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Phase Angle Deviation is Associated with Multidomain Disease Burden in Adults Across a Broad Age-range

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Abstract

Phase angle (PhA) is a bioelectrical parameter associated with body cell mass, fluid distribution, frailty, and adverse clinical outcomes. Because PhA varies with age and sex, absolute values are difficult to interpret. Whether deviation from age- and sex-expected PhA reflects multidomain clinical burden across adulthood is unknown. We investigated whether phase angle deviation (ΔPhA), defined as observed PhA minus age- and sex-expected PhA, is associated with the presence and accumulation of clinically confirmed diagnoses across five major clinical domains in adults 18 to 90 years. Outcomes were the presence of at least one clinically confirmed diagnosis in the cardiovascular, malignant, psychological, chronic inflammatory, or metabolic-syndrome domain and the number of domains present. Modified Poisson regression estimated adjusted Prevalence Ratios (PRs), and multivariable linear regression quantified the burden gradient. The analysis included 94,552 adults (60,803 women [64.3%]; mean [SD] age, 46.44 [15.10] years), including 51,955 controls and 42,597 participants with at least one clinical domain. Each 1° lower ΔPhA was associated with a 13.3% higher adjusted prevalence of at least one domain (PR, 1.133; 95% CI, 1.123–1.144; p < .001). Compared with controls, adjusted ΔPhA was − 0.154° with one domain, -0.209° with two, -0.317° with three, and − 0.391° with four or more domains. In conclusion, PhA values below those expected for age and sex were associated with progressively greater multidomain disease burden.

Introduction

Adults of the same chronological age can differ markedly in physiological reserve, body composition, inflammatory status, and chronic disease burden. This heterogeneity is central to aging and healthspan research and complicates interpretation of biomarkers that change physiologically across the life course. Measures that are noninvasive, quick, inexpensive, repeatable, and interpretable by age and sex may therefore help describe clinical status across adulthood. We investigated whether bioelectrical impedance analysis (BIA) provides such a measure.

Phase angle (PhA) is a directly measured bioelectrical parameter calculated from resistance (R) and reactance (Xc) as arctan(Xc/R) × 180/π. It reflects the relationship between the resistive and capacitive properties of tissues and has been associated with body cell mass and intracellular and extracellular fluid distribution.[1,2] PhA varies substantially with age and sex and is also influenced by body mass index (BMI) and body composition.[3–6] Consequently, identical absolute PhA values may represent different physiological states in people of different ages or sexes.

Results from clinical studies have repeatedly shown the association of lower PhA with higher mortality, frailty, chronic kidney disease, cardiovascular disease, and inflammatory states; longitudinal studies have also linked low or declining PhA with subsequent cardiovascular events and mortality.[7–14] The BIA-ACC system used in the present study has been applied in large multicenter and real-world investigations of stress and inflammation, body composition, osteosarcopenic adiposity, fluid distribution, autonomic function, and multidomain chronic diseases.[15–20]

Most previous studies have presented PhA as an absolute value or as a value standardized within a defined population. We asked a different but clinically straightforward question: How much does an individual's PhA deviate from the value expected for someone of the same age and sex? We therefore defined ΔPhA as observed PhA minus age- and sex-expected PhA and examined its association with clinically confirmed diagnoses in five prespecified domains: cardiovascular, malignant, psychological, chronic inflammatory, and metabolic-syndrome conditions. We also tested whether ΔPhA changed progressively as the number of domains increased.

Results

Population Characteristics and Reference Trajectories

The study included 94,552 adults: 60,803 women (64.3%) and 33,749 men (35.7%), with a mean (SD) age of 46.44 (15.10) years. Participants with at least one clinical domain were older, had a higher mean BMI, and had a lower absolute PhA than controls. Table 1 presents these characteristics separately for women and men.

Table 1
Population Characteristics by Sex and Clinical Status

Variable	Women: controls (n = 31,272)	Women: ≥1 domain (n = 29,531)	Men: controls (n = 20,683)	Men: ≥1 domain (n = 13,066)
Age (years)	41.97 ± 13.56	52.65 ± 13.91	39.65 ± 13.78	53.82 ± 14.49
BMI (kg/m²)	25.43 ± 5.01	27.37 ± 6.04	26.56 ± 4.46	28.64 ± 5.25
PhA at 50 kHz (°)	5.882 ± 0.827	5.525 ± 0.903	6.781 ± 0.889	6.069 ± 0.990
ΔPhA (°)	0.000 ± 0.781	-0.120 ± 0.834	0.000 ± 0.770	-0.193 ± 0.792

BMI, body mass index; PhA, Phase Angle; ΔPhA, observed PhA minus age and sex expected PhA. Values are mean (SD). All Ps between controls and participants with ≥ 1 clinical domain were < .0001 for each variable for both women and men.

Among controls, the PhA relation with age was nonlinear and differed by sex. Figure 1 shows the trajectories that constitute the study's internal reference. Therefore, ΔPhA does not compare each patient with a single cut-off, but with the value expected for a person of the same sex and age, supporting the use of age and sex specific reference trajectories.

Primary Association

In the primary model, each 1° lower ΔPhA was associated with a 13.3% higher prevalence of at least one clinical domain after adjustment for age, sex, and BMI (PR, 1.133; 95% CI, 1.123–1.144; p < .001).

However, this estimate describes a cross-sectional association and should not be interpreted as prospective risk. The association was not linear across the full ΔPhA distribution. A spline model fit the data better than a linear model (likelihood-ratio $\chi^2 = 424.5$; p for nonlinearity < .001). Adjusted marginal prevalence of at least one domain was approximately 43.3% at ΔPhA = 0°, 47.3% at -0.5°, and 52.8% at -1.0°; the corresponding estimates at + 0.5° and + 1.0° were 40.1% and 38.2%, respectively (Fig. 2). This pattern visually manifests that negative distance from the expected trajectory carries clinical information along a continuum rather than only beyond an arbitrary threshold.

Multidomain Burden

A clear gradient was present as the number of clinical domains increased. Absolute PhA progressively decreased from 6.240° in controls to 5.172° in participants with four or more domains. In the pooled population, after adjustment for age, sex, and BMI, the ΔPhA difference vs. controls remained − 0.154° with one domain, -0.209° with two, -0.317° with three, and − 0.391° with ≥ 4 domains (Fig. 3).

The same ordered pattern was observed in women and men (Table 2). When burden was modeled continuously, each additional domain was associated with an adjusted mean ΔPhA decrease of 0.114° (95% CI, 0.107°-0.122°; p < .001).

Table 2
Phase Angle and ΔPhA by Multidomain Burden by Sex

Panel A. Women				
No. of domains	**n**	**Mean PhA°**	**Mean ΔPhA°**	**Adjusted ΔPhA° vs. female controls (95% CI)**
0	31,272	5.882 ± 0.827	0.000	Reference
1	21,512	5.583 ± 0.888	-0.111	-0.131 (-0.145 to -0.116)
2	6,313	5.410 ± 0.914	-0.131	-0.181 (-0.205 to -0.158)
3	1,480	5.225 ± 0.956	-0.178	-0.273 (-0.320 to -0.225)
≥ 4	226	5.159 ± 0.889	-0.205	-0.310 (-0.413 to -0.207)
Panel B. Men				
No. of domains	**n**	**Mean PhA°**	**Mean ΔPhA°**	**Adjusted ΔPhA° vs. male controls (95% CI)**
0	20,683	6.781 ± 0.889	0.000	Reference
1	9,555	6.183 ± 0.964	-0.171	-0.199 (-0.219 to -0.178)
2	2,796	5.838 ± 0.984	-0.220	-0.269 (-0.303 to -0.236)
3	635	5.492 ± 0.983	-0.352	-0.420 (-0.487 to -0.353)
≥ 4	80	5.208 ± 0.813	-0.537	-0.617 (-0.762 to -0.471)

CI, confidence interval; PhA, phase angle; ΔPhA, observed PhA minus age and sex expected PhA. Adjusted differences were derived from sex specific multivariable linear regression models including nonlinear age and body mass index, with heteroscedasticity-consistent robust standard errors type 3 (HC3).

Domain-Specific Consistency and Robustness

All five clinical domains showed the same direction of association. Adjusted ΔPhA vs. controls ranged from − 0.140° for cardiovascular disease and metabolic syndrome to -0.292° for cancer, and all domain

specific associations remained significant after Holm correction (eTable 1 and eFigure 1 in Supplement 1). Although the magnitude of association varied across domains, the most relevant information was the directional convergence: five biologically distinct clinical domains showed a PhA below the value expected for age and sex. The supplementary analysis in participants with a single clinical domain confirmed the same signal, reducing the possibility that domain-specific differences were explained solely by coexisting diseases. The association was present in both women (PR, 1.106) and men (PR, 1.193), with a significant ΔPhA by sex interaction ($p < .001$). PRs were 1.293 at ages 18 to 39 years, 1.143 at 40 to 59 years, and 1.057 at 60 years or older; the global interaction by age group was also significant ($p < .001$). These interaction analyses were secondary and are interpreted as exploratory. They do not indicate that PhA loses relevance with age; rather, they suggest that the same deviation from the expected value may have different relative discriminative power across stages of adult life.

The main finding was robust and stable across sensitivity analyses. The PR was 1.133 when BMI was included directly in construction of the reference trajectory and 1.131 after adjustment for year of acquisition and remained virtually unchanged when the flexibility of the reference spline was varied. Excluding the lowest and highest 1% of ΔPhA values did not alter the association (PR, 1.172; 95% CI, 1.160–1.184). Internal split sample validation, based on 25,977 development controls and 25,978 independent validation controls, confirmed both the association (PR, 1.094; 95% CI, 1.086–1.102) and the burden gradient. These and other statistical analyses to show robustness, heterogeneity, and overlap structure across the five clinical domains are presented in eTables 2–7 and eFigures 2–6 in Supplement 1.

Discussion

The main finding is that PhA provides more comprehensive clinical information when interpreted as an individual's position relative to an age- and sex-expected trajectory. Lower ΔPhA was associated with a higher prevalence of clinically confirmed diseases across five domains, and the deviation became progressively more negative as the number of clinical domains increased. The association extended across the ΔPhA continuum but was nonlinear, so the average PR is a useful summary rather than a constant effect throughout the distribution. Among 94,552 adults included in this study, negative distance from the reference trajectory was associated not only with disease presence but also with an ordered increase in the number of major clinical domains. Thus, this study proposes not a new universal cutoff, but a different way to interpret PhA.

This approach is important because the use of absolute values is inevitably conditioned by physiological differences related to age and sex and differs from the use of a single absolute threshold. Because PhA varies substantially with age and sex,[3–6] a value of 5.5° does not convey the same biological characteristic in a young and an older adult. ΔPhA retains the familiar unit of degrees while placing the measurement in an age and sex specific context. This may be especially useful when the same individual is followed over time.

The graded relationship with multidomain burden was among the most consistent findings. The adjusted difference changed from − 0.154° with one domain to -0.391° with four or more domains, and each additional domain was associated with a further mean decrease of 0.114°. The direction of association was concordant across cardiovascular, malignant, psychological, chronic inflammatory, and metabolic-syndrome conditions. Previous studies have related standardized PhA to disease severity in older adults[13] and low or declining PhA to cardiovascular events and mortality.[11,12] Prognostic associations have also been reported in older adults with multimorbidity.[24] The present study extends this research across a broad adult age range using internal reference trajectories, multidomain-burden and single-domain analyses, and split-sample validation.

The association was stronger in younger adults and in men. These findings were secondary and should not be taken to mean that PhA loses clinical relevance at older ages. Rather, the relative meaning of a negative deviation may differ across adulthood as chronic disease becomes more common and physiological heterogeneity increases. Whether these differences have prognostic importance will require longitudinal study.

PhA should not be regarded as a disease-specific biomarker. It is derived from R and Xc and is influenced by body cell mass, fluid distribution, and electrical properties of tissue.[1,2,6] Chronic conditions with different etiologies may converge on these features through changes in body composition, inflammation, oxidative stress, and physiological reserve.[14] This may explain why the direction of association was similar across clinically distinct domains.

From a clinical perspective, the same measurement can be communicated in two complementary ways: an absolute PhA value and its deviation from the value expected for age and sex. For example, “PhA 5.4°; ΔPhA − 0.8°” gives more context than “PhA 5.4°” alone. ΔPhA does not diagnose a specific disease and is not a substitute for clinical assessment; its potential value is as an additional measure for risk-oriented stratification and longitudinal monitoring. Because PhA at 50 kHz is derived from R and Xc, the concept is not limited to the BIA-ACC® platform; it can be tested with other medical BIA systems using standardized acquisition. Interdevice studies will be useful to determine whether reference equations can be shared directly or require calibration.

Longitudinal evaluation would be the next step, particularly for healthspan and aging research. A single ΔPhA describes a participant's position at one time point, whereas repeated measurements could show whether that position is stable, improving, or deteriorating. Prospective studies could determine whether baseline ΔPhA or changes in ΔPhA precede incident disease, transition to multimorbidity, functional decline, hospitalization, or mortality. Such work would establish whether PhA trajectories contribute to healthspan and aging research beyond the cross-sectional associations reported here.

Limitations and Strengths

This study has several limitations and strengths, some of which overlap. The cross-sectional design does not establish causality or temporal sequence, but the lrge number of participants provides enough power for all statistical analyses. Diagnoses were clinically confirmed at participating centers; however, source records were unavailable for centralized retrospective readjudication. The five clinical domains encompass heterogeneous conditions but were intentionally selected to capture distinct outcomes. Information on physical activity, smoking, medication use, disease severity, biochemical markers, and socioeconomic factors was not uniformly available and was therefore excluded. Although deriving the reference trajectory internally from 51,955 controls strengthened the current analysis, external comparison and harmonization across instruments and acquisition protocols will be important in other populations. Other strengths include the large adult sample (94,552 participants), age- and sex-specific nonlinear modeling, BMI adjustment, Holm correction, single-domain analyses, assessment of distributional extremes, stratified analyses, and split-sample validation. Consistency across these analyses makes it unlikely that the central finding depends on a single modeling choice.

Conclusions

Among 94,552 adults, PhA values at 50 kHz provided clinically relevant information beyond the absolute value alone. When expressed as distance from the age and sex expected trajectory, progressively more negative values were associated with a higher prevalence of disease and a graded increase in burden across five major clinical domains. The relationship was continuous and significantly nonlinear, concordant across cardiovascular, metabolic, psychological, malignant, and chronic inflammatory domains, and robust to the main sensitivity analyses.

The applied novelty is straightforward: expressing PhA as ΔPhA provides a simple way to add age and sex specific context to an absolute bioimpedance measurement. In that way, PhA can be interpreted not only as 'how high the value is,' but also as 'where the individual lies relative to the expected value.' This shift from an absolute number to an individualized trajectory may make bioimpedance easier to interpret in clinical practice and more informative in aging research, especially in view of its ease of use.

The further steps require longitudinal studies of ΔPhA rather than reliance on a single measurement. Such studies could test whether the bioelectrical trajectory anticipates multimorbidity, functional decline, and reduced healthspan. In this context, ΔPhA could become a scalable measure for studying healthy aging and longevity, identifying early deviations from the expected trajectory, and quantifying responses to preventive interventions. These applications require prospective validation, but the present study provides a large, coherent quantitative basis for further development.

Methods

Study Design and Participants

The present study was a retrospective secondary analysis of de-identified data collected during routine medical evaluations; no experimental intervention or new participant contact was undertaken for this analysis. The original study was approved in Italy by the Consortium for the Science and Technology Research (AREA), Trieste, and was conducted in accordance with the Declaration of Helsinki principles. The data were collected from February 1, 2018, through December 31, 2023.[19] The current analyses were performed in September and October 2026. Adults aged 18 to 90 years with one valid PhA assessment were eligible. The sample included 94,552 adults: 51,955 controls with no known disorders or diseases and 42,597 participants with at least one clinically confirmed diagnosis within the five predetermined domains.

Ethical considerations

The clinical research and retrospective data collection followed protocol covering BIA-ACC data obtained during routine medical evaluations was reviewed and approved by the Ethics Committee of the University Research Institute of Maternal and Child Health and Precision Medicine, National and Kapodistrian University of Athens, Athens, Greece, as previously reported for the same data collection framework.[15,19,20] The Committee confirmed that the study procedures were conducted in accordance with the applicable ethical standards and the Declaration of Helsinki and its later amendments. Before the original measurements, all participants received information about the procedures and provided informed consent. The present analysis used only de-identified data from adults aged 18 years or older.

Bioimpedance Acquisition

Measurements were obtained with BIA-ACC® (BioTekna, Marcon-Venice, Italy), a noninvasive, CE-marked medical device for bioimpedance assessment. It has been CE-certified for diagnostic and monitoring use in the European Union since 2004.[19,20] Although some published BIA-ACC protocols used multifrequency acquisition, the present study used PhA measured at 50 kHz, consistent with earlier studies.[15–20] Participants were assessed supine on a nonconductive surface, with limbs relaxed and separated from the trunk. Four disposable electrodes were placed in a right-sided tetrapolar hand-to-foot configuration at the metacarpal region and wrist and at the metatarsal region and ankle. At 50 kHz, the device directly measures R and Xc and calculates PhA as $\arctan(Xc/R) \times 180/\pi$, expressed in degrees (°). Proprietary body-composition estimates were not primary outcomes in this analysis. Height and weight were measured using standardized procedures with participants in light clothing and without shoes; BMI was calculated as kg/m^2.

Clinical Domains

Diagnoses were clinically confirmed at participating centers and then coded in the multicenter database. Because of privacy, de-identification, and governance requirements, source clinical records were not centrally available for a new participant level retrospective adjudication. The prespecified domains were cardiovascular disease (n = 16,540), cancers (n = 4,015), psychological disorders (n = 7,903), chronic inflammatory disorders (n = 18,196), and metabolic syndrome (n = 10,227). Domains were not mutually

exclusive and the number of domains present in each participant (0–5) was used as the measure of multidomain burden.

Reference Trajectory and ΔPhA

The reference trajectory was derived from the 51,955 adult controls. Because PhA differs by sex and changes nonlinearly with age, separate sex specific models were fitted using natural cubic splines of age with seven degrees of freedom. For each participant, ΔPhA was calculated as observed PhA minus the age and sex expected PhA. Negative values therefore indicated a PhA below the reference trajectory, whereas positive values indicated a PhA above it.

Statistical Analysis

Continuous variables are reported as mean (SD) and categorical variables as number (percentage). All tests were two-sided, and estimates are presented with 95% confidence intervals (CIs). The primary outcome was the presence of at least one of the five clinical domains. Because this outcome was common, its association with ΔPhA was estimated using modified Poisson regression with a log link and heteroscedasticity-consistent type 3 robust standard errors (HC3) to obtain adjusted prevalence ratios (PRs).[21,22] The primary model included ΔPhA, nonlinearly modeled age, sex, and BMI. For clinical interpretation, PRs are reported per 1° lower ΔPhA.

The shape of the continuous association was examined with logistic regression using a natural cubic spline for ΔPhA (four degrees of freedom), adjusted for age, sex, and BMI. Multidomain burden was analyzed both categorically (0, 1, 2, 3, or ≥ 4 domains) and continuously using multivariable linear regression. Multiplicity across the 5 prespecified domain specific analyses was controlled with the Holm procedure. Sensitivity analyses included sex and age stratified models, alternative construction of the reference trajectory, adjustment for year of acquisition, exclusion of the lowest and highest 1% of ΔPhA values, restriction to participants with a single domain, and internal split sample validation. Interactions of ΔPhA with sex and age groups were considered secondary analyses.

Analyses were conducted in Python 3.13.5 using pandas 2.2.3 and NumPy 2.3.5 for data management and numerical operations, statsmodels 0.14.6 for regression modeling and robust covariance estimation, Patsy 1.0.2 for statistical formulas and natural cubic splines, SciPy 1.17.0 for complementary numerical procedures, and Matplotlib 3.10.8 for figure generation. Reporting followed STROBE guidance.[23]

Declarations

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Author Contributions: Dario Boschiero: Conceptualization, methodology, formal analysis, data curation, supervision, visualization. Alice Boschiero: Writing, review & editing. Jasminka Z. Ilich: Methodology,

validation, visualization, writing, review & editing. All authors reviewed and approved the final manuscript.

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Data Sharing Statement: Individual level data are not publicly available because of privacy, de-identification, and governance requirements of the multicenter data collection. Aggregate data and documentation of the analytical workflow may be considered upon reasonable request to the corresponding author, subject to applicable ethical, regulatory, and governance constraints.

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Use of generative AI: Grammarly software was used to cut down the number of words and for language and grammar editing. All analyses, results, references and final wording were reviewed and approved by the authors. The authors take full responsibility for the content.

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Figures

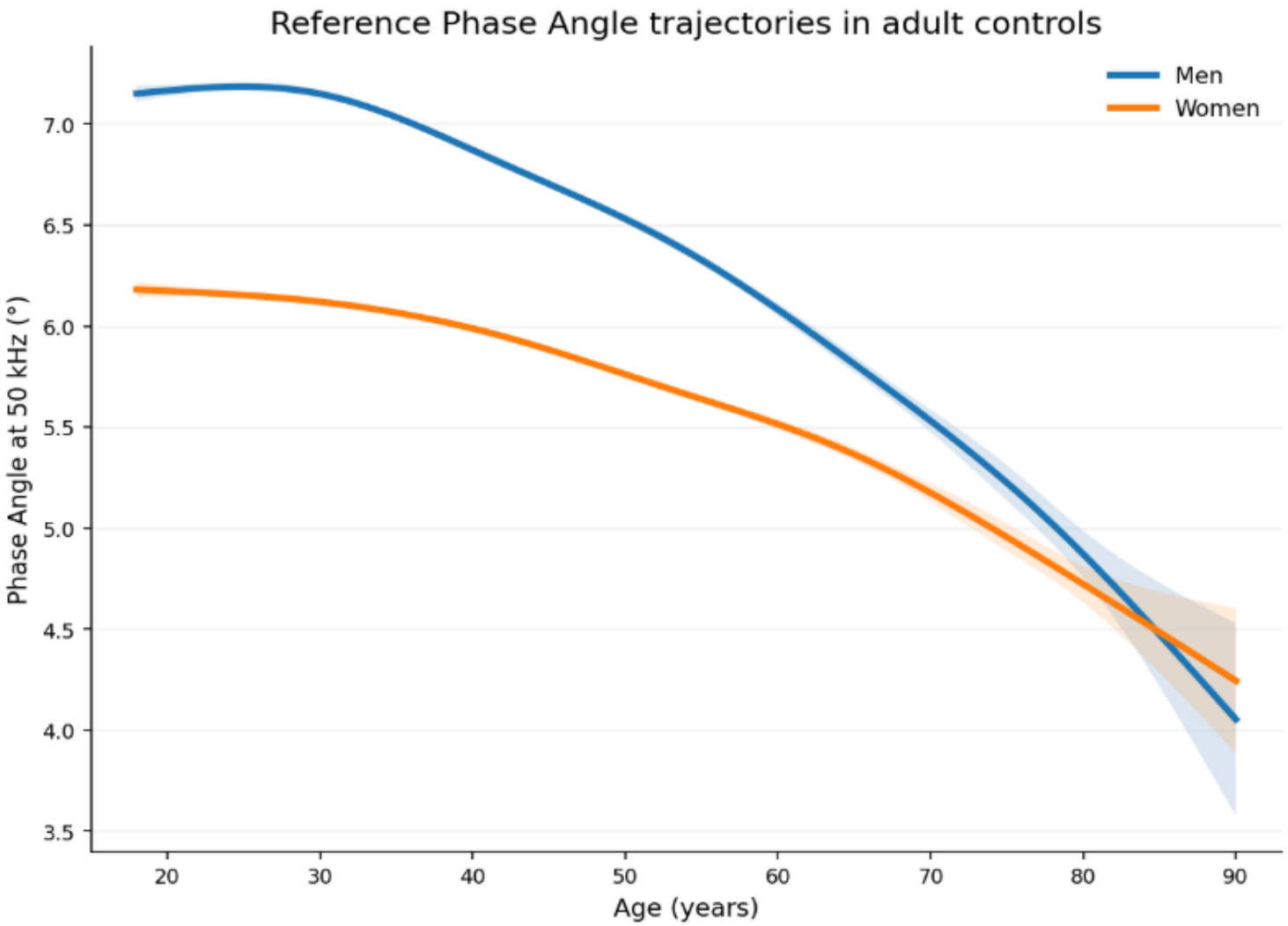


Figure 1

Reference phase angle trajectories in adult controls

Sex specific natural cubic spline trajectories of Phase Angle at 50 kHz among controls. Shaded bands indicate 95% confidence intervals (CI).

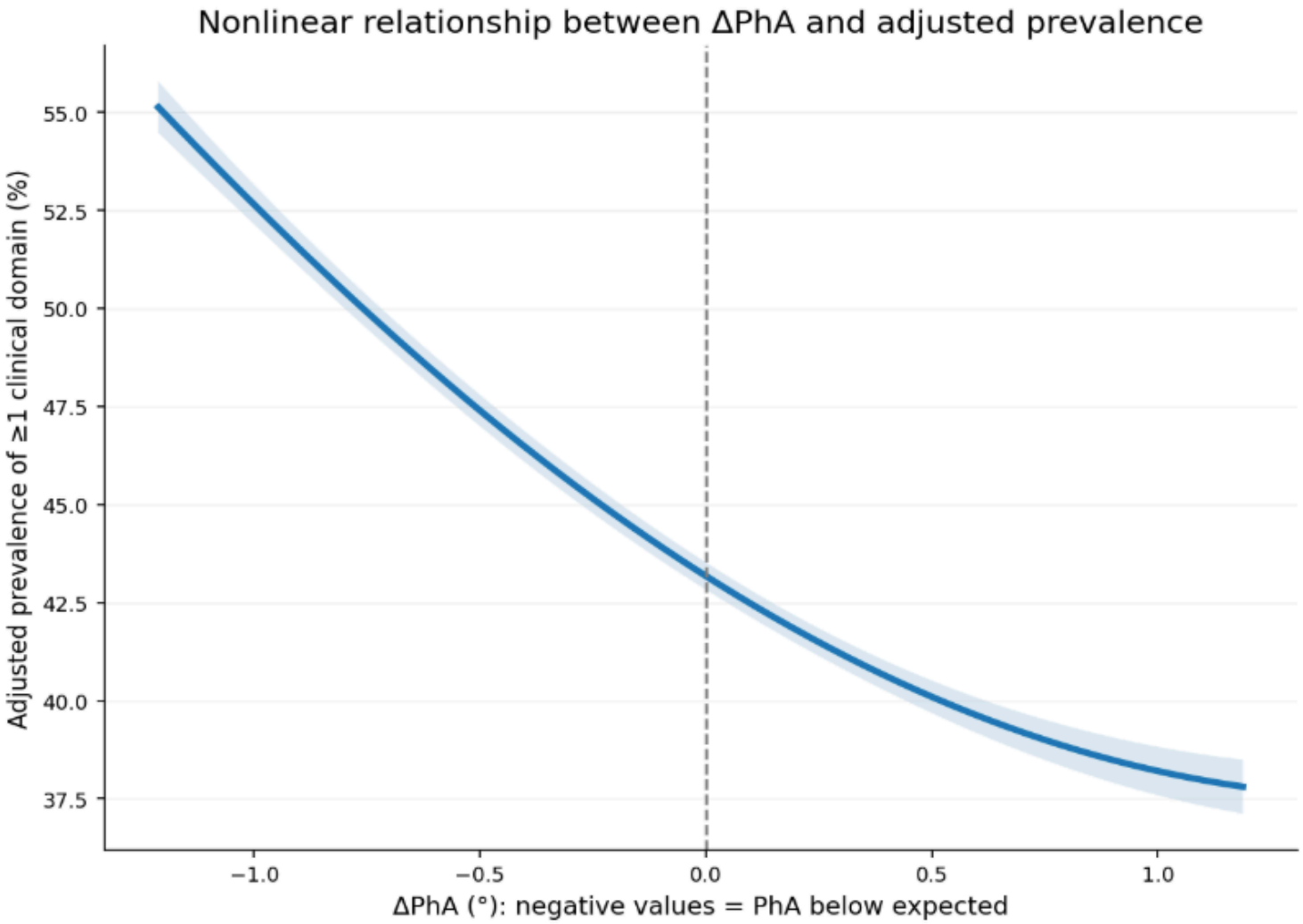


Figure 2

Adjusted prevalence across the phase angle deviation (ΔPhA) continuum

Adjusted marginal prevalence (%) of at least one clinical domain from the 5th to 95th percentile of phase angle deviation (ΔPhA). Estimates were derived from logistic regression with a natural cubic spline of ΔPhA adjusted for age, sex, and body mass index. Shaded bands indicate 95% confidence intervals (CI).

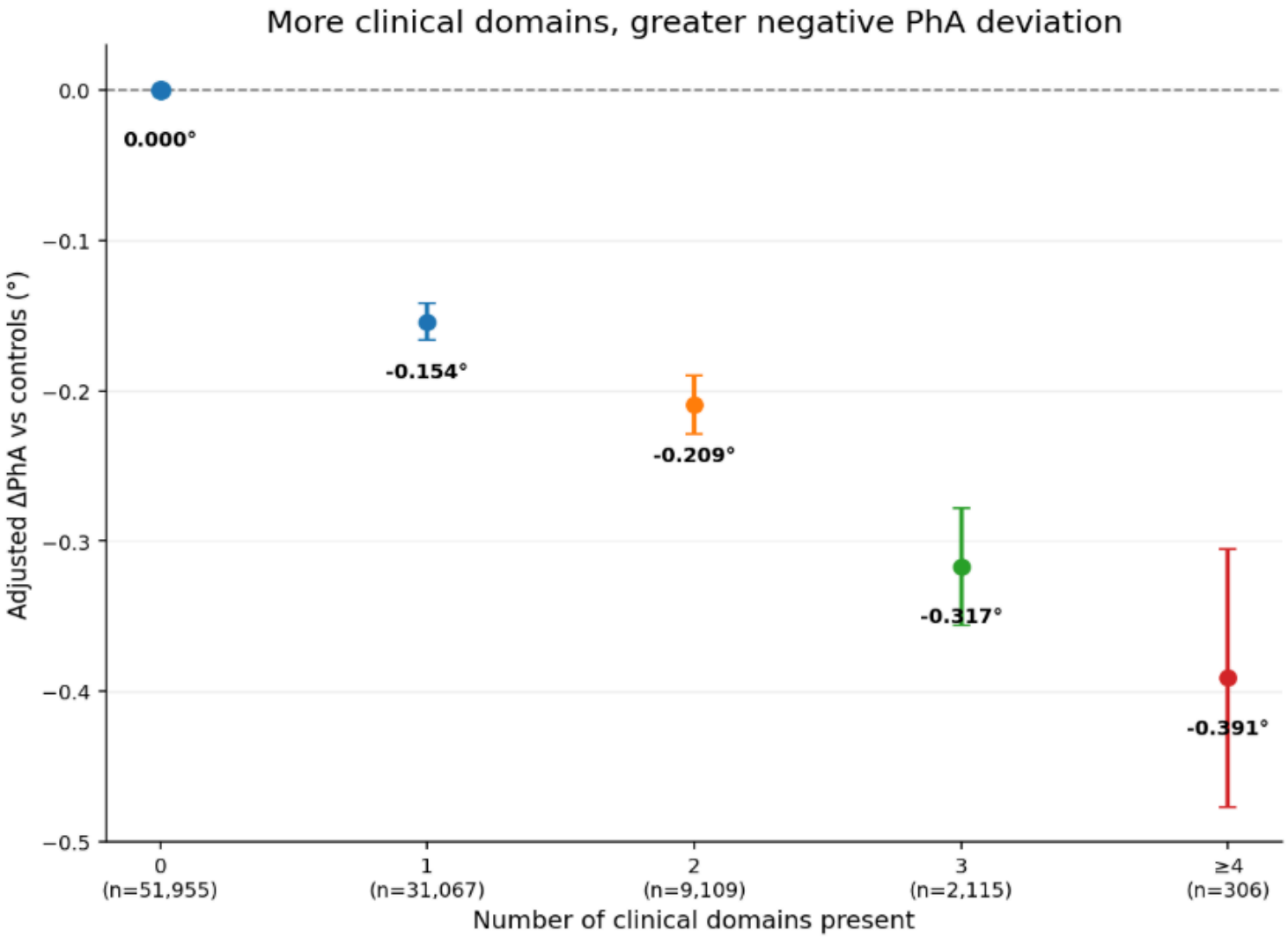


Figure 3

Multidomain burden and adjusted phase angle deviation (ΔPhA)

Adjusted phase angle deviation (ΔPhA) difference vs. controls according to the number of clinical domains present. Error bars indicate 95% confidence intervals (CI). ΔPhA indicates observed phase angle minus age and sex expected phase angle.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement1.docx