Clinical Data-Driven Classification of Pre-Frailty Reveals Sex-Specific Patterns – Data from the Berlin Aging Study II (BASE-II)

Supplementary figure legends

Supplementary table 1: Characteristics, measurables and definitions of the 5-item *Fried et al*. frailty phenotype including adjustments for BASE-II. As reported by *Fried et al*. in 2001 [12], modifications by *Spira et al*. in 2015 [29]. BMI body mass index

Supplementary table 2: Summary of features removed during pre-processing of the models. The values in parenthesis represent the applied thresholds for each context and step of feature removal. For the continuous features, the variance-to-mean ratio was measured to define near-constancy. The categorical features were removed if the minority class sample size is below or equal the number of cross-validation splits. Continuous, mixed-type, and categorical associations were measured by the Spearman rank coefficient, the point bi-serial correlation coefficient, and the Cramér's V correlation coefficient corrected for binary and discrete features, respectively. p95 95th percentile, * equalling 0.6499, ** equalling 0.6621

Supplementary table 3: Minimum information required for medical AI reporting. Description of the minimum information for medical AI reporting as suggested by and adapted here from *Hernandez-Boussard et al*. [86]. In brief, the most important information is shown on the 4 main chapters: study population and setting (1), participant demographic characteristics (2), model architecture (3), and model evaluation (4). SD standard deviation, ROC receiver operating characteristics, CV cross-validation, DOR diagnostics odds ratio, TP true positive, TN true negative

Supplementary table 4: Preselected parameter ranges used in exhaustive grid search. The table shows the different preselected parameter ranges separated into the categories of SVM classifier parameters (1), resampling parameters (2), feature transformation parameters (3), and feature selection parameters (4). SVM support vector machine, RBF radial basis function, SMOTE synthetic minority over-sampling technique, LDA linear discriminant analysis, PCA principal component analysis

Supplementary table 5: BASE-II cohort characteristics of the 30 most predictive features of the complete and subgroup data-driven models show significant differences in pre-frail/frail and non-frail participants. Cohort characteristics of the top 30 most predictive features in the complete (top 30) and single subgroup (bottom 30) data-driven men (A) and women (B) models. P values obtained with the Cramér's V correlation algorithm corrected for binary and discrete data types. Continuous features underwent Welch's unequal variance T-test after assessing the equality of variances between the non-frail and pre-frail/frail group with the Levene's test. SD standard deviation, BMI body mass index, ALM appendicular lean mass, BMD bone mineral density, 2D-4D digit 2-to-digit 4 ratio, BMC bone mineral content, HDL high density lipoprotein, LDL low density lipoprotein, ns non-significant, $0.01 < * < 0.05$, $0.001 < ** < 0.01$, $0.0001 < *** < 0.001$, $0.00001 < **** < 0.0001$

Supplementary figure 1: Sex-specific differences across the main continuous features associated with physical frailty observed between non-frail and pre-frail/frail participants. Welch's unequal variance T-test (assessed by the Levene's test) of hallmark frailty risk factors between non-frail and pre-frail/frail participants in BASE-II (A); and the context-specific distribution of some of the most prominent frailty hallmark risk factors (B); showing Welch's t-test significance threshold (grey, dashed line) at 0.05 and the context-specific p-values per feature in negative log base 10 of mixed-sex (black), men (yellow), women (blue), pre-frail/frail and non-frail (hatched) participants. BMI body mass index, ALM appendicular lean mass, WHR waist-hip ratio

Supplementary figure 2: Sex-specific differences across the main binary and discrete features associated with physical frailty observed between non-frail and pre-frail/frail participants. Corrected Cramér's V coefficient of hallmark frailty risk factors between non-frail and pre-frail/frail participants in BASE-II (A); and the context-specific distribution of some of the most prominent frailty hallmark risk factors (B); showing Corrected Cramér's V significance threshold (grey, dashed line) with a p-value of 0.05 and the context-specific p-values per feature in negative log base 10 of mixed-sex (black), men (yellow), women (blue), pre-frail/frail and non-frail (hatched) participants.

Supplementary figure 3: Data-type specific correlation analysis of pre-processed data show weak associations in the complete (A) and best performing subgroup (B) data-driven models. Context and data type specific

correlation analysis of the input features for the machine-learning classification pipeline after removing constant, near constant, and mutually high correlated features according to the specific model configurations (cf. **Fig. 3**). Spearman Rank correlation (continuous – continuous association), corrected Cramér's V (binary/discrete – binary/discrete association) and point bi-serial correlation (binary/discrete – continuous association) algorithms were used to study the associations between each input feature. The columns represent the mixed-sex, men, and women groups, respectively.

Supplementary figure 4: Feature permutation importance behaviour in the complete data-driven models. The corresponding violin plots visualize the distributions of the different permutation exercises (n=1000 for mixed-sex, n=500 for men and women), ranked by the absolute mean CV score loss. CV cross-validation

Supplementary figure 5: Feature permutation importance behaviour in the single subgroup data-driven models. The corresponding violin plots visualize the distributions of the different permutation exercises (n=1000 for mixed-sex, n=500 for men and women), ranked by the absolute mean CV score loss. CV cross-validation

Supplementary figure 6: Frailty proportion in BASE-II increases with the accumulation of deficits. Participants in BASE-II are more likely to be frail with the accumulation of the three deficits heart insufficiency, vitamin D deficiency, and sarcopenia. It is notable that among the participants without any of the three deficits, 21.75%, 23.53%, and 19.71% are still considered frail in mixed-sex, men, and women, respectively. Mixed-sex total count of 0 deficit: 97/446, 1 deficit: 185/580, 2 deficits: 84/160, 3 deficits: 14/24. Men total count of 0 deficit: 56/238, 1 deficit: 75/267, 2 deficits: 39/75, 3 deficits: 8/13. Women total count of 0 deficit: 41/208, 1 deficit: 110/313, 2 deficits: 45/85, 3 deficits: 6/11.

Supplementary figure 7: Frailty proportion decreases with the independent and accumulated gastroenterology and ophthalmology medication intake in BASE-II men. While both independent drugs and their accumulation show lower frailty proportion in men, the opposite can be observed in the women group, where specifically ophthalmological medications show a strong increase in frailty proportion with the increasing amount of medication intake.

Supplementary figure 8: Frailty proportion increases with the independent and accumulated alcohol and dental medication information in BASE-II women. Among the top discrete features of the *women-ALL* model is the number of alcoholic beverages (regular and distilled) and the intake of dental medication. As they are all representing increasing consumption with higher values, the combination of features shows an increasing frailty proportion among women especially consuming alcoholic beverages, while the intake of dental medications alone shows the highest proportion of frail participants taking 1 dental drug.

Supplementary figure 9: Single continuous features show weak associations with frailty. The most contributing continuous features of the complete and subgroup data-driven men (A) and women (B) models are represented between non-frail and pre-frail/frail participants of the mixed-sex, men, and women group using the model-specific scaling approaches (min-max, robust, or standard scaled). The error bars visualize the mean and standard deviation within each group. The letter-value plots show the median and the corresponding percentiles, equivalent to the number of layers. The p-values were calculated using the Welch's unequal variance T-test, with the equality of variances assessed by the Levene's test. $0.01 < * < 0.05$, $0.001 < ** < 0.01$, $0.0001 < *** < 0.001$, $0.00001 < **** < 0.0001$

Supplementary figure 10: Independent feature analysis suggests that the best performing features of the models were selected due to their combinatory effect. Inferential analysis of the mean z-score differences in continuous features (A), and Cramér's V score corrected for binary and discrete features (B) between non-frail and pre-frail/frail participants, with the bordered annotations being among the 30 most important features of the respective models by sex (*ALL* model and subgroup model combined). The p-value threshold was in both analyses adjusted by the Bonferroni method and are represented by the horizontal dashed lines. The vertical dotted lines show the respective statistical threshold. In A, the absolute z-score threshold of 0.2 was arbitrary set to represent a variation of at least 20% of the population standard deviation shifted towards frailty (blue features are lower, and red features higher in frail participants), and the p-value was calculated using the Welch's unequal variance T-test, with the equality of variances assessed by the Levene's test. In B, the corrected Cramér's V threshold of 0.1 represents a small association of the respective feature and frailty, considering a degree of freedom of one (comparison between two classes).

Supplementary figure 11: Multivariate analysis of variance confirms the combinatory effect of the ten most contributing features in dispersing non-frailty from frailty. Each model included their specific resampling and scaling technique according to the best performing configuration. Combinations from single to all ten features (1023 combinations in total) were tested and the performance was measured by the Wilk's lambda coefficient and represented as "1-Wilk's lambda". The resulting p-value was log base-10 transformed. Significant combinations are marked in red while the best performing set of n features are marked in dark red star shapes and annotated with the respective n. Single features are represented by triangles, with significant single features coloured in black. The table underneath the figure shows the top ten features in decreasing performance order and the components of the n best combinations are highlighted in dark red (black in case of single top significant feature). The p-value threshold of 0.05 was adjusted by the Bonferroni method and is visualized by the horizontal dashed line. BF body fluids, PM physical measurements, RUS random under-sampling, SMOTE synthetic minority over-sampling technique, sign. significant

Supplementary tables

Tab. S1: Characteristics, measurables and definitions of the 5-item *Fried et al*. frailty phenotype including adjustments for BASE-II.

A) Characteristics of Frailty	B) Cardiovascular Health Study Measure [12], and BASE II adjustments [29]
Shrinking - Weight loss (unintentional) - Sarcopenia (loss of muscle mass) 	**Weight loss** - >10 lbs (4.5 kg) lost unintentionally in the prior year - **BASE II:** > 5% of the body weight lost unintentionally in the prior year
Weakness 	**Grip strength** - lowest 20% (by gender and BMI) - **BASE II:** no adjustments
Poor endurance 	**Exhaustion** - self-report - **BASE II:** no adjustments
Slowness 	**Gait** - walking time/15 feet (4.6 m); slowest 20% (by gender and BMI) - **BASE II:** timed Up&Go test, subjects needing >10 seconds
Low activity 	**Physical activity** - lowest 20%; ♂ < 383 Kcals/week; ♀ < 270 Kcals/week - **BASE II:** self-report to the question 'Are you seldom or never physically active?'
C) Presence of Frailty	**≥ 3 positive criteria:** positive for frailty phenotype **1 or 2 positive criteria:** intermediate frail or pre-frail

Tab. S2: Summary of features removed during pre-processing of the models.

Context	Near-constant continuous features	Near-constant categorical features	Strictly constant features	Continuous associations	Mixed-type associations	Categorical associations
Mixed ALL	2 (0.001)	8 (10)	11	143 (0.9)	3 (0.9)	2 (0.9)
Mixed BF	3 (0.01)	0 (10)	0	7 (0.9)	0 (0.9)	0 (0.9)
Men ALL	2 (0.001)	10 (10)	13	221 (p95) *	7 (0.6)	5 (0.6)
Men PM	1 (0.001)	0 (10)	7	27 (0.9)	1 (0.9)	0 (0.9)
Women ALL	4 (0.001)	12 (10)	12	217 (p95) **	7 (0.6)	6 (0.6)
Women BF	3 (0.01)	0 (10)	0	8 (0.9)	0 (0.9)	0 (0.9)

Tab. S3: Minimum information required for medical AI reporting.

Features	Information	Notes
1. Study population and setting		
Population	Older people	Age > 60 years
Study setting	Cross-sectional clinical ageing study	Follow-up study of BASE
Data source	Multiple sources	Laboratory, survey, and clinical measurements
Cohort selection	Selection within greater metropolitan area of Berlin by age and sex	According to the German Socio-Economic Panel Study
2. Participant demographic characteristics		
Age (years)	Mean (± SD): 68.73 years (± 3.71)	
Sex	Women: 50.66% Men: 49.34%	
Race	Not provided	
Ethnicity	German: 0.99 Others: 0.01	From the BASE-II cohort profile publication [42]
Socioeconomic status	Employment: 0.14 High school degree: 0.51 Divorced: 0.29	From the BASE-II cohort profile publication [42]
3. Model architecture		
Model output	Frailty phenotype	Presence or absence of the Fried et al. frailty phenotype
Target user	Researchers, clinicians, physicians, geriatricians	
Data splitting	80% and 20% Training and hold-out test	
Gold standard	Fried et al. 5-item frailty phenotype for frailty phenotype [12]	Adjusted for BASE-II [29]
Model task	Binary classification	
Model architecture	Support Vector Machines classifier with linear kernel	
Input features	942 total input features before processing <200 after processing 11 subgroups of features	Provided in detail for all models
Missingness	Features removed with less than 80% coverage Missing values imputed in reference to training set	Mean for continuous features Mode for binary and discrete features
Data pre-processing	(Near-) constancy checks Removing highly correlated features Removing input used for engineering	1 unique value, non-zeros below cross-validation splits, and variance-to-mean threshold Corrected Cramér's V, Spearman Rank and Point bi-serial coefficient thresholds Features used to engineer other features
Normalization	Standard, minmax, and robust scaler	Provided in detail for all models
Imbalance resampling	Random under-sampling and synthetic minority over-sampling	Provided in detail for all models
Dimensionality reduction	Principal component and linear discriminant analysis	Provided in detail for all models
Feature importance	Best model score difference after n times feature permutation	With n=500 for both men and women, n=1000 in mixed-sex
Feature extraction	Top 30 context-specific important features re-used as input features	Reset of parameter grid while conserving technical model structure
4. Model evaluation		
Optimization	Model optimized with exhaustive parameter grid search	Provided in detail for all models
Model selection scoring	F-β-2	Prioritizing recall over precision
Performance monitoring	F-β-scores (β-1, β-2) Diagnostics odds ratio (DOR) Receiver operating characteristics (ROC) True positives and negatives	F-β-scores and ROC in CV, training, and test set DOR in training and test set TP and TN in training and test set
Internal model validation	Internal 10-fold cross-validation during training	
External model validation	Hold-out test set (20%)	
Transparency	Clinical Data not publicly available, code is available on GitHub	https://github.com/sysbiolux/Clinical_Biomarker_Detection

Tab. S4: Preselected parameter ranges used in exhaustive grid search.

Parameter	Value range	Notes
1. SVM classifier parameters		
Kernel	[linear; polynomial; RBF; sigmoid]	polynomial, RBF, and sigmoid being non-linear kernels
Regularization	[0.01; 0.1; 1; 10; 100; 1000; 10000; 100000; 1000000]	Used by all SVM kernels
Shrinking	[True; False]	Used by all SVM kernels
Tolerance	[0.0001; 0.001; 0.01]	Used by all SVM kernels
Gamma	[Scale; Auto; 0.00001; 0.0001; 0.001; 0.01; 0.1; 1.0; 10]	Only for non-linear SVM kernels
Degree	[2; 3; 4; 5]	Only for polynomial SVM kernel
Coef0	[0.0; 0.01; 0.1; 0.5]	Only for both polynomial and sigmoid SVM kernels
2. Resampling parameters		
SMOTE k-neighbours	[3; 5; 7]	Only if SMOTE resampling
3. Feature transformation parameters		
LDA shrinkage	[None]	Allowed for all SVM kernels
LDA priors	[None]	Allowed for all SVM kernels
LDA tolerance	[0.0001; 0.001; 0.01]	Allowed for all SVM kernels
Linear PCA tolerance	[0.0]	Allowed for all SVM kernels
Non-linear PCA kernel	[polynomial; RBF; sigmoid]	Only if SVM kernel is linear
Non-linear PCA tolerance	[0.0; 0.001; 0.01]	Only if SVM kernel is linear
Non-linear PCA gamma	[None; 0.1; 1.0; 10.0]	Only if SVM kernel is linear
Non-linear PCA degree	[2; 3; 4; 5]	Only if SVM kernel is linear
Non-linear PCA coef0	[0.1; 0.5; 1.0]	Only if SVM kernel is linear
4. Feature selection parameters		
K best categorical	[1; 2; 5; 10; 15]	Allowed for all SVM kernels
LDA component	[1]	Allowed for all SVM kernels
Linear PCA component	[2; 5; 10; 15; 20]	Allowed for all SVM kernels
Non-linear PCA component	[2; 5; 10; 15; 20]	Only if SVM kernel is linear

Tab. S5: BASE-II cohort characteristics of the 30 most predictive features of the complete and subgroup data-driven models show significant differences in pre-frail/frail and non-frail participants.

A) Most important features (men-ALL)	Non-frail men (N=513, 33.93%)	Pre-frail / frail men (N=233, 15.41%)	P-value
Heart insufficiency	0: 451 1: 62	0: 185 1: 48	2.37e-03 (**)
Gastroenterology medications (U)	0: 416 1: 83 2: 14	0: 199 1: 32 2: 2	1.65e-01 (ns)
Age (years) mean ± SD; [min, max]	68.68 ± 3.46 [60.16, 78.12]	69.76 ± 4.33 [60.74, 82.79]	8.62e-04 (***)
Ophthalmology medications (U)	0: 465 1: 36 2: 12	0: 214 1: 17 2: 2	3.84e-01 (ns)
Height (cm) mean ± SD; [min, max]	176.09 ± 6.17 [160.0, 194.8]	174.53 ± 6.21 [156.3, 191.0]	1.46e-03 (**)
Mean corp. hemogl. conc. (g/dL) mean ± SD; [min, max]	34.43 ± 0.99 [31.3, 37.5]	34.43 ± 1.00 [31.3, 37.6]	9.66e-01 (ns)
Head fat (g) mean ± SD; [min, max]	1171.00 ± 147.21 [861.82, 1710.11]	1189.52 ± 157.57 [826.91, 1663.2]	1.20e-01 (ns)
Testosterone level (ng/mL) mean ± SD; [min, max]	4.65 ± 1.97 [0.05, 14.19]	4.40 ± 1.94 [0.05, 11.69]	1.08e-01 (ns)
Trail Making Test Part B (s) mean ± SD; [min, max]	89.35 ± 34.73 [35.0, 266.0]	95.28 ± 37.92 [28.0, 295.0]	3.63e-02 (*)
Sodium level (mmol/L) mean ± SD; [min, max]	139.35 ± 2.68 [125.0, 147.0]	139.51 ± 2.76 [131.0, 148.0]	4.57e-01 (ns)
Eosinophilia (G/L) mean ± SD; [min, max]	0.18 ± 0.15 [0.02, 2.17]	0.19 ± 0.12 [0.01, 0.78]	7.05e-01 (ns)
Estradiol level (pmol/L) mean ± SD; [min, max]	89.03 ± 42.56 [9.2, 277.0]	89.90 ± 46.12 [9.2, 282.7]	8.02e-01 (ns)
ALM BMI Sarcopenia	0: 468 1: 45	0: 200 1: 33	2.57e-02 (*)
Sex hormone binding globulin (nmol/L) mean ± SD; [min, max]	44.57 ± 16.40 [8.99, 136.1]	45.90 ± 18.32 [14.8, 137.3]	3.22e-01 (ns)
Kitchen waste (g/day) mean ± SD; [min, max]	3.16 ± 1.57 [0.27, 6.97]	3.17 ± 1.56 [0.5, 7.64]	9.12e-01 (ns)
ALM BMI ratio mean ± SD; [min, max]	0.96 ± 0.13 [0.63, 1.47]	0.89 ± 0.11 [0.59, 1.31]	3.65e-10 (****)
Thoracic spine area (cm²) mean ± SD; [min, max]	155.80 ± 24.29 [80.3, 282.1]	151.24 ± 23.84 [72.03, 212.16]	1.70e-02 (*)
Nonadecylic acid (g/day) mean ± SD; [min, max]	0.005 ± 0.004 [0.0, 0.03]	0.005 ± 0.003 [0.0, 0.02]	9.54e-01 (ns)
Cytomegalovirus IgG titer (IU/mL) mean ± SD; [min, max]	5.82 ± 5.83 [0.26, 41.72]	6.75 ± 7.47 [0.28, 49.37]	9.37e-02 (ns)
Fell in the past 12 months	0: 490 1: 23	0: 207 1: 26	6.48e-04 (***)
Trail Making Test Part A (s) mean ± SD; [min, max]	40.77 ± 12.80 [16.0, 92.0]	43.42 ± 13.93 [19.0, 120.0]	1.11e-02 (*)
Appendicular lean mass (g) mean ± SD; [min, max]	25486.42 ± 3064.90 [18910.53, 35100.72]	24747.02 ± 3173.83 [17423.04, 35815.85]	2.62e-03 (**)
Chloride level (mmol/L) mean ± SD; [min, max]	102.09 ± 3.05 [94.0, 111.0]	102.09 ± 2.69 [94.0, 112.0]	9.94e-01 (ns)
Non resorb. oligosaccharides (g/day) mean ± SD; [min, max]	0.42 ± 0.16 [0.14, 1.6]	0.42 ± 0.17 [0.19, 1.25]	6.69e-01 (ns)

B) Most important features (women-ALL)	Non-frail women (N=515, 34.06%)	Pre-frail / frail women (N=251, 16.60%)	P-value
Alcohol distilled drinks (AU)	0: 320 1: 148 2: 27 3: 13 4: 5 5: 2	0: 147 1: 73 2: 14 3: 11 4: 4 5: 2	6.46e-01 (ns)
Heart insufficiency	0: 412 1: 103	0: 165 1: 86	1.73e-05 (****)
ALM BMI Sarcopenia	0: 500 1: 15	0: 216 1: 35	6.57e-09 (****)
Dental medications (U)	0: 431 1: 82 2: 2	0: 181 1: 68 2: 2	8.58e-04 (***)
Appendicular lean mass (g) mean ± SD; [min, max]	17290.69 ± 2457.20 [9284.27, 25307.89]	17128.66 ± 2564.11 [11970.53, 26183.56]	3.99e-01 (ns)
Appendicular lean mass (kg) mean ± SD; [min, max]	17.29 ± 2.46 [9.28, 25.31]	17.13 ± 2.56 [11.97, 26.18]	3.99e-01 (ns)
Alcohol amount (AU)	0: 454 1: 58 2: 3	0: 211 1: 35 2: 4	1.53e-01 (ns)
Correct wordlist learning total score mean ± SD; [min, max]	23.18 ± 2.79 [15.0, 30.0]	22.74 ± 3.18 [9.0, 29.0]	5.20e-02 (ns)
Wordlist discriminability z score mean ± SD; [min, max]	0.12 ± 0.70 [-3.16, 0.95]	0.11 ± 0.72 [-2.54, 0.87]	8.98e-01 (ns)
Trail Making Test Part B (s) mean ± SD; [min, max]	84.84 ± 29.63 [36.0, 238.0]	94.49 ± 33.71 [42.0, 233.0]	5.80e-05 (****)
Relative leukocyte telomere length (T S ratio) mean ± SD; [min, max]	1.08 ± 0.19 [0.58, 1.79]	1.09 ± 0.19 [0.38, 1.71]	6.13e-01 (ns)
Fail to stop drinking alcohol (AU)	0: 511 1: 3 3: 1	0: 244 1: 5 4: 1	1.33e-01 (ns)
Gamma globulins (%) mean ± SD; [min, max]	14.72 ± 2.27 [9.1, 22.2]	14.63 ± 2.76 [5.5, 27.2]	6.69e-01 (ns)
Semantic animal words fluency score mean ± SD; [min, max]	26.38 ± 5.88 [9.0, 47.0]	25.15 ± 5.78 [10.0, 44.0]	6.72e-03 (**)
Kitchen waste (g/day) mean ± SD; [min, max]	2.47 ± 1.14 [0.24, 5.46]	2.44 ± 1.05 [0.4, 6.23]	7.26e-01 (ns)
Morbidity Index without metastasis	0: 222 1: 162 2: 81 3: 36 4: 8 5: 4 8: 2	0: 86 1: 66 2: 53 3: 25 5: 10 4: 8 6: 3	1.98e-04 (***)
Apolipoprotein B level (g/L) mean ± SD; [min, max]	0.99 ± 0.24 [0.36, 2.06]	0.98 ± 0.21 [0.51, 1.63]	7.50e-01 (ns)
Vitamin D deficiency	0: 267 1: 248	0: 97 1: 154	5.96e-04 (***)
Albumin in urine (mg/L) mean ± SD; [min, max]	13.11 ± 29.26 [1.5, 397.5]	14.51 ± 41.72 [1.5, 579.3]	5.91e-01 (ns)
Haemoglobins (g/dL) mean ± SD; [min, max]	13.27 ± 0.84 [10.5, 16.4]	13.24 ± 0.87 [11.0, 16.9]	6.77e-01 (ns)
Left 2D 4D digit ratio mean ± SD; [min, max]	0.97 ± 0.03 [0.86, 1.11]	0.97 ± 0.03 [0.89, 1.07]	4.65e-01 (ns)
Trail Making Test B A ratio mean ± SD; [min, max]	2.25 ± 0.75 [0.63, 6.56]	2.34 ± 0.71 [0.83, 5.06]	1.13e-01 (ns)
Alanine aminotransferase level (U/L) mean ± SD; [min, max]	19.52 ± 8.88 [2.0, 140.0]	19.76 ± 9.16 [5.0, 88.0]	7.30e-01 (ns)
Height (cm) mean ± SD; [min, max]	163.41 ± 6.06 [146.0, 182.5]	161.63 ± 6.18 [144.0, 176.0]	1.68e-04 (***)

Thrombocytes (G/L) mean ± SD; [min, max]	211.99 ± 55.88 [52.0, 648.0]	211.40 ± 53.09 [33.0, 437.0]	8.91e-01 (ns)	**Tumours without metastasis (U)**	0: 465 2: 50	0: 218 2: 33	1.51e-01 (ns)
Left rib area (cm²) mean ± SD; [min, max]	138.74 ± 26.83 [73.21, 214.48]	141.23 ± 30.10 [66.92, 217.67]	2.81e-01 (ns)	**Indirect bilirubin level (mg/dL)** mean ± SD; [min, max]	0.44 ± 0.15 [0.18, 1.22]	0.42 ± 0.15 [0.11, 1.04]	8.40e-02 (ns)
Transferrin level (mg/L) mean ± SD; [min, max]	252.05 ± 31.74 [169.0, 361.0]	252.50 ± 33.46 [125.0, 365.0]	8.62e-01 (ns)	**Sex hormone binding globulin (nmol/L)** mean ± SD; [min, max]	60.91 ± 26.86 [15.4, 229.0]	57.54 ± 25.64 [14.4, 162.0]	9.87e-02 (ns)
Galactose (g/day) mean ± SD; [min, max]	0.53 ± 0.44 [0.03, 2.21]	0.56 ± 0.47 [0.04, 2.37]	4.19e-01 (ns)	**ALM BMI ratio** mean ± SD; [min, max]	0.68 ± 0.10 [0.42, 1.03]	0.64 ± 0.11 [0.38, 0.93]	3.19e-07 (****)
Reticulocytes (%) mean ± SD; [min, max]	1.17 ± 0.37 [0.4, 2.8]	1.25 ± 0.40 [0.5, 2.5]	6.54e-03 (**)	**Inorganic phosphate level (mmol/L)** mean ± SD; [min, max]	1.12 ± 0.13 [0.74, 1.51]	1.11 ± 0.14 [0.74, 1.48]	6.37e-01 (ns)
Circulating IL 10 (%) mean ± SD; [min, max]	0.86 ± 2.08 [0.0, 25.38]	0.77 ± 1.36 [0.0, 10.73]	5.32e-01 (ns)	**Albumin level (%)** mean ± SD; [min, max]	62.59 ± 3.06 [51.5, 70.0]	61.92 ± 3.49 [50.4, 70.4]	1.01e-02 (*)

Most important male features (men-PM)	**Non-frail men** (N=513, 33.93%)	**Pre-frail / frail men** (N=233, 15.41%)	**P-value**	**Most important features (women-BF)**	**Non-frail women** (N=515, 34.06%)	**Pre-frail / frail women** (N=251, 16.60%)	**P-value**
Trunk fat (g) mean ± SD; [min, max]	13812.02 ± 4071.45 [3965.92, 28361.59]	15024.44 ± 4742.30 [4878.38, 33258.54]	3.72e-04 (***)	**Vitamin D deficiency**	0: 267 1: 248	0: 97 1: 154	5.96e-04 (***)
ALM BMI ratio mean ± SD; [min, max]	0.96 ± 0.13 [0.63, 1.47]	0.89 ± 0.11 [0.59, 1.31]	3.65e-10 (****)	**Estradiol level (pmol/L)** mean ± SD; [min, max]	35.73 ± 59.27 [9.2, 817.2]	44.03 ± 60.11 [9.2, 471.4]	7.03e-02 (ns)
Trunk mass (g) mean ± SD; [min, max]	41614.36 ± 6726.38 [24496.4, 72459.25]	42853.48 ± 8159.18 [25029.34, 74016.79]	4.34e-02 (*)	**Indirect bilirubin level (mg/dL)** mean ± SD; [min, max]	0.44 ± 0.15 [0.18, 1.22]	0.42 ± 0.15 [0.11, 1.04]	8.40e-02 (ns)
Left arm fat (%) mean ± SD; [min, max]	31.03 ± 5.85 [13.71, 52.38]	33.04 ± 5.82 [16.98, 51.9]	1.53e-05 (****)	**Monocytes (G/L)** mean ± SD; [min, max]	0.40 ± 0.14 [0.16, 1.1]	0.43 ± 0.16 [0.13, 1.51]	2.41e-02 (*)
Appendicular lean mass (g) mean ± SD; [min, max]	25486.42 ± 3064.90 [18910.53, 35100.72]	24747.02 ± 3173.83 [17423.04, 35815.85]	2.62e-03 (**)	**Insulin level 2nd probe (µU/mL)** mean ± SD; [min, max]	59.35 ± 50.15 [5.45, 460.1]	62.76 ± 52.07 [6.86, 502.5]	3.83e-01 (ns)
Left arm fat (g) mean ± SD; [min, max]	1422.53 ± 405.07 [445.24, 3374.5]	1494.40 ± 435.79 [615.73, 3556.75]	2.86e-02 (*)	**Eosinophilia (G/L)** mean ± SD; [min, max]	0.15 ± 0.10 [0.01, 0.9]	0.18 ± 0.15 [0.01, 1.46]	4.30e-03 (**)
Whole body total BMD (g/cm²) mean ± SD; [min, max]	1.24 ± 0.11 [0.94, 1.62]	1.23 ± 0.10 [0.96, 1.65]	1.11e-01 (ns)	**Glucose level 2nd probe (mg/dL)** mean ± SD; [min, max]	109.05 ± 29.00 [38.0, 278.0]	114.24 ± 37.36 [56.0, 333.0]	3.53e-02 (*)
Left arm BMC (g) mean ± SD; [min, max]	206.54 ± 33.64 [115.55, 484.77]	199.43 ± 33.22 [121.59, 314.21]	7.43e-03 (**)	**High density lipoprotein cholesterol level (mg/dL)** mean ± SD; [min, max]	70.18 ± 16.03 [35.0, 134.0]	67.68 ± 16.98 [32.0, 153.0]	4.81e-02 (*)
Trunk fat (%) mean ± SD; [min, max]	32.62 ± 5.57 [14.66, 47.71]	34.39 ± 5.36 [17.46, 51.87]	5.02e-05 (****)	**Leukocytes (G/L)** mean ± SD; [min, max]	5.56 ± 1.44 [2.7, 11.8]	5.92 ± 2.02 [2.1, 24.4]	4.95e-03 (**)
Left arm lean mass (g) mean ± SD; [min, max]	3123.96 ± 487.39 [1737.97, 4738.63]	2991.33 ± 504.83 [1911.19, 4546.69]	6.95e-04 (***)	**Deoxypyridinoline in urine (nmol/moK)** mean ± SD; [min, max]	59.34 ± 24.88 [1.0, 191.0]	60.55 ± 25.29 [3.5, 152.0]	5.27e-01 (ns)
Head BMD (g/cm²) mean ± SD; [min, max]	2.28 ± 0.37 [1.31, 4.1]	2.31 ± 0.36 [1.31, 3.51]	2.38e-01 (ns)	**Free triiodothyronine level (ng/L)** mean ± SD; [min, max]	3.07 ± 0.81 [1.96, 15.54]	3.03 ± 0.68 [0.87, 9.58]	5.18e-01 (ns)
Left arm BMD (g/cm²) mean ± SD; [min, max]	0.86 ± 0.08 [0.69, 1.83]	0.85 ± 0.07 [0.65, 1.2]	1.39e-02 (*)	**C reactive protein level (mg/L)** mean ± SD; [min, max]	1.96 ± 2.78 [0.15, 21.5]	2.61 ± 4.38 [0.15, 50.0]	1.38e-02 (*)
Left forefinger length (cm) mean ± SD; [min, max]	7.33 ± 0.40 [6.3, 8.52]	7.32 ± 0.42 [6.23, 8.54]	8.02e-01 (ns)	**Eosinophilia (%)** mean ± SD; [min, max]	2.82 ± 1.65 [0.05, 14.0]	3.14 ± 2.31 [0.05, 22.0]	4.88e-02 (*)
Lumbar spine BMD (g/cm²) mean ± SD; [min, max]	1.14 ± 0.22 [0.7, 2.22]	1.16 ± 0.26 [0.6, 3.01]	2.68e-01 (ns)	**Vitamin D level z score** mean ± SD; [min, max]	0.11 ± 0.99 [-2.02, 6.17]	-0.19 ± 0.89 [-2.02, 2.29]	6.82e-05 (****)
Right forefinger length (cm) mean ± SD; [min, max]	7.67 ± 0.44 [6.54, 9.09]	7.64 ± 0.46 [6.28, 8.91]	4.34e-01 (ns)	**Uric acid level (mg/dL)** mean ± SD; [min, max]	4.66 ± 1.14 [2.3, 11.0]	4.88 ± 1.14 [2.5, 10.6]	1.27e-02 (*)
Left arm area (cm²) mean ± SD; [min, max]	238.84 ± 24.11 [147.36, 300.33]	234.71 ± 27.40 [165.71, 342.38]	4.85e-02 (*)	**Apolipoprotein A1 level (g/L)** mean ± SD; [min, max]	1.79 ± 0.26 [1.13, 2.66]	1.77 ± 0.27 [1.19, 2.77]	4.53e-01 (ns)
Lumbar spine area (cm²) mean ± SD; [min, max]	59.60 ± 12.39 [36.25, 114.15]	59.96 ± 11.82 [26.77, 107.06]	7.08e-01 (ns)	**Total bilirubin level (mg/dL)** mean ± SD; [min, max]	0.56 ± 0.21 [0.2, 1.6]	0.52 ± 0.21 [0.2, 1.4]	2.52e-02 (*)
Age (years) mean ± SD; [min, max]	68.68 ± 3.46 [60.16, 78.12]	69.76 ± 4.33 [60.74, 82.79]	8.62e-04 (***)	**Neutrophils (G/L)** mean ± SD; [min, max]	3.19 ± 1.01 [1.1, 7.4]	3.39 ± 1.17 [0.9, 8.5]	1.44e-02 (*)
Left leg fat (g) mean ± SD; [min, max]	3479.00 ± 967.08 [1480.53, 7800.47]	3710.91 ± 1080.33 [1434.84, 7462.59]	3.56e-03 (**)	**Iron level (µg/dL)** mean ± SD; [min, max]	95.43 ± 26.56 [26.0, 217.0]	91.27 ± 25.16 [38.0, 175.0]	3.88e-02 (*)
Lumbar spine BMC (g) mean ± SD; [min, max]	68.29 ± 21.85 [27.05, 218.27]	69.79 ± 22.12 [28.3, 179.02]	3.88e-01 (ns)	**Aspartate aminotransferase level (U/L)** mean ± SD; [min, max]	24.25 ± 8.33 [13.0, 164.0]	23.74 ± 6.46 [12.0, 67.0]	3.96e-01 (ns)
Head lean mass (g) mean ± SD; [min, max]	4076.80 ± 434.99 [2924.12, 6232.03]	4097.36 ± 448.41 [3018.8, 5363.89]	5.54e-01 (ns)	**Alpha amylase level (U/L)** mean ± SD; [min, max]	67.24 ± 39.00 [20.0, 743.0]	67.78 ± 26.51 [15.0, 221.0]	8.41e-01 (ns)

Body mass Index (kg/m²) mean ± SD; [min, max]	26.93 ± 3.45 [19.13, 44.24]	27.97 ± 3.77 [19.97, 42.61]	2.13e-04 (***)	**Direct bilirubin level (mg/dL)** mean ± SD; [min, max]	0.14 ± 0.07 [0.05, 0.43]	0.14 ± 0.07 [0.05, 0.39]	1.56e-01 (ns)
Thoracic spine area (cm²) mean ± SD; [min, max]	155.80 ± 24.29 [80.3, 282.1]	151.24 ± 23.84 [72.03, 212.16]	1.70e-02 (*)	**Folic acid level (µg/L)** mean ± SD; [min, max]	12.02 ± 5.65 [3.0, 40.1]	12.04 ± 6.03 [3.9, 40.1]	9.58e-01 (ns)
Right rib area (cm²) mean ± SD; [min, max]	148.18 ± 31.41 [77.15, 250.98]	151.07 ± 34.16 [76.76, 242.7]	2.57e-01 (ns)	**LDL HDL cholesterol ratio** mean ± SD; [min, max]	2.07 ± 0.76 [0.3, 5.6]	2.12 ± 0.78 [0.7, 4.8]	4.32e-01 (ns)
Waist hip ratio mean ± SD; [min, max]	1.01 ± 0.05 [0.81, 1.25]	1.02 ± 0.05 [0.88, 1.17]	9.36e-03 (**)	**International normalised ratio** mean ± SD; [min, max]	1.02 ± 0.20 [0.42, 2.93]	1.00 ± 0.15 [0.87, 2.62]	2.61e-01 (ns)
Left leg BMD (g/cm²) mean ± SD; [min, max]	1.37 ± 0.16 [1.02, 2.59]	1.34 ± 0.17 [1.06, 2.88]	1.96e-02 (*)	**Thrombocytes (G/L)** mean ± SD; [min, max]	249.91 ± 65.61 [68.0, 945.0]	255.45 ± 70.56 [146.0, 984.0]	2.86e-01 (ns)
Right arm lean mass (g) mean ± SD; [min, max]	3392.58 ± 558.44 [2077.51, 5231.33]	3268.70 ± 529.80 [2118.66, 4792.35]	4.45e-03 (**)	**Circulating IL 6 (%)** mean ± SD; [min, max]	2.85 ± 4.48 [0.0, 73.09]	2.82 ± 3.09 [0.22, 27.88]	9.30e-01 (ns)
Right arm BMD (g/cm²) mean ± SD; [min, max]	0.87 ± 0.08 [0.7, 1.71]	0.85 ± 0.06 [0.7, 1.05]	1.45e-02 (*)	**Activated creatine kinase level (U/L)** mean ± SD; [min, max]	101.69 ± 50.25 [26.0, 458.0]	102.75 ± 62.59 [31.0, 508.0]	8.02e-01 (ns)
Right 2D 4D digit ratio mean ± SD; [min, max]	0.96 ± 0.04 [0.82, 1.06]	0.96 ± 0.03 [0.87, 1.05]	3.12e-01 (ns)	**Circulating IL 10 (%)** mean ± SD; [min, max]	0.92 ± 3.20 [0.0, 46.9]	0.58 ± 0.76 [0.0, 5.97]	8.99e-02 (ns)
Left rib area (cm²) mean ± SD; [min, max]	138.74 ± 26.83 [73.21, 214.48]	141.23 ± 30.10 [66.92, 217.67]	2.81e-01 (ns)	**Zinc level (µmol/L)** mean ± SD; [min, max]	12.82 ± 4.87 [8.1, 90.0]	12.33 ± 1.86 [5.9, 20.1]	1.21e-01 (ns)

135

Supplementary figures

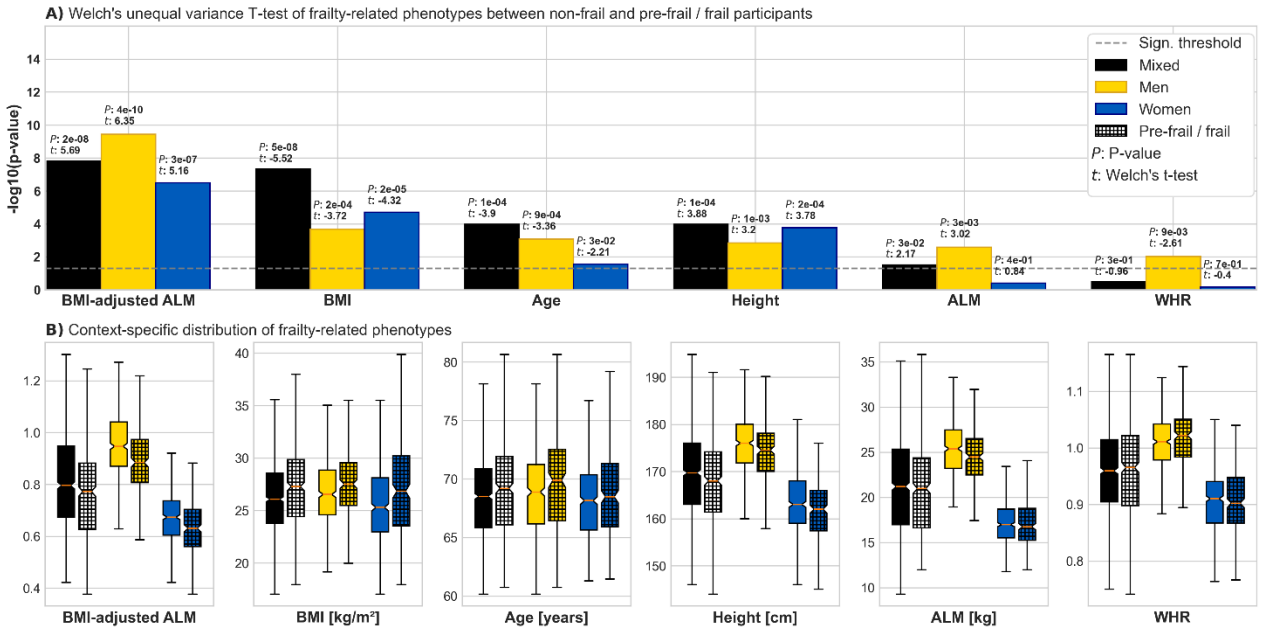
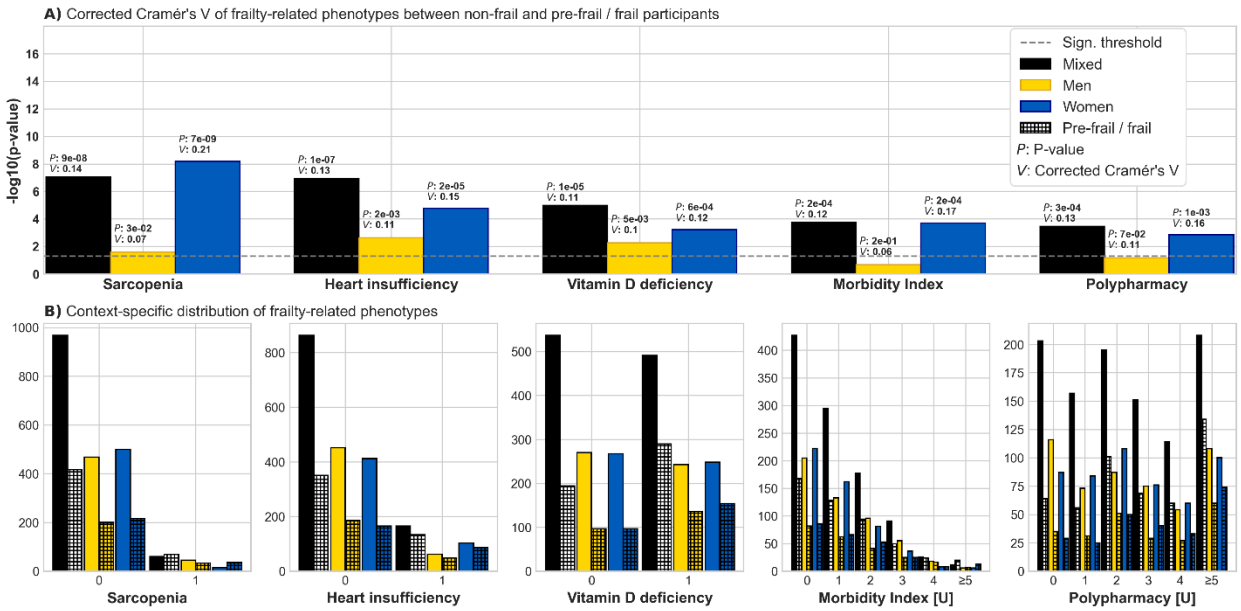


Fig. S1: Sex-specific differences across the main continuous features associated with physical frailty observed between non-frail and pre-frail/frail participants.



139 **Fig. S2: Sex-specific differences across the main binary and discrete features associated with physical frailty**

140 **observed between non-frail and pre-frail/frail participants.**

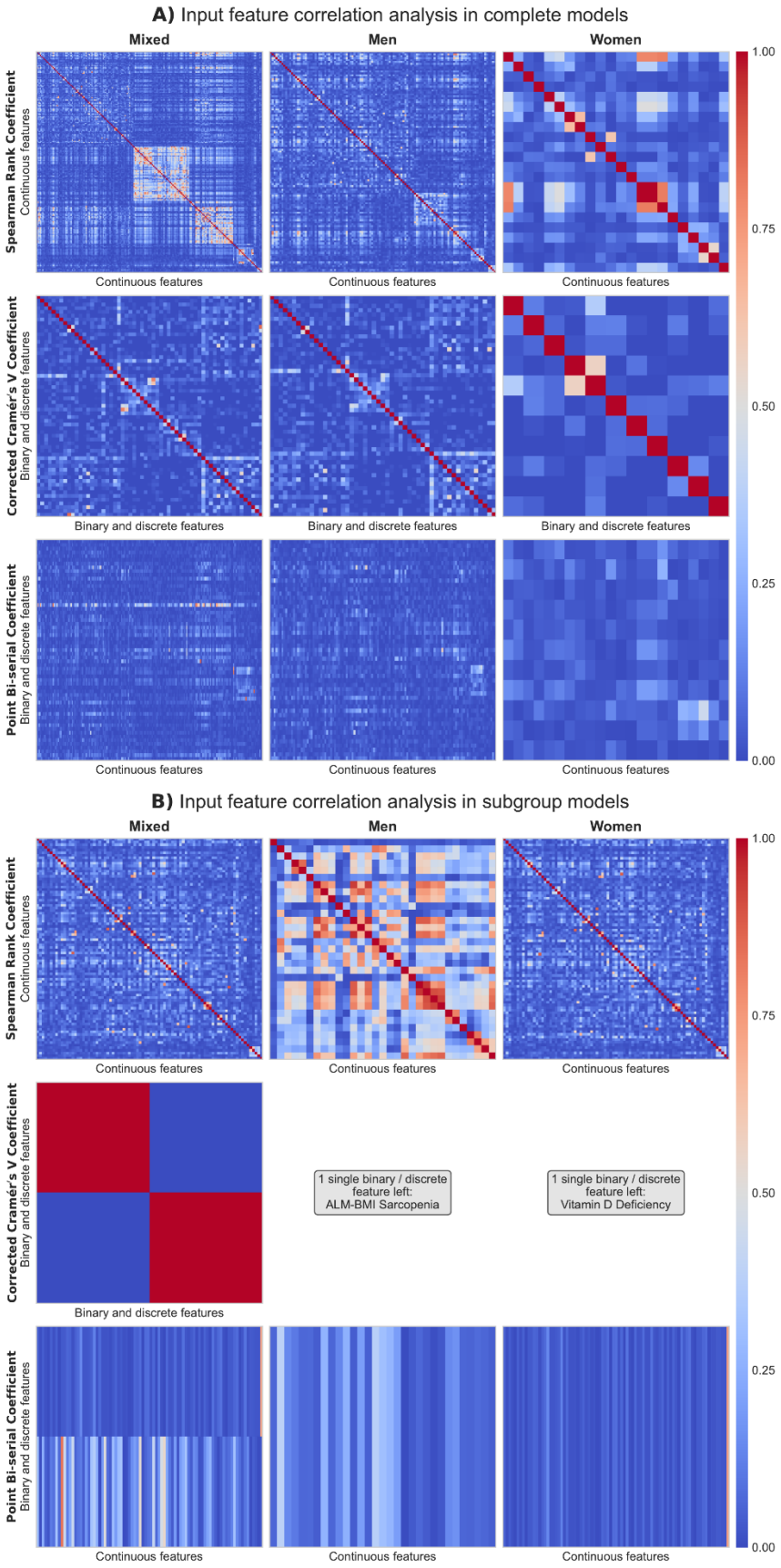
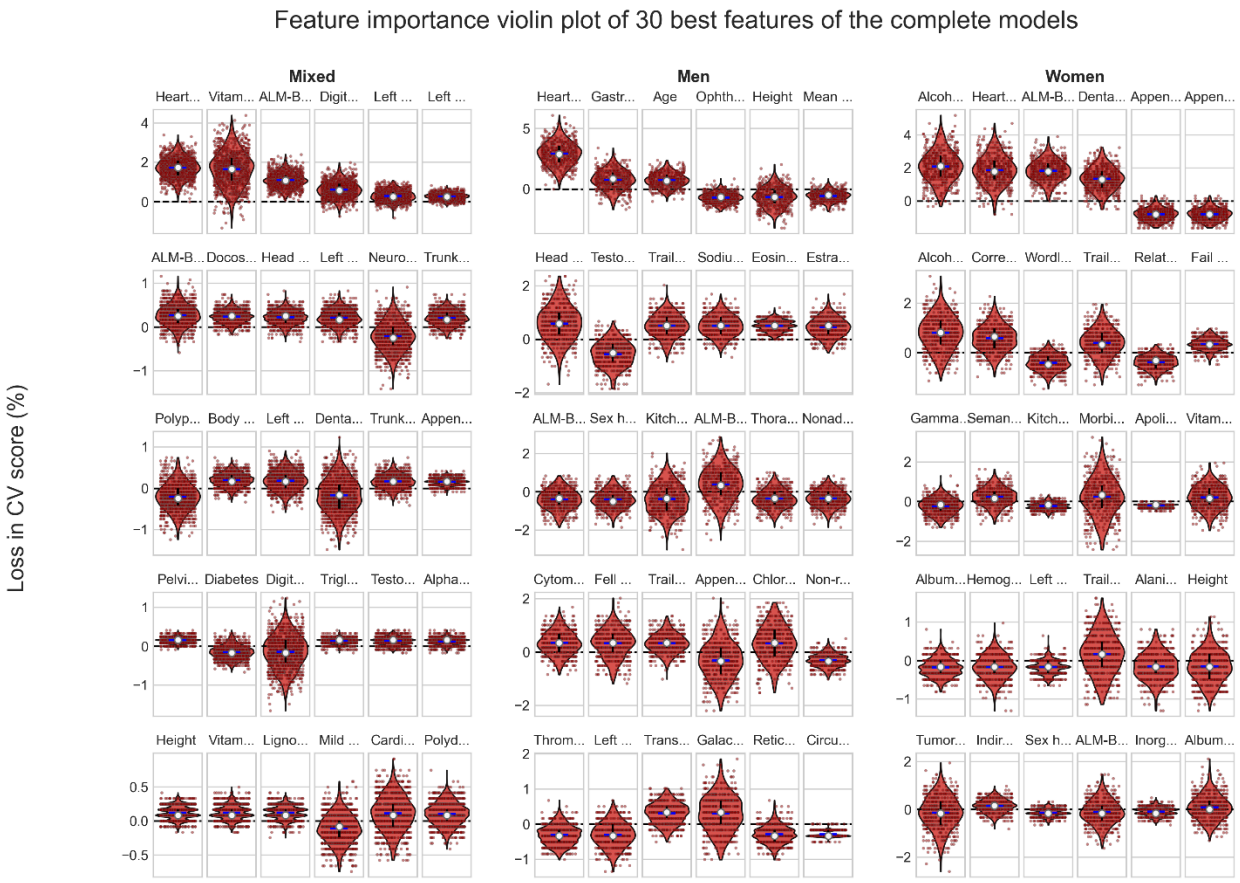
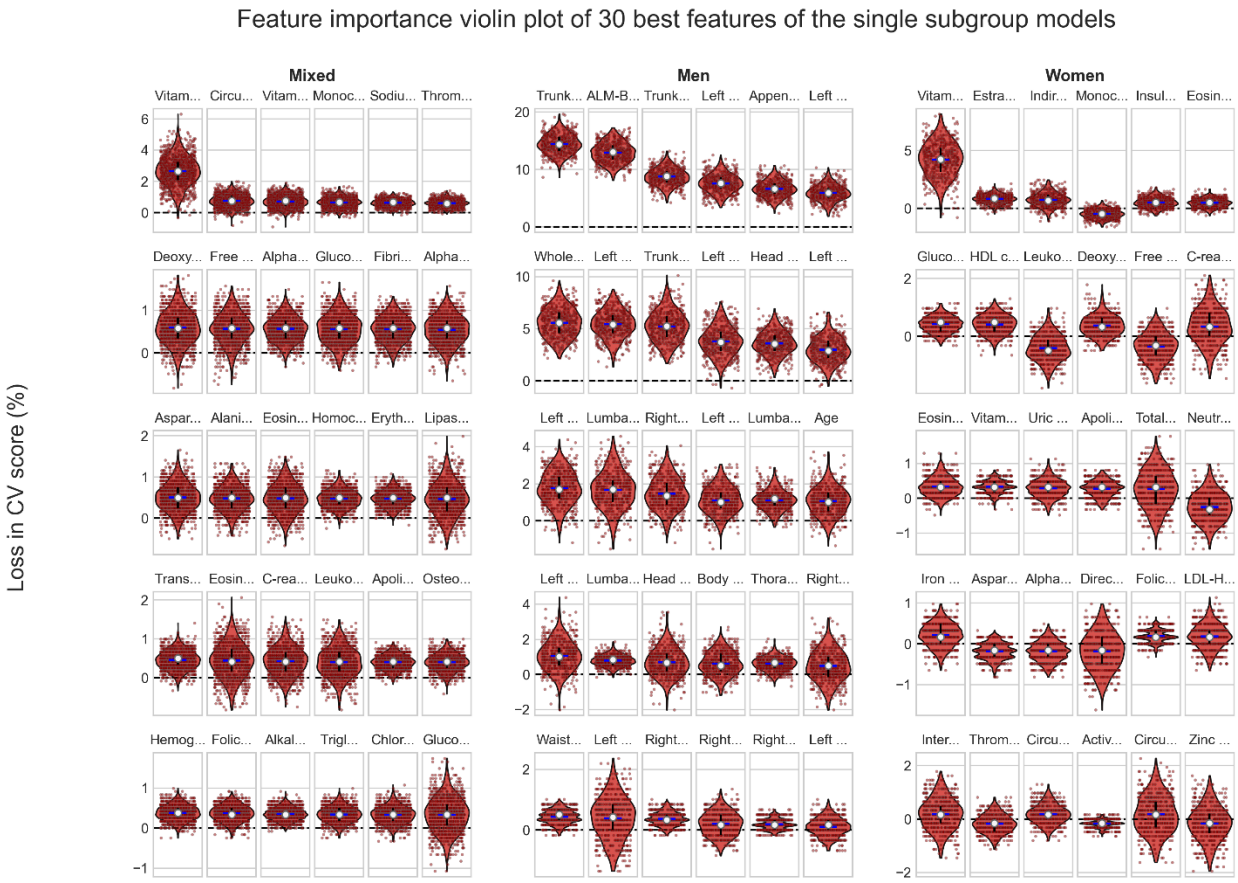


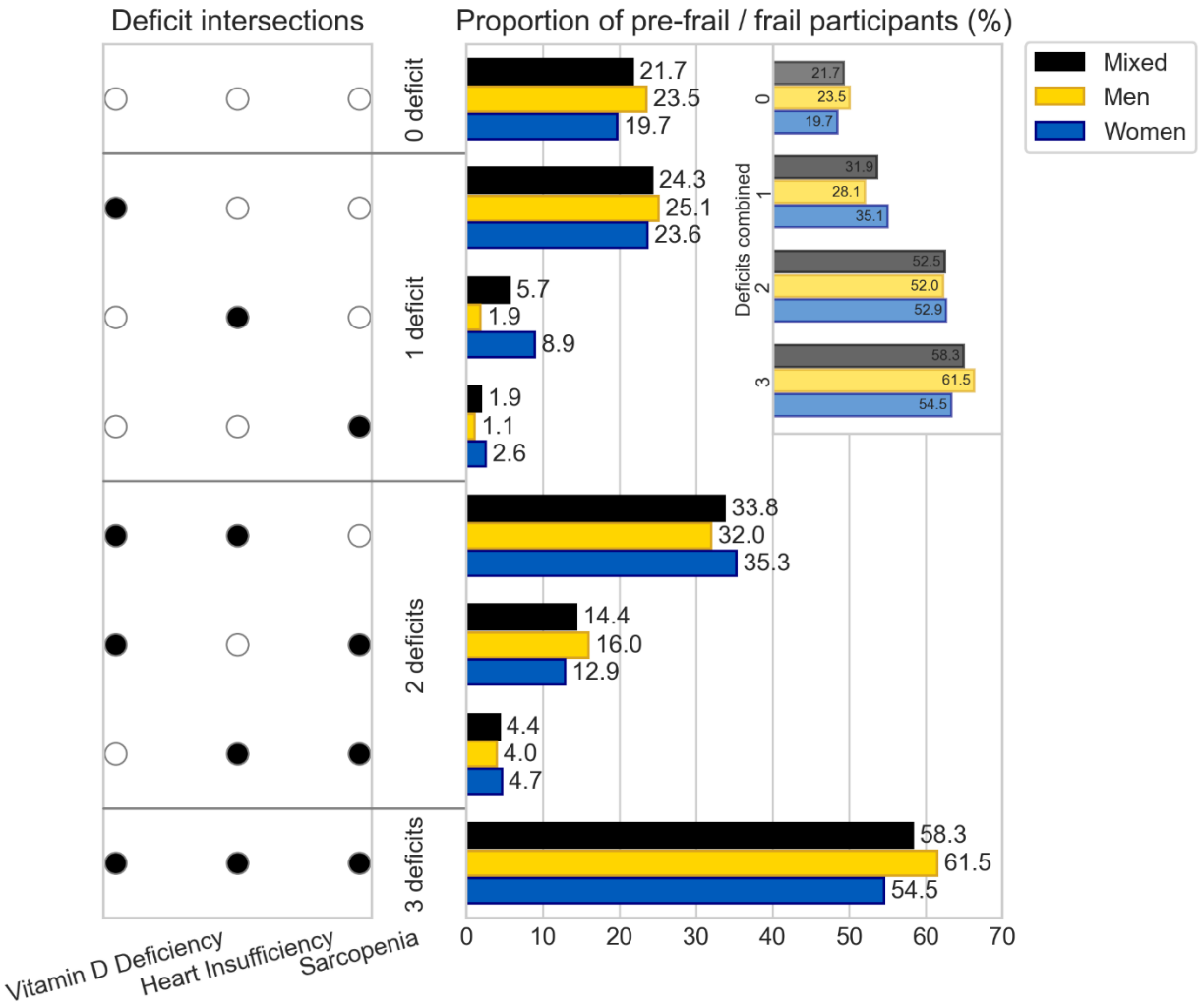
Fig. S3: Data-type specific correlation analysis of pre-processed data show weak associations in the complete (A) and best performing subgroup (B) data-driven models.



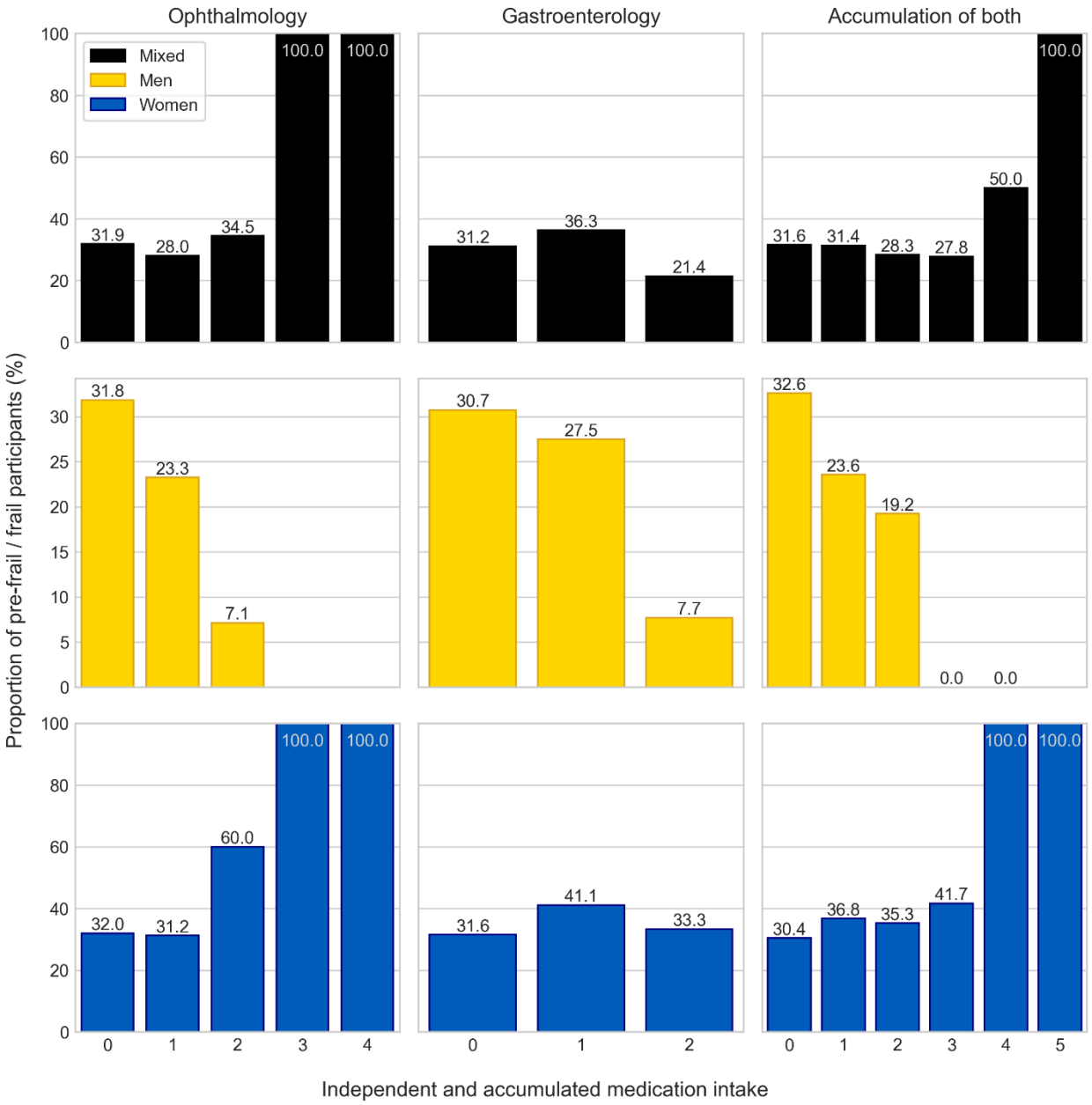
147 **Fig. S4: Feature permutation importance behaviour in the complete data-driven models.**



148 **Fig. S5: Feature permutation importance behaviour in the single subgroup data-driven models.**

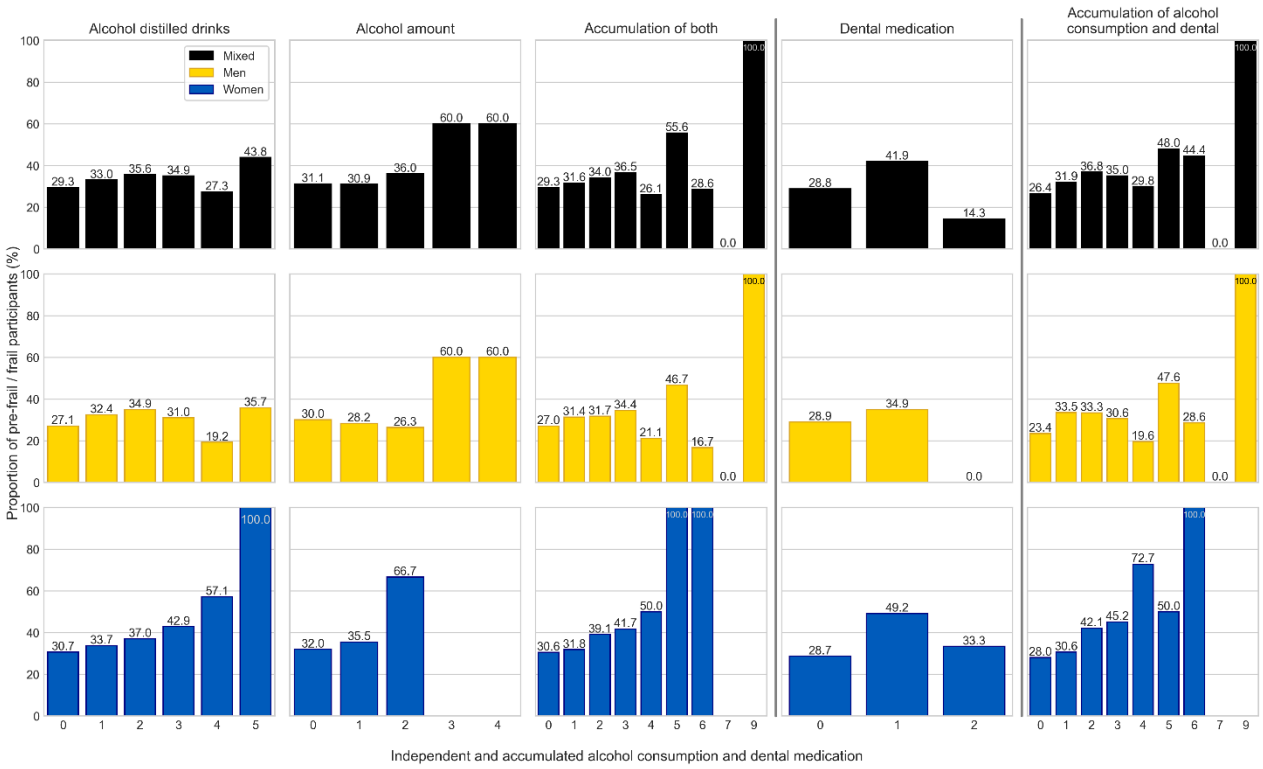


149 **Fig. S6: Frailty proportion in BASE-II increases with the accumulation of deficits.**



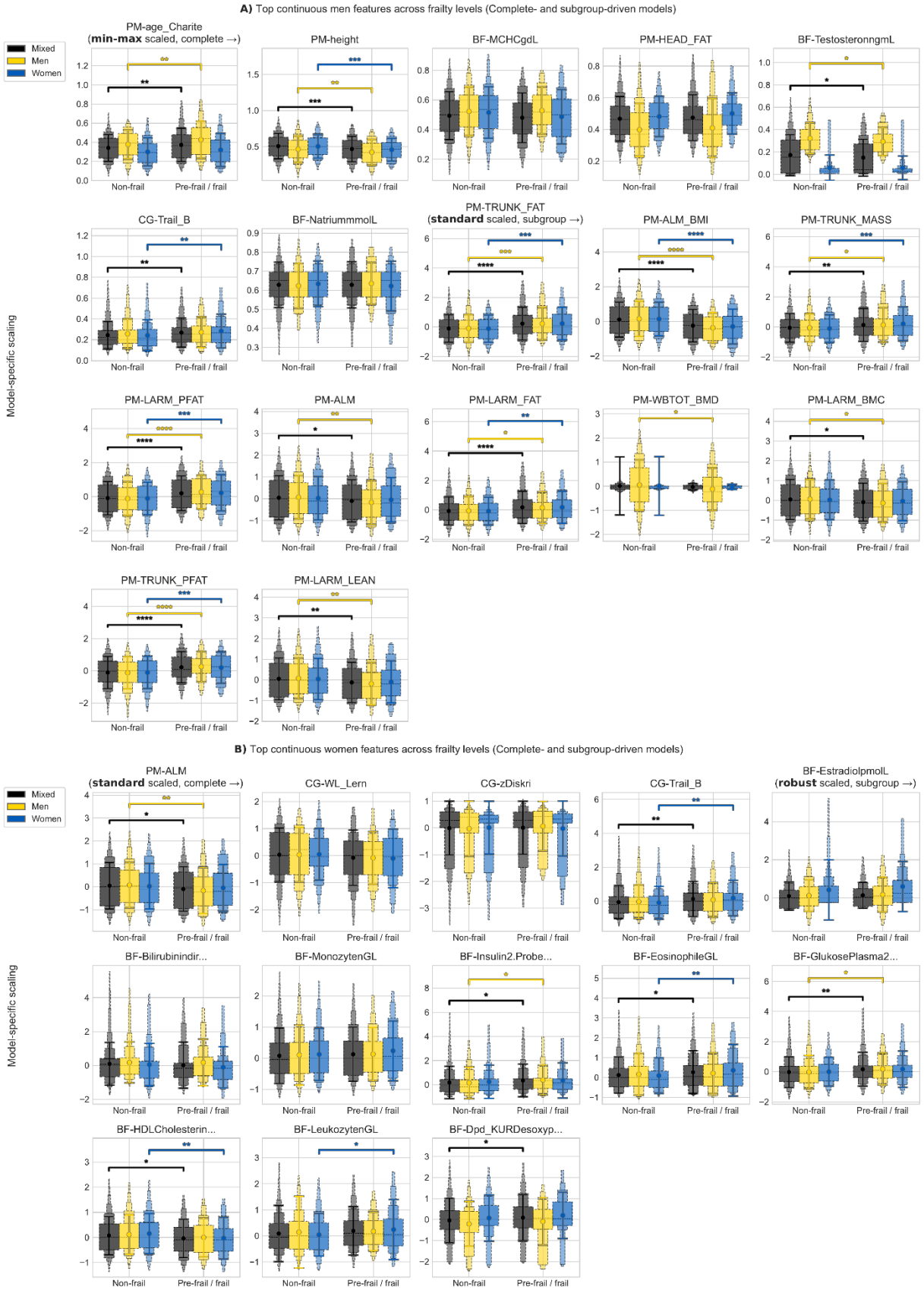
150 **Fig. S7: Frailty proportion decreases with the independent and accumulated gastroenterology and**

151 **ophthalmology medication intake in BASE-II men.**

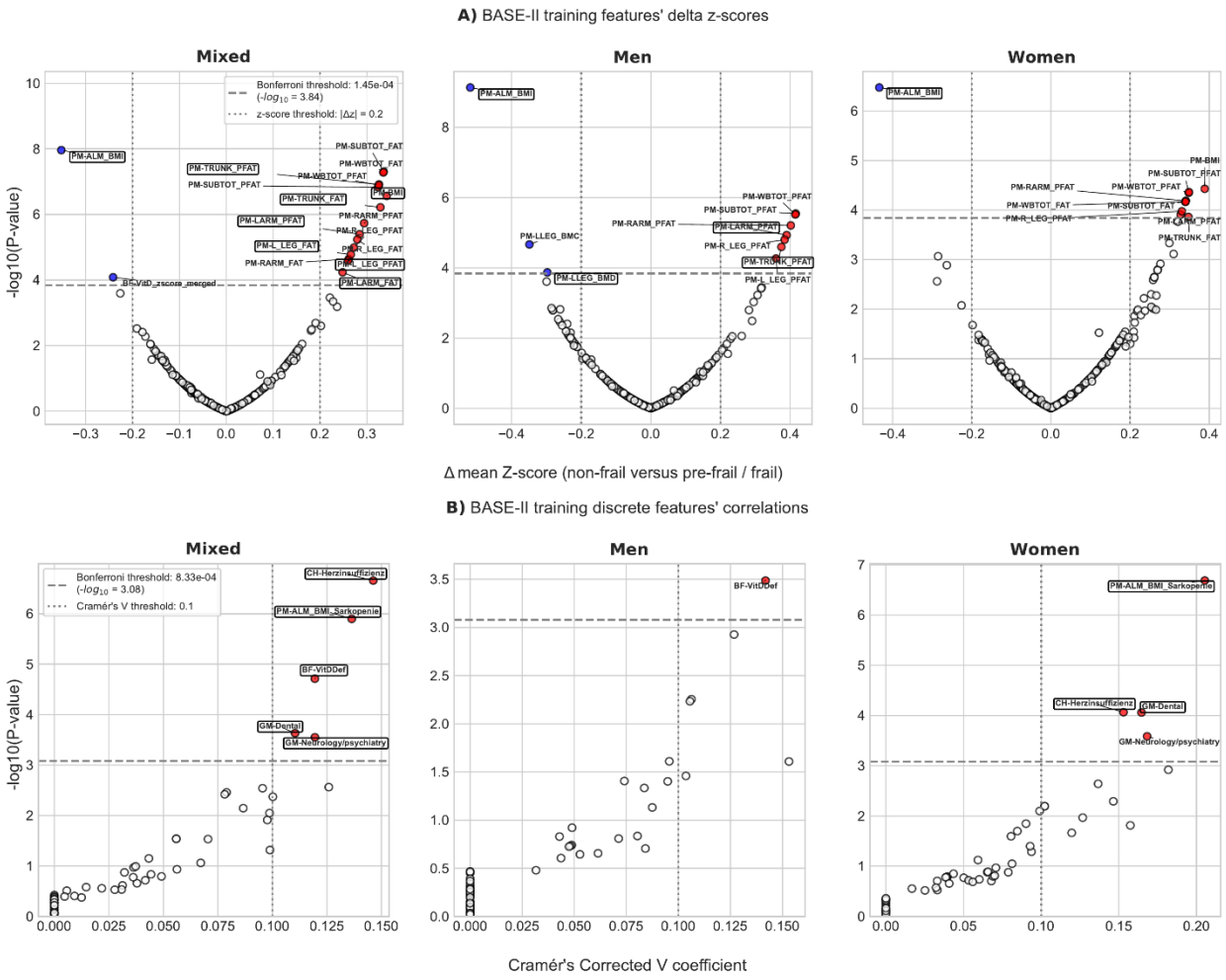


152 **Fig. S8: Frailty proportion increases with the independent and accumulated alcohol and dental medication**

153 **information in BASE-II women.**

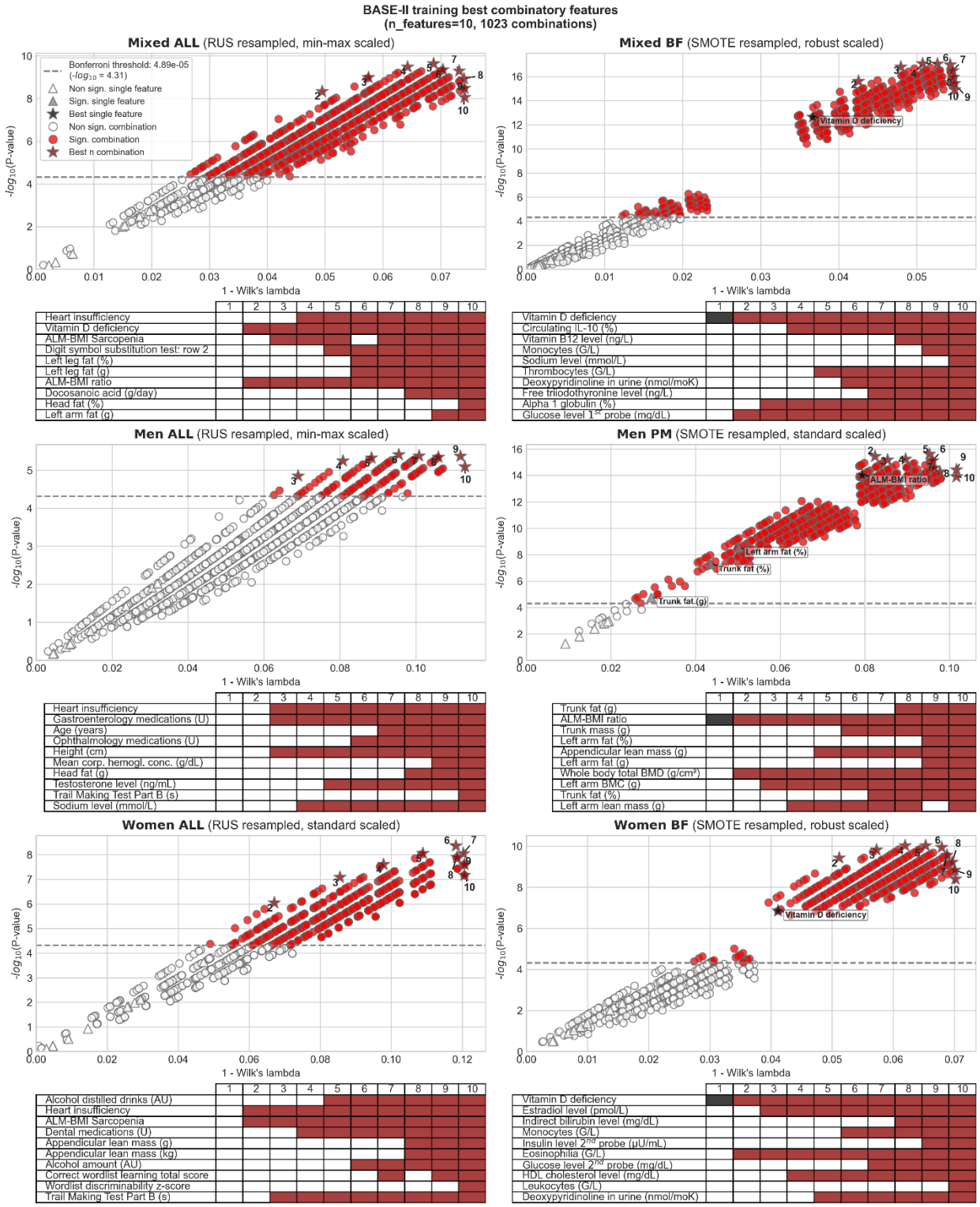


154 **Fig. S9: Single continuous features show weak associations with frailty.**



155 **Fig. S10: Independent feature analysis suggests that the best performing features of the models were selected**

156 **due to their combinatory effect.**



157 **Fig. S11: Multivariate analysis of variance confirms the combinatory effect of the ten most contributing**

158 **features in dispersing non-frailty from frailty.**