to generalize to new observations.

By the classical Representer Theorem [Schölkopf et al., 2001], the solution to (7) is known to take the form $\hat{m}(\cdot) = \sum_{i \in S} \alpha_i K(\cdot, X_i)$, so that the estimator is a linear combination of the kernel features $K(\cdot, X_i)$ with coefficients α_i . Solving (7) under this restricted form of m results in the coefficient estimates

$$\hat{\alpha} = \begin{bmatrix} \hat{\alpha}_1 \\ \vdots \\ \hat{\alpha}_n \end{bmatrix} = \begin{bmatrix} \begin{pmatrix} K(X_1, X_1), \dots, K(X_1, X_n) \\ K(X_2, X_1), \dots, K(X_2, X_n) \\ \vdots \\ K(X_n, X_1), \dots, K(X_n, X_n) \end{pmatrix} + \lambda \begin{pmatrix} 1 \\ & \ddots \\ & & 1 \end{pmatrix} \end{bmatrix}^{-1} \begin{bmatrix} Y_1 \\ \vdots \\ Y_n \end{bmatrix},$$
(8)

which can be written compactly as $\hat{\alpha} = (K + \lambda I)^{-1}Y$.

To introduce survey design in the optimization problem, we can use the Horvitz-Thompson version of the estimator, namely

$$\hat{m} = \arg\min_{m \in V} \sum_{i \in S} w_i (Y_i - m(X_i))^2 + \lambda \|f\|^2.$$
 (9)

As (9) remains a convex objective function, the Representer Theorem holds and the solution will retain the same structure, $\hat{m}(\cdot) = \sum_{i \in S} \alpha_i K(\cdot, X_i)$. However, the coefficients take the form of regularized weighted least squares estimates $\hat{\alpha} = (WK + \lambda I)^{-1}WY$, with W being a diagonal matrix with the weights w_i constituting the diagonal elements.

An notable advantage of the kernel ridge regression is that it preserve some computational advantages of linear models, as the optimal solution can be calculated via weighted least squares. This fact also simplifies selection of the tuning parameter λ , for example using Leave One Out Cross-Validation (LOOCV), given that explicit leave-one-out formulas are available for linear estimators [Golub et al., 1979].

Besides the regularization parameter, a crucial choice that determines these model's empirical performance is that of the RKHS learning space V or, equivalently, the kernel K. In our preliminary test, the best results are obtained with the Laplace kernel, so in the following, we consider only this kernel. Let x, y two points belong to input space, the Laplacian kernel K(x, y) is

$$K(x,y) = e^{-\|x-y\|/\sigma},$$
 (10)

where $\sigma > 0$ is a scale parameter that can be chosen heuristically as [Garreau et al., 2017]

$$\hat{\sigma} = \sqrt{\text{median}\{||X_i - X_j||^2 : 1 \le i < j \le n\}},\tag{11}$$

according Horvitz-Thompson estimator [Horvitz and Thompson, 1952].

4 Result

4.1 Outline of Analysis Performed

To show the potential of the new representation of accelerometer data and the application of new nonparametric survey regression estimators, we performed the analysis described below with the sample described in Section 2.

- 1. We analyzed four different response variables, namely age, Body Mass Index (BMI), blood pressure, and cholesterol levels. Kernel ridge regression was used to compare our functional representation with total activity count (TAC), the most relevant physical variable used before in different studies with this database [Leroux et al., 2019, Smirnova et al., 2019].
- 2. We assess the ability of our functional representation to predict five-year mortality with the Nadayara-Watson survey estimator. Furthermore, we do an exhaustive clinical analysis of the results provided by the algorithm.
- 3. In personalized medicine, practitioners often form patient groups, generally called phenotypes, using unsupervised techniques. In practice, these phenotypes can be highly useful as they often correspond to different clinical evolutions. Exploiting this idea, we perform a clustering analysis with our distributional representation of accelerometer data, and we identify five patients phenotypes. To assess the posterior clinical relevance of these, we fit a survey two predictive models using each patient's assigned phenotype as a categorical predictor: i) logistic regression using as response if the patient is live or deceased after 5-years; ii) Kaplan-Meier estimator with the response censored variable time until death considering 12 years follow-up.

At this point, it is essential to note that classical summary metrics described in Table 1 are captured directly by our representation as TAC due; they are variables that can calculate from the distribution of physical activity levels, so we do not consume time in predicting these variables. To avoid making an extensive comparison with these summary metrics, we restrict the comparative in assessments the gains of our representation against TAC metric. TAC metric in the NHANES database show be the most relevant physical activity variable in other studies (see for example [Leroux et al., 2019]).

We do not introduce a comparative with the usual finite-dimensional compositional metrics since it requires a prior subjective definition of specific cut-offs that are usually adapted to the target population. In addition, the information is automatically registered by our representation, and we saw in some experiments that not provide comparable results with our new methods.

4.2 Comparison of Distributional Representation with TAC

One way to illustrate that the proposed representation provides useful information beyond stanard TAC metrics is to compare the ability to capture essential biomarkers associated with the health and decline of physiological function. For this purpose, we select age, Body mass index (BMI), blood pressure, and cholesterol as response variables. As a regression estimator, we select the kernel ridge-regression introduced in Section 3.3.2, with the Laplacian Kernel in

(10). In constructing this kernel, we employ the Wasserstein distance when the predictors are distributions (which can be expressed as a norm via the quantile representation), and the Manhattan or ℓ_1 distance in the case of vector-valued TAC predictors. To make a conservative assessment of physical activity levels, we calculate a survey-weighted leave-one-out version of R-square, defined as

$$R^{2} = 1 - \frac{\sum_{i \in S} w_{i} (Y_{i} - \hat{f}^{-i}(X_{i}))^{2}}{\sum_{i \in S} w_{i} (Y_{i} - \overline{Y}_{w})^{2}},$$
(12)

where w_i 's are the survey weights, \overline{Y}_w is defined in (3), and $\hat{f}^{-i}(\cdot)$ is a generic regression estimate obtained after deleting the *i*-th observation. As the models are nonlinear and leave-one-out estimators are used, R^2 as defined in (12) can be negative, as seen for blood pressure as response with TAC as predictors in Table 2, where all results are compiled.

As we can see, the predictive capacity is low to moderate for all models, with age and BMI being the most predictable variables. In all cases, it is clear that our representation outperforms the summary metric TAC. It is reasonable to hypothesize that the differences can be more significant with more extensive databases due to the increase of complexity of new representation than summary accelerometer metrics..

	New representation	TAC
Age	0.15	0.07
BMI	0.05	0.01
Blood pressure	0.02	-0.01
Cholesterol total	0.034	0.016

Table 2: R-square obtained with each representation used in Kernel Ridge-Regression models with continuous variables examined

4.3 Prediction of five-year mortality

We fit a Nadayara-Watson estimator to predict five-year mortality with both our representation and the TAC metric. Once again, we use as model output results obtained with leave-one-out prediction error to avoid over-fitting. According to the solution selected, 23 patients were well classified with our representation, while 36 patients who did not die were classified as dead. In the TAC metric, the model predicted that all patients would die. To appreciate the practical clinical interpretation of this analysis, consider the following two patient groups:

- A (risk-group): Patients that were predicted to die but they did not die.
- B (non-risk group): Patients that non died and are corrected classified by the model.

Additionally, consider the following age stratification: 68-75 years, 76-80 years, and 81-85 years. Figure 3 show apparent differences in physical activity distribution between subjects in different risk groups and distinct age strata. Survival curves that presented more pronounced mortality rates along

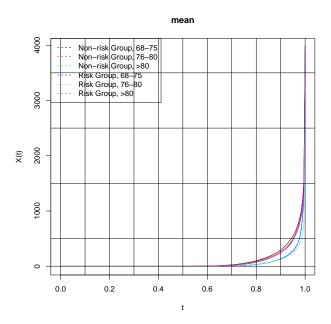


Figure 3: Mean functional profile of different groups composed according algorithm output and age-group $\,$

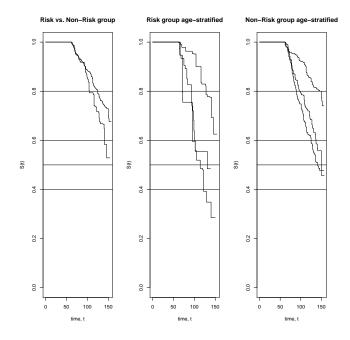


Figure 4: Survival curves of risk and non-risk group, so in general and stratified analysis $\,$

times considered, corresponding with risk-group and age strata composed with patients more elderly.

We can also see significant differences in survival curves of different groups ($\alpha=0.05$, being α significance-level), according to our previous energy-distance survival methodology [Matabuena and Padilla, 2019] adapted to handle other sampling mechanism as the complex survey design of NHANES database. Clearly, in a graphical sense (Figure 4), the survival trajectories are different. Survival curves that presents more pronounced mortality rates along times period considered, correspond with the risk-group and age strata composed with patients more elderly

Finally, we performed complementary analyses of clinical groups defined in Figures 5 and 6 $\,$

In these analyses, we recognize a higher percentage of patients with more than 75 years and significantly higher-body mass levels in non-risk group. In addition, the percent of oncology patients is higher in non-risk groups. This facts can explain the incorrect label assignment of our fitted algorithm in some cases.

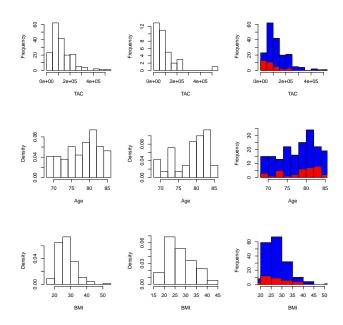


Figure 5: Distributional composition of some relevant outcomes related to mortality and healthy: TAC, Age, and BMI, in risk and non-risk group. First column, density estimation of the variables mentioned above using patients that belong to the non-risk group. Second column, density estimation with the provious variables using patients that belong to the risk group. Third column, histograms of mentioned variables, in Red color (risk-group patients), Blue color (non-risk-group patients)

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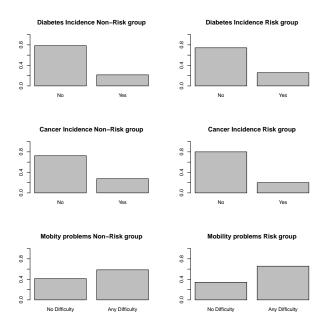


Figure 6: Distributional composition of some relevant binary variables related with mortality in risk and non risk-group

4.4 Clustering and Phenotype Analysis

A clustering method based on the energy-distance [Székely and Rizzo, 2017], as introduced in [Matabuena et al., 2021] and [Franca et al., 2020], was applied to the functional representation to divide the cohort into five subgroups. Figure 7 shows the pointwise mean and standard variance curves of each group, with the mean curves constituting 5 distinct phenotypes identified by the algorithm. There are important differences in physical activity patterns and, perhaps more noticeably, between the survival trajectories of the groups, as shown in Figure 8. Summaries of different clinical variables for each phenotype group are shown in Table 3. Phenotypes 3 and 5 correspond to the groups with the largest proportion of dead patients (more than 25%). The patients in these two groups are balanced between men and women, have slightly larger average age than other groups, and engage in markedly less physical activity as measured by TAC, and also by our functional representation.

Lastly, we show the ability of these phenotypes to predict five year mortality using logistic regression. Table 4.4 gives the coefficient estimates and p-values, with phenotype 2 being used as the reference group, as this group contains the smallest percentage of patients that died. This explains why all of the the coefficients are positive, since the other groups have higher risk of death. Phenotypes 1, 3, and 5 demonstrate significant differences in mortality risk compared to phenotype 2. The AUC of this model is 0.703, while those of similar logistic regresion models using age and TAC are 0.695 and 0.678, respectively. These values are slightly lower than those obtained in [Leroux et al., 2019], due to the restriction of our analysis to higher-risk patients. This indicates that

AUC is not the best metric for model assessment in this setting. As we say, clinical interpretations and long-term patient evolution must be used in the model evaluation as we do in a similar way to that performed in the previous Section.

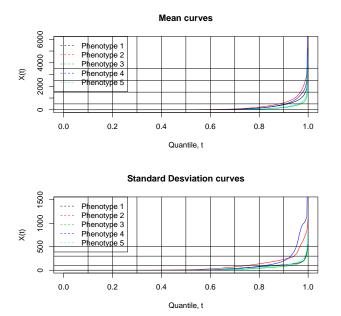


Figure 7: Mean and standard deviation curves of our representation along five phenotypes obtained with the cluster analysis

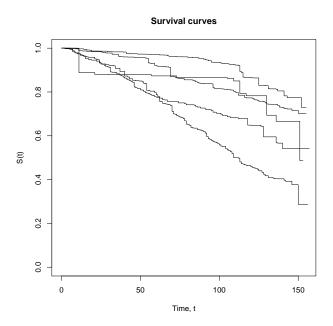


Figure 8: Survival trajectories of unsupervised physical activity phenotypes

_	Phenotype 1 $(n = 337)$	Phenotype 2 $(n = 241)$	Phenotype 3 $(n = 408)$	Phenotype 4 $(n = 42)$	Phenotype 5 $(n = 192)$
Age	71.86 (4.34)	70.98 (3.48)	75.39 (5.18)	(70.25) (3.02)	73.63 (5.14)
BMI	28.88 (5.7)	26.51 4.21	28.74 (6.22)	27.98 (5.13)	31.57 (7.81)
TAC	179051.43 (65304.85)	283539.46 (115491.62)	95496.93 (42787.72)	(283708.44) (145476.6)	(115065.66) (48559.71)
% Gender	52	68	49	69	50
% patients died	10	8	27	10	26

Table 3: Clinical characteristics of phenotypes defined according clustering algorithm. Mean (standard deviation) are show

	Estimation value	p-value
(Intercept)	-3.5015	0.0000
Phenotype 1	1.0952	0.0130
Phenotype 3	2.2680	0.0001
Phenotype 4	1.5707	0.1081
Phenotype 5	2.2374	0.0000

Table 4: Estimation values and significance variable value in a simply survey logistic regression as covariate the categorical variable phenotype number that patient belong (Phenotype 2 reference-group)

5 Discussion

In this work, we have introduced a new functional profile of an individual's physical activity to quantify more comprehensively the energy expenditure over a given period among a group of individuals monitored in free-living conditions. Our procedure can be seen as a functional extension of the so-called compositional metrics that constitute the most popular approach to date in the accelerometer field. A fundamental advantage of the new method is that it automatically captures information from compositional metrics, regardless of the cutoffs used to define them. As such, one loses no information compared to these metrics, and simultaneously avoids the need to define a-priori different cut-off points [Biagi et al., 2019a, Dumuid et al., 2018]. Even with expert knowledge, such a selection introduces subjectivity into the anlaysis, with the cutoffs inevitably depending on sample characteristics or the analysis task at hand.

In the different regression tasks considered in this paper, we have seen that the new representation shows stronger predictive power than other common summary measures such as TAC, which has been shown to be the most successful variable, for example, in predicting 5-year mortality in the NHANES database in other studies [Leroux et al., 2019, Smirnova et al., 2019]. Overall, the different models assessing the associations between our representation and clinically relevant covariates, as quantified by the leave-one-out R-square metric, is moderate (perhaps with the exception of age), indicating that there is a large amount of variability in many biomarkers associated with patient health, such as cholesterol, blood pressure, or BMI, that is not associated with physical activity [Atienza et al., 2011, Luke et al., 2011]. Several epidemiological studies have used multivariate regression models with these biomarkers as response variables and summary measures of physical activity as covariates. Although some have found physical activity to be a statistically significant factor, many of these models only assess the statistical significance of the variable, rather than its practical significance or predictive capacity [Pepe et al., 2004]. Assessing only statistical significance fails to accurately assess the magnitude of impact physical activity has on biomarker prediction, and obscures the conclusions and reproducibility of findings reached.

The evaluation of a clinical diagnostic model that aims to predict 5-year mortality and includes physical activity levels as a covariate is not straightforward. We cannot hope with physical activity patterns alone to predict whether a patient will die or not. However, we can identify subjects who are at risk

of disease or have a higher risk of death because of their inactivity. From this point of view, the AUC used by other authors may not be the most adequate metric. For instance, there is a critical imbalance problem, and false positives do not necessarily have a negative connotation in this task.

In this predictive model, we have also performed a clinical validation based on the longitudinal evaluation of the two groups of patients whose outcome can not match the one predicted by our model. In particular, we have considered a group of at-risk patients and a group of non-risk patients. Risk subjects are defined as those predicted by the model to die but who do not die in reality. In contrast, non-risk subjects do not die and are correctly classified by the model. As we can see in Section 4.3, despite the fact that there are lower percentages of both non-cancer patients and elderly patients in the at-risk group, survival is lower in that group compared to non-risk patients. Moreover, this finding persists after stratifying by age into three categories. This fact demonstrates the effectiveness and clinical sensitivity of our representation and the physical activity information provided by accelerometer. Furthermore, a model including only the TAC metric does not provide any relevant information in clinical decision support. It cannot detect any patients who die.

In personalized medicine, the essential problem is to identify sub-types of patients that show different behavior patterns in various forms such as genetic profiles, physiological signals, or any group of variables that impact patients' health, their evolution and prognosis [Bierma-Zeinstra and Van Middelkoop, 2017, Parimbelli et al., 2018, Ahlqvist et al., 2018. Here, we have followed that approach through cluster analysis of the proposed physical activity distributions. From this clustering analysis [McLachlan, 1992], we identified five groups of patients in which clinical phenotypes characterized by lower levels of physical activity have lower survival and higher five-year mortality. In the future, with a more extensive database, it would be interesting to fit different prediction models in each of the clusters obtained, including other relevant covariates in mortality and survival prediction, to assess more accurately the clinical impact of the clinical phenotypes defined according to physical activity patterns and their reproducibility and stability with other populations of study. In our case, with a simple categorical model, we obtained a higher AUC than the TAC variable or even age, the marker that has shown greater discriminatory capacity in an univariate analysis in other cohorts such as the UK-Biobank [Leroux et al., 2020].

Despite the large number of studies that have analyzed the impact of physical activity in the NHANES cohort against different biomarkers associated with health or with mortality and survival, few studies incorporate the complex survey mechanism in the analyses, which is very crucial for obtaining reliable and reproducible results. In fact, our preliminary analysis we see that if we do not introduce the specific sampling design effect, the results are entirely different (the same issue are illustrated in NHANES tutorials https://wwwn.cdc.gov/nchs/nhanes/tutorials/module3.aspx). The correct analysis of survey data can yield more robust findings than those obtained with observational data. To increase reliability of the analyses, we model relationships between the covariates and response variable nonparametrically. To the best of our knowledge, this work is the first to combine survey methods for the estimation of nonparametric regression models involving complex predictors such as the physical activity distributions we consider. In particular, we have demonstrated how to implement the Nadaraya-Watson kernel smoother as

well as kernel ridge regression models in this context.

We believe that proposed model constitutes an important step forward in the use of complex objects with this type of data, which appear naturally in some of the world's most important physical activity cohorts, to obtain data representative of the physical activity patterns of a population, and not only in NHANES as a particular case. It is likely that with the technological revolution in which we live, the use of biosensors and smart-phones in surveys in digital medicine will become increasingly common to characterize the population health [Rafei et al., 2020] and, in particular, the physical activity levels of a population.

Currently, one of the main hot topics in the field of physical activity and exercise science is to establish the impact of high-intensity exercise on patient mortality and lifespan [Ekelund et al., 2019]. Following the methodology defined in Section 3.1, we have found that the high-intensity physical pattern analyzed may not result in noteworthy additional benefits to reduce mortality. Recently, a randomized clinical trial has reached similar conclusions [Stensvold et al., 2020]. However, other observational studies have established the essential benefits of this mode of exercise [Gill, 2020]. Therefore, we believe that the NHANES data with a complex survey design may provide a unique source of information for answering these relevant questions more reliably than other studies with less ideal design studies such as that of the UK-Biobank [Leroux et al., 2020, Strain et al., 2020].

One of the main reasons used to justify high-intensity exercise in this context is that it increases maximal-oxygen consumption more significantly [Milanović et al., 2015] than lower intensity exercise; in more prolonged exercise therapies such as endurance training. maximal oxygen consumption is an essential physiological variable related to the prognosis and health of patients [Matabuena et al., 2018, Mikkelsen et al., 2020, Hoppeler, 2018. However, it has been shown that, in diseased and elderly populations, regular exercise increases fitness but does not necessarily increase this cardiovascular maximal parameter value [Hoppeler, 2018], existing a massive inter-individual exercise response. In this sense, more personalized training programs and refined patient evaluation are required for the therapy to be successful [Matabuena et al., 2019, Buford et al., 2013]. In [Matabuena et al., 2018], to provide a solution for the problem of assessing physical condition in a straightforward and accessible way, using complex statistical techniques based on functional data analysis, we have proposed a sub-maximal test to estimate maximal oxygen consumption accurately that only requires a minimal intensity exercise test. However, its implementation with clinical populations is still an open problem, and potential solutions and protocol test adaptations for elderly and chronic patients that compose clinical target populations are discussed in [Matabuena et al., 2019].

We believe that to analyze more comprehensively, realistically, and accurate assessment of physical activity benefit in some environments. Instead of predicting physical exercise association in subjects monitored in free-living conditions with some outcomes such as BMI. A good design of experiments should be performed, where a series of interventions based on different long-term training programs should be proposed in different groups of patients and longitudinally analyze how these patients' health therapies impact in some relevant outcomes such as weight or glucose values, in more control-environments. For pursue this aim, it would be interesting to use a randomized clinical trial. However, perhaps because of cost and operational reasons, it might make more sense to use other

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study designs or even dynamic clinical trials following the SMART methodology or similar [Kosorok and Moodie, 2015], which can be supported by machine learning techniques for dynamic patient treatment assignment, even with observational data, to handle larger patient databases.

In this set-up, the proposed representation would continue to measure and represent variations in physical activity levels over a period given more comprehensively than existing methods. Moreover, we think our method will present more pronounced clinical sensitivity than the analysis performed here, in which patients showed very heterogeneous physical activity patterns as they were monitored in free-living conditions.

The use of digital medicine [Topol, 2019] strategies using biosensors may lead to improved disease management, diagnosis, and prescription. For the advancement of this area, together with precision medicine, it is fundamental to develop a new statistical methodology to handle the complex data that registers healthy patients, such as the functional profiles of physical activity proposed here, and which can be used with data from other biosensors, wearables or smartphones to better register patient health [Li et al., 2017]. Undoubtedly, this is a fascinating field of research, and the new health care revolution has only just begun; according to [Dorsey and Topol, 2020], in coming years, telemedicine will "simply become medicine".

Data Availability

The raw data used in this research is public and can be downloaded at https://www.cdc.gov/nchs/nhanes/index.htm. Data filtering are performed following the analysis [Leroux et al., 2019], and the scripts used for these purpose are freely avalaible at https://andrew-leroux.github.io/rnhanesdata/articles/vignette_prediction.html.

Competing Interests

The authors declare no competing interests.

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