Area under the expiratory flow-volume curve: normative values in the National Health and Nutrition Survey (NHANES) study

Octavian C Ioachimescu,1,2 Kevin McCarthy,3 James K Stoller4

ABSTRACT
The area under the expiratory flow-volume (AEX-FV) loop has been evaluated before as a spirometric tool for assessing respiratory functional impairment. We computed the AEX-FV curves in spirometry tests performed on 20,313 participants in the National Health and Nutrition Examination Survey (NHANES) study. We analyzed 108,939 spirometry tests performed between 2007 and 2012 (5964 children; 14,349 adults). In these tests, we computed the three areas from existing NHANES raw data on instantaneous expiratory flows measured at 0.01 s intervals. Mean best-trial measurements for AEX-FV were 3.4 in boys, 2.8 in girls, 11.8 in men and 7.7 L²/s in women. We characterized indices of central tendency and dispersion of the measurements (eg, means and fifth percentiles—lower limits of normal) by age group (children vs adults), gender, race or ethnicity group and effort grading. Simple regression equations using logarithmic transformations of the above areas and using age, gender and height as inputs provided good predictive ability for the variable AEX-FV.

Regular, digital spirometry could and should make available to clinicians and researchers the area under the curves for flow versus volume graph, providing additional tools in our armamentarium to evaluate ventilatory impairments and patterns, and possibly respiratory disability.

INTRODUCTION
Normative values or lower limits of normal (LLN) for respiratory function are generally dependent on the subjects’ demographic and anthropometric characteristics such as race, gender, age, height and weight.1,2 In practice, for every measured lung volume or flow, calculated volume or capacity, values below the fifth percentiles (or z scores ≤ −1.645) of gender and race-referenced healthy individuals define the LLN. The most important spirometric parameters that are validated and widely used in respiratory physiology, clinical practice and trial assessments are derived from the expiratory phase of testing: (forced) vital capacity (FVC or VC), forced expiratory volume in 1 s (FEV₁), forced expiratory volume in 6 s (FEV₆), instantaneous isovolumic flows at 25%, 50% or 75% of FVC, or FEF₂₅, FEF₅₀, and FEF₇₅, respectively, and occasionally, forced expiratory flow between 25% and 75% of FVC or FEF₂₅–₇₅.

Significance of this study
What is already known about this subject?
⇒ Traditional spirometric measurements provide clinically meaningful information: defining normal versus abnormal values, severity stratification of functional defects and the pattern of impairment (eg, obstruction, restriction, mixed defects, small airway disease).
⇒ In an era of digital signal processing and significant computational capabilities, alternative spirometric measurements, such as the area under the expiratory flow-volume curve, became available.
⇒ Several studies found that area under the expiratory flow-volume loop may become more useful in respiratory functional assessment. So far, no population-based normative data (ie, predicted normal values or lower limits of normal (LLN)) for this measurement have been published.

What are the new findings?
⇒ We computed on a large cohort of US population (National Health and Nutrition Examination Survey (NHANES) study) the areas under flow-volume curves. In addition, we characterized their means and LLNs (fifth percentiles), in both adults and children, and we developed simple regression models that predict these functional parameters by age, gender and height.

How might these results change the focus of research or clinical practice?
⇒ Current study provides normative data for these alternative spirometric measurements. While the value of area under the expiratory flow-volume curve for diagnosis and severity stratification is currently better understood, further characterization of the other two measurements is warranted in both normal individuals and various disease states.
Some of these became important functional parameters more than a century and a half ago (eg, Hutchinson’s VC), while others have been developed and used more extensively in the 20th century. Their importance in pulmonary function testing (PFT) has been quite significant, yet it may have reached a phase of diminishing returns in providing useful and actionable information on respiratory physiology impairments. Nevertheless, several additional measurements are still available from simple spirometry testing, and their usefulness has not been fully evaluated to date.

We previously evaluated an alternative spirometric measurement, area under the expiratory flow-volume (AEX-FV) curve, and its approximations computed from FEF_{25}, FEF_{50}, and FEF_{75} as global tools for diagnosis of obstructive, restrictive or mixed ventilatory impairments, for identification of small airway disorders or bronchodilator responsiveness and for severity stratification of respiratory functional impairments. The area approximations were found to be good surrogates of the actual area, fact especially relevant when the PFT software did not provide the actual results of the integral function of flow by volume.

In this paper, we expand on prior assessments by presenting by the instantaneous flows and the (unequal) intervals of volume, the latter being derived from the formula: delta volume = instantaneous flow multiplied by the time interval.

The data for the raw spirometry curves in the variable SPXRAW were recorded at ATPS (ambient temperature and pressure saturated). For the purpose of these analyses, they were converted to BTPS (body temperature ambient pressure saturated) by using the correction factor provided, that is, multiplying by the variable SPAFACT from the NHANES datasets (online supplemental material).

Descriptive statistical analysis of the available variables was performed. Categorical variables were summarized as frequencies or percentages. Continuous variables were characterized by mean, median and 25th–75th IQR (expressed as the difference 75th minus 25th percentile values), as most distributions were non-Gaussian. The Anderson-Darling test was used for goodness of fit of continuous variables. Since usual transformations did not achieve fitting to normality, we used for comparisons mostly non-parametric methods with native or log-transformed variables (eg, Welch’s analysis of variance (ANOVA), Mann-Whitney or Wilcoxon rank score test or Kruskal-Wallis test, as appropriate). The Levene test was used as the default test to compare for unequal variances (an F test from an ANOVA where the response is the absolute value of the difference of each observation and the group mean).

Statistical analyses were performed using JMP Pro16 software (SAS Institute). Institutional research oversight approvals were obtained to conduct the study.

RESULTS
A total of 108,939 PFT sets from 20,313 participants (5964 children, ie, of age <18 years) were analyzed: 34,857, 36,421 and 37,661 tests from NHANES 2007–2008, 2009–2010 and 2011–2012, respectively (figure 2). Mean age was 11 (range: 6–17, median 11, IQR 6) years in children (49% girls) and 44 (range: 18–79, median 45, IQR 30) years in adults (49% women).

The main anthropometric characteristics and PFT parameters of the combined cohorts are shown in table 1. Among children, race or ethnicity groups were represented as follows: 22%, 29%, 12%, 31% and 6% as non-Hispanic whites, non-Hispanic blacks, non-Hispanic Asians, Hispanics (both Mexican Americans and other Hispanics) and other or multiracial, respectively. Among adults, 36%, 27%, 14%, 21% and 3% were non-Hispanic whites, non-Hispanic blacks, non-Hispanic Asians, Hispanics (both Mexican Hispanics or other Hispanics) and other or multiracial, respectively.

Approximately 37% of the adult participants interviewed about smoking habits reported lifetime smoking of ≥100 cigarettes cumulatively up to the survey date (18% missing...
response rate); they reported starting to smoke cigarettes at a median age of 17 (25th–75th percentiles: 15–20) years. Smoking history, quantified based on the report of number of cigarettes smoked per day at the time they quit, was as follows: mean 20, median 10, 25th–75th percentiles: 2–29 pack-years.

Mean best-trial AEX-FV values were 3.4 in boys and 2.8 in girls (L²/s, p<0.0001); 11.8 in men and 7.7 in women (L²/s, p<0.0001). Figure 3 shows, in bar graph format, medians and LLNs for AEX-FV by gender and age groups, respectively. Figure 4 illustrates, for better illustration of distribution and dispersion, the same area by gender and age groups as box-and-whisker plots (with means) and side histograms. AEX-FV linear fit versus FEV₁, FVC and FEF₂₅–₇₅% was characterized by R² of 0.07, 0.02 and 0.10 in children and 0.01, 0.04 and 0.12 in adults, respectively. Even when analyzed by gender, age group and effort category, R² remained below 0.33, which explains the added value of the new physiologic measurement.

For the AEX-FV variable, we found significant differences by gender and race or ethnicity group (table 2). The AEX variables were larger in black girls and boys, while in adults, they were largest in white men and women (bold values in table 2). Adults and children of Asian ancestry had among the lowest AEX values. Perhaps in keeping with the fact that Hispanics and whites shared the same effects (p<0.0001) remained in multivariate analyses, using native or logarithmic transformations of the three Y variables after adjusting for FET, testing position and their interaction (in all models, R² was 0.75 in both the derivation and the validation sets). Overall in these models, testing position contributed slightly less (variable importance main effect 0.46 for AEX-FV) than the main determinant of the Y variables, that is, FET (main effect 0.54 for AEX-FV by dependent resampled method using k nearest neighbors’ technique).

In adults and children with spirometry characterized by good effort, reproducible and acceptable curves by visual inspection (NHANES 2009–2012 selected group—figure 2), the calculated AEX-FV measurements were predicted by models that included the following parameters: age, gender and height, as weight and race or ethnicity group were trimmed off due to their minor, yet significant contribution (figure 5). More complex models based on generalized regression or neural network approaches did not provide considerable improvements to warrant their inclusion here (data not shown). Also, cigarette smoking status or intensity, as established from adult participants’ interviews, as well the serum concentrations of cotinine (a metabolite of nicotine) or urinary concentrations of NNAL (4-(methylnitrosamino)−1-(3-pyridyl)−1-butanol, a metabolite of a tobacco-specific nitrosamine) did not influence the AEX-FV measurements (data not shown).

Among all valid tests (ATS grades A, B or C, plateau present and FET >6 s), 18,897 subjects were tested only with ‘baseline’ spirometry (n=66,307), while 1511 individuals underwent both pre-bronchodilator and post-bronchodilator testing (due to initial FEV₁/FVC ratios <LLN, n=5290). After bronchodilator administration, best AEX-FV increased from 3.0 to 4.6 in children and from 8.7 to 17.0 L²/s in adults.

DISCUSSION
In this investigation, we computed in a large cohort representative of the US population, the alternative spirometric measurement called AEX-FV curves. Additionally, we characterized indices of central tendency and we identified LLN (as fifth percentiles of the distributions) for various subgroups. Further, we developed a simple regression model for these areas, based on subjects’ age, height and gender, which could be used as predictive equations for this population. These new measurements, easily made available with any modern, digital spirometry software, could become new tools in our armamentarium to characterize global respiratory function impairments.

Several years ago, a few PFT vendors made available to clinicians and researchers, together with other spirometric measurements, the AEX for the flow-volume loop, which is, in fact, the integral function of expiratory flow by the volume loop. Either unnoticed, not well understood, or simply unexplored, it took a few years for the flow-volume loop to be studied in more detail and then used to assess various conditions. However, the idea is by no means completely new, as other investigators have entertained the

Figure 2 Flow diagram of the study (N: number of participants, n: number of spirometry tests). ATS, American Thoracic Society; FET, forced expiratory time; NHANES, National Health and Nutrition Examination Survey.
A few comments are warranted here. First, AEX-FV variables were the largest in black children of both genders, while in adults, they were the largest in whites (Table 2). While still unclear why, it is our hypothesis that this may

idea of exploring in other ways flow-volume loop concavity, defects beyond the classic obstructive–restrictive–mixed small airway disease categorization, more global assessment tools, etc.19–22
be due to different rates of truncal growth in various racial or ethnic groups (which directly influences their lung function). Second, both children and adults of Asian heritage had among the lowest AEX-FV values; however, this group

Figure 3  Median values and lower limit of normal ((LLN) fifth percentile) for best area under the expiratory flow-volume (AEX-FV) curves by age group (<18 or >18 years) and gender. BTPS, body temperature ambient pressure saturated.

Figure 4  Box-and-whisker plots (means shown) and side histograms of best area under the expiratory flow-volume (AEX-FV) curves by gender and age group (<18 years in upper panel and >18 years of age in lower panel). BTPS, body temperature ambient pressure saturated.

Table 2  Mean best value for AEX-FV by gender and race or ethnicity group

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Table 3  Best AEX-FV (BTPS, L/s)

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Effort grades: A, exceeds the minimum ATS criteria (three acceptable and two reproducible curves); B, meets ATS criteria (three acceptable and two reproducible curves); C, potentially usable value, but does not meet ATS standards, and estimates are usually based on two curve results with values within 200 mL of each other; D, questionable results, use with caution.

*AEX-FV, area under the expiratory flow-volume; ATS, American Thoracic Society; BTPS, body temperature ambient pressure saturated.
was under-represented in the NHANES cohorts. Third, the differences between whites and Hispanics were both statistically and clinically relevant, while the FEV₁, FVC and FEV₁/FVC were very similar, perhaps in line with the fact that they share same GLI predictive equations. This points toward the fact that these new spirometric measurements may be able to better separate normal lung function in non-Hispanic whites versus Hispanics of either Mexican or non-Mexican origin.

Several authors have also derived and published the past linear regression-based predictive equations for normal AEX-FV, based on subjects’ age, gender and/or height.⁶⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻安倍仓

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Several limitations of this investigation also warrant comment. First, to assure the generalizability of our observations, the computed AEX-FV measurements require further investigation in patients with different pathologies or disease phenotypes, that is, in chronic obstructive pulmonary disease, asthma, small airway disease, restrictive disorders. Second, the 2007–2012 NHANES cohorts included relatively few individuals of Asian origin, hence their normative values may lack the precision of the other ethnic or racial groups. This limitation could be overcome in the future by extending the geographic coverage and the diversity of the pooled tests. Third, the NHANES study did not exclude those with a history of past or present cigarette

Figure 5 Model for the variable LogAEX-FV (natural logarithm of the area under the expiratory flow-volume curve) based on age (years), height (m) and gender (the coefficient is positive for males and negative for females). The main effects listed represent the variable contribution, as assessed by the dependent resampled inputs method (using k nearest neighbors’ technique). BTPS, body temperature ambient pressure saturated; R², per cent of variance explained by the model; RASE, square root of the mean squared prediction error.
smoking (an older criticism of the NHANES cohorts being representative of the ‘normal’ US population). While in our analyses on the 2007–2012 surveys, smoking status and its intensity did not significantly influence neither the normative data nor the LLNs, the effects of recall bias and/or secondary smoking exposure could not be completely eliminated. Fourth, standard spirometry is done today in the sitting position, which was not the default position in the NHANES examinations. Once made available on standard commercial PFT platforms, these assessments need to be reproduced in future cohorts and testing conditions. Fifth, the AEX measurements may not be easily available on most spirometry testing equipment at this time. However, digital PFT platforms could very easily resolve the calculation of the AEX for flow-volume curves by computing the integral function of the Y variables versus the X inputs and include them in the standard reporting systems. Lastly, the utility of different AEX measurements needs to be further explored over a broad spectrum of respiratory impairments and disease severities.

CONCLUSION

While traditional spirometry measurements inform clinical management in important ways, it is conceivable that newer measurements may add materially to the diagnostic value of spirometry. Specific questions include: how much actionable information can these new parameters provide about respiratory physiology impairments or levels of disability, and what is the separation between normal and abnormal by using ‘hard’ LLN? In an era of advanced digital signal processing, now is the time to explore new technologies and other innovative ways of assessing respiratory function. Fortunately, several new metrics are still available in spirometry, and their contribution to clinical assessment has yet to be fully evaluated. To address this gap, the current analysis computed actual and predicted values of AEX-FV curves, prompting consideration of how these new parameters can inform clinically meaningful distinctions in patients.

Acknowledgements  These analyses were performed in accordance with the relevant rules, guidelines and regulations (and regulatory approvals obtained from institutional review boards).

Contributors  OCI contributed to concept, data collection and analysis, manuscript writing; KMC and JKS contributed to manuscript writing; OCI is responsible for the overall content as guarantor.

Funding  The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer  OCI is employed by the US federal government; no specific copyright statement is required.

Competing interests  OCI is a Journal of Investigative Medicine Editorial Board member. No other competing interests declared.

Patient consent for publication  Not applicable.

Ethics approval  Emory IRB #00049576/Atlanta VA R&D Ioachimescu-002.

Provenance and peer review  Not commissioned; externally peer reviewed.


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Supplemental (Online) Material:

For NHANES 2007-08, 2009-2010 and 2011-2012 spirometry datasets, the test results for the most frequently used spirometric parameters are included in the files SPX_E, SPX_F and SPX_G, respectively, together with instructions and analytic recommendations. Data on smoking habits were available for adult participants in the files named SMQ_E, SMQ_F and SMQ_G, respectively; serum concentrations of cotinine (a nicotine metabolite) and urinary concentrations of NNAL [4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanonol, a metabolite of a tobacco-specific nitrosamine] were available in the files COTNAL_E, COTNAL_F and COTNAL_G, respectively. In the SPXRAW_E, SPXRAW_F and SPXRAW_G datasets, the variable SPXRAW was made available as a comma-delimited string of numeric values between -64 and 192. These values represent the raw instantaneous flows measured during a forced expiratory maneuver and expressed as changes in exhaled volume (in milliliters) over equal, standard 0.01-second time intervals. In order to compute a timed, cumulative volume estimate, sequential volume-change values are summed over the time period desired. For example, to calculate the FEV_1, consecutive volume-change values are summed from the start of expiration up to and including the measured value at one second (including the 100th value). The total number of data points in a specific comma-delimited string vary from one spirometry curve to another, depending on the duration of a particular expiratory maneuver. The variable SPXPTS in the datasets provided the total number of data points for a particular data curve.

A number of additional variables are available in the NHANES datasets for each individual curve: SPAPOS (spirometry testing position - standing or seated); SPAPLAT (whether an exhalation plateau was achieved during the maneuver); SPAACC (if the individual curve was acceptable by American Thoracic Society or ATS criteria - A, B or C grades); and SPAQEFF (the effort rating for the individual curve, A through F grades). The latter two variables are based on ATS data collection standards: A, exceeds the minimum ATS criteria (3 acceptable and 2 reproducible curves); B, meets ATS criteria (3 acceptable and 2 reproducible curves); C, potentially usable value, but does not meet ATS standards, and estimates are usually based on 2 curve results with values within 200 mL of each other; D, questionable results, use with caution; F: results not valid (none of the spirometry curves were in the latter category).

In all three datasets, survey participants of age 6 to 79 years, who were deemed eligible for spirometry were included. All tests were done using Ohio 822/827 dry-rolling seal volume spirometers (https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/manuals/spirometry_procedures_manual.pdf). The normal predicted values used were those derived on the NHANES III cohort by Hankinson et al.15 Per the NHANES protocol, participants eligible for spirometry performed an initial or ‘baseline’ 15 test
spirometry examination. If certain criteria were met (i.e., FEV₁/FVC < LLN by NHANES III predicted values), participants then underwent a 2nd spirometry examination, after inhaling a β₂-adrenergic bronchodilator. Multiple individual spirometry curves were thus obtained, during both the 1st and the 2nd test spirometry examinations. Given some unintended under- or over-sampling in various NHANES cohorts, in order to accurately reflect the U.S. population characteristics, the recommended NHANES full-sample 2-Year MEC Examination Weight (WTMEC2YR) values were used to analyze the NHANES spirometry data; as such, we used weighted measurements in the analytic reports.

Some of the prior models for PFT normal values used regular linear regression (standard least squares method) by gender and race or ethnicity group, relying on predictive variables such as age, height and occasionally weight. In this set of analyses, both regular regression and generalized (‘regularized’ or ‘penalized’ personality) regression models were performed, employing optimization techniques such as ridge regression, lasso, elastic net and double lasso methods (with or without adaptive features), and using either native values, or logarithmic, gamma, Weibull or SHASH (sinh-arcsinh) transformations of the response variables. Among the distributions fit of the response variables, the logarithmic transformation provided an acceptable trade-off between ease of implementation and adjustment to normality, so we used it in the presented models, which were regular regression models. In various models investigated, we assessed the AEX-FV as Y variable versus the following inputs (which on univariate analyses were independent predictors of the Y variable): gender; race or ethnicity group; age, height, weight and their interactions; forced expiratory time; and effort grade. For internal validation of all models developed, we randomly partitioned the combined NHANES cohorts into a training set (70%) and a validation set (30%). We dropped from the model the variables that contributed to the validation R² (which the model tried to maximize) by less than 0.02, albeit significant on multivariate analyses. Significant interactions on multivariate analyses were also ignored if their estimates or beta coefficients were very small (<0.001). In each model, we generated variable importance reports, which compute indices of factor contribution that are independent of the model type and fitting method used, estimating variability in the predicted response based on a range of variation for each factor. As such, if the variation in one factor causes a high variability of the response, then that effect is important relative to the model. We used two approaches: (1) the independent resampled inputs method, in which for each factor, Monte Carlo samples are obtained by resampling its set of observed values (this option works best when the factors are uncorrelated and their values are not represented by a uniform distribution); and (2) the dependent resampled inputs method, in which factor values are constructed from observed combinations using a k-nearest neighbors’ approach in order to account for
correlation (this option treats observed variance and covariance as representative of the covariance structure for the model’s likely correlated factors). Factors that contributed by less than 5% to the total effect by both methods were excluded. The maximum likelihood estimation method was preferred to ridge, lasso, elastic net or double lasso optimized regression methods if the $R^2$ did not increase by more than 0.02. Similarly, neural networks (machine learning algorithms) were not included if they did not lead to an improvement in $R^2$ by more than 0.02 over the generalized regression models.