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Original article

Associations of the bioimpedance-derived phase angle with early and advanced stages of dysglycemia: Cross-sectional findings from a large population-based study

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SUMMARY

Background & aims: Bioelectrical impedance analysis (BIA) has been widely applied for assessing body composition. The phase angle (PhA), a raw parameter derived from BIA, reflects body cell mass, cellular hydration, and cell membrane integrity. Although the PhA has been proposed as a potential marker for various aspects of diseases, its role in dysglycemia remains uncertain. We therefore aimed to investigate its associations with early and advanced stages of dysglycemia in a large population-based sample.

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Methods: This cross-sectional study used data from participants (19–74 years) enrolled at the baseline assessment (2014–2019) from a large population-based cohort. The whole-body PhA at 50 kHz was obtained from multi-frequency BIA. Two samples were analyzed. In the main sample (N = 178,097), the types of known diabetes (type 1, type 2, and a history of gestational diabetes vs. no diabetes) were ascertained. Among individuals with known type 2 diabetes, data on disease duration, current treatment, glycemic control (hemoglobin A1c levels), and diabetes-related microvascular complications were further analyzed. Additionally, in a random subsample without known diabetes (N = 16,153), oral glucose tolerance tests (OGTT) were performed to ascertain early stages of glucose dysregulation (prediabetes and newly detected diabetes vs. normoglycemia). Logistic regression was applied to assess sex-specific associations of the PhA with glucose dysregulation at different stages.
Results: In the main sample (mean age: 49.5 years; 50.1% men), 309 individuals (0.2%) reported having known type 1 diabetes, 8234 (4.6%) type 2 diabetes, and 1044 (1.2% of women) a history of gestational diabetes. In the OGTT subsample, 2662 participants (16.5%) had prediabetes and 534 (3.3%) had newly detected diabetes. A higher PhA (per 1°) was associated with a lower odds of known type 1 diabetes (relative risk ratio [RRR] and 95% confidence intervals [CIs], men: 0.33 [0.27, 0.40]; women: 0.39 [0.29, 0.52]) and known type 2 diabetes (RRR [95% CIs], men: 0.72 [0.69, 0.76]; women: 0.88 [0.81, 0.96]) after adjustment for age, lifestyle factors, obesity, and disease markers. Stronger inverse associations of the PhA with known type 2 diabetes were observed for those with longer disease duration (i.e., > 10 years), advanced-stage treatment (i.e., insulin only), poorer glycemic control (i.e., hemoglobin A1c $\geq$ 64 mmol/mol), or microvascular complications. Men showed stronger inverse associations with advanced dysglycemia than women ($p_{sex\text{-}interaction} < 0.001$). In contrast to the inverse associations observed for known type 1 and type 2 diabetes, the PhA showed positive associations with early dysglycemia. Specifically, a higher PhA (per 1°) was associated with a higher odds of a history of gestational diabetes (RRR [95% CIs]: women: 1.69 [1.51, 1.88]), prevalent prediabetes (RRR [95% CIs]: men: 1.45 [1.32, 1.59]; women: 1.34 [1.13, 1.58]) and newly detected diabetes (RRR [95% CIs]: men: 1.33 [1.11, 1.60]; women: 1.37 [1.05, 1.79]).
Conclusions: The bioimpedance-derived PhA showed positive cross-sectional associations with early dysglycemia and inverse cross-sectional associations with advanced dysglycemia. The observed associations may partly reflect reverse causation and disease-related changes in body composition accompanying advanced dysglycemia. Longitudinal studies are warranted to assess temporal relationships between the PhA and dysglycemia.

1. Introduction

Diabetes poses a significant global health threat, affecting more than 589 million adults worldwide in 2024 according to the most recent estimates of the International Diabetes Federation [1], while its prevalence, including type 1 diabetes [2], type 2 diabetes [3], and gestational diabetes [4] is expected to increase further. Given its substantial public health burden and detrimental effects on individual health and quality of life, the surveillance and management of diabetes remain an ongoing challenge. Beyond hyperglycemia, diabetes is characterized by profound alterations in body composition and alterations in cellular metabolism and homeostasis, such as fat steatosis [5], muscle strength and quality of life decline [6], inflammation and impaired cell integrity [7]. Therefore, identifying potential metabolic changes across stages of dysglycemia could enhance the understanding of pathophysiological changes, potentially enabling disease course monitoring and facilitating the evaluation of disease severity.

Bioelectrical impedance analysis (BIA) may facilitate this assessment, as it is an affordable, simple, safe, and non-invasive technique for body composition assessment [8]. It has emerged as a promising alternative to more expensive methods, such as dual-energy X-ray absorptiometry, computerized tomography, and magnetic resonance imaging in clinical practice [9]. In particular, the phase angle (PhA), which is calculated directly from raw BIA-measured parameters of resistance (R) and reactance (Xc), has gained increasing attention as a composite indicator of body cell mass (BCM), extracellular/intracellular fluid distribution, and cell membrane integrity and function [10]. Recent evidence suggests that the PhA has the potential to reflect cellular inflammation and oxidative stress [11,12] and is strongly associated with protein markers related to cell proliferation [13]. The PhA has also been suggested to reflect the nutritional (e.g, albumin levels) and functional status (e.g, timed up and go test performance), and lower PhA values have been associated with a variety of metabolic and chronic conditions, such as overweight and obesity, cardiovascular disease, chronic kidney disease, and cancer [14–18]. As a non-invasive and physiologically informative parameter, the PhA has also shown potential for assessing metabolic status and disease severity in individuals with diabetes [19–21], indicating its clinical relevance. Prior studies have reported that individuals with prevalent type 1 and/or type 2 diabetes tend to have lower PhA values than those without diabetes [22–28]. Lower PhA has also been linked to longer disease duration [23] and the presence of diabetes-related complications [29]. However, existing findings are inconsistent. A few studies have observed higher PhA values in individuals with prevalent type 1 and/or type 2 diabetes compared to those without [30,31]. Notably, prior studies were limited by relatively small sample sizes, and most relied on univariate group comparisons, lacking adjustments for potential confounding factors, such as age, sex, obesity, and comorbidities. Moreover, sparse data are available on how the PhA relates to different types of diabetes and to dysglycemia, from early impairments to advanced stages. Additionally, the sex-specific associations of the PhA with diabetes remain uncertain, although sex differences have been reported for both PhA values [32] and diabetes [33]. Therefore, despite the potential as a non-invasive indicator of metabolic status or cellular impairments, the independent relationship of the PhA with different stages of glucose dysregulation, from prediabetes to advanced stages of diabetes, remains unclear.

Using baseline data from the largest population-based cohort in Germany, we aimed to investigate the aforementioned research gaps in men and women separately. First, we assessed the cross-sectional association of the PhA with known type 1, type 2, and a history of gestational diabetes. Second, we examined the associations of the PhA with subgroups of disease duration, current treatment, glycemic control levels, and the presence of diabetes-related microvascular complications among individuals with known type 2 diabetes. Third, to explore its relevance in the early stages of glucose dysregulation, we investigated the associations of the PhA with oral glucose tolerance test (OGTT)-defined prediabetes and newly detected diabetes in a randomly selected subsample of individuals without known diabetes.

2. Methods

2.1. Study design and participants

This cross-sectional population-based study used baseline data from the German National Cohort (NAKO), the largest cohort study in Germany to date, which enrolled more than 205,000 participants aged 19–74 years across 18 study centers in Germany between 2014 and 2019 [34]. All study participants were selected from compulsory registries of residents within the study areas, including urban and industrialized areas as well as rural regions using age- and sex-stratified random sampling [34]. Individuals with insufficient German language skills, or who withdrew consent after the invitation were excluded [35]. Data quality was ensured through centralized and local quality assurance procedures, including standardized protocols and training, regular site visits, and continuous automated data monitoring [35]. A standardized, computer-assisted face-to-face interview, self-administered questionnaires, and various biomedical examinations were performed among all study participants (main sample). An extended 4-h examination protocol was employed in addition to the general examinations on a representative subsample, which was proportionally distributed over all study centers and age groups [34].

In the main sample (Fig. S1), 204,653 individuals, comprising both men and women, were initially included. Exclusions were (i) 6840 participants ineligible for BIA measurement according to the instructions of the user's manual; (ii) 8034 participants with missing values on the PhA; (iii) 258 participants with unclear self-reported diabetes status; (iv) 325 participants with unclear diabetes types; (v) 924 participants with unclear fasting status; and (vi) 10,175 participants with missing values on continuous covariates. Finally, 178,097 participants were included in the main sample. At baseline, excluded participants were slightly older and more obese than included participants but most other characteristics were broadly comparable between both groups (Table S1).

In the OGTT subsample (Fig. S2), 25,238 participants without known diabetes, who were not on glucose-lowering medication or insulin treatment and were not in special conditions such as acute gastrointestinal infection, acute fever-related infection, allergies to the OGTT solution ingredients, pregnancy, or severe gastrointestinal diseases, were randomly assigned to a standard 75 g OGTT following an overnight fast ($\geq$ 8 hours). Exclusions were (i) 7967 participants without valid OGTT data; (ii) 268 participants who were ineligible for BIA measurement; (iii) 566 participants with missing values on the PhA; and (iv) 284 participants with missing values on continuous covariates. A total of 16,153 participants were included in this subsample.

2.2. Bioelectrical impedance analysis (BIA)

The 8-point method with the phase-sensitive multi-frequency device, Medical Body Composition Analyzer (mBCA) 515 seca (Hamburg, Germany), was used for BIA measurements following a standardized protocol by trained staff [36]. Prior to the measurement, pregnant women, participants with electronic or metal implants or portable electronic medical devices, active joint prostheses, amputations of limbs, paralysis, and bandages were excluded [36]. Eligible participants were asked to empty their bladders, avoid physical activity, remove all metallic objects (e.g., jewelry and watches), and remain upright for at least 10 minutes without lying down. During measurement, participants were barefoot and wearing light clothing in a room with a comfortable temperature. Participants were instructed to stand upright, remain still, and avoid speaking. Data were automatically transferred from the device to the database. The 100 μA alternating current and impedance measurement were introduced using stainless steel electrodes, with one pair connected to the feet and three pairs to the hands. The hand electrodes were at three different heights on the device, allowing participants of varying heights to adopt an optimal posture for the measurement. The BIA devices are regularly maintained and checked for accuracy. Center-specific data were compared with the overall means to assess potential systematic differences across study centers. Whole-body average parameters obtained at 50 kHz were utilized, as it is the most widely used frequency for the PhA [37]. The effective bioimpedance-derived components R and Xc in Ω were used to calculate the whole-body PhA: PhA (°) = (arctangent (Xc/R) × 180°/π). Height-normalized R and Xc (Ω/m) were calculated (R/H and Xc/H) to eliminate the conductor length effect.

2.3. Outcomes

Dysglycemia was classified into early stages (prediabetes, newly detected diabetes, and a history of gestational diabetes) and advanced stages (known type 1 and type 2 diabetes). Given the sufficient sample size, our main analysis focused on advanced stages of glucose dysregulation, particularly type 2 diabetes.

In the main sample, participants were classified as having no diabetes (reference group), known type 1, type 2, or a history of gestational diabetes. Known diabetes was ascertained through interviewer-administered questionnaires by asking participants about a previous clinical diagnosis of diabetes. Furthermore, all medications taken within the last 7 days before the interview were documented. All participants with self-reported diabetes were additionally asked how they are currently treated. Classification of diabetes types was based on information on self-reported clinically diagnosed diabetes, age at first diabetes diagnosis, first diagnosis during pregnancy, time interval between diabetes diagnosis and insulin treatment initiation, current use of glucose-lowering medication, age at initiation of insulin treatment and/or oral medication treatment, and baseline body mass index (BMI) (supplementary methods). Women with a history of gestational diabetes who subsequently developed type 2 diabetes were assigned to the type 2 diabetes group. Among participants with known diabetes, data on diabetes duration, types of current antidiabetic treatment, and presence of diabetes-related microvascular complications were also collected via interviewer-administered questionnaires. Additionally, glycemic control was assessed using hemoglobin A1C (HbA1c) levels. Participants with known diabetes were further classified into the following

subgroups. (i) Diabetes duration was defined as the time interval between the age at first diagnosis of diabetes and the age at the baseline examination. It was categorized into short- (0–5 years), medium- (6–10 years), and long-term (> 10 years) durations based on previous literature [38]. (ii) Current anti-diabetic treatment included 'diet only', 'oral glucose-lowering medication only', 'the combined use of insulin and oral glucose-lowering medication', and 'insulin only'. (iii) Glycemic control was classified as 'well-controlled' (HbA1c < 48 mmol/mol [< 6.5%]), 'moderately controlled' (HbA1c ≥ 48 but < 64 mmol/mol [≥ 6.5% but < 8.0%]), and 'poorly controlled' (HbA1c ≥ 64 mmol/mol [≥ 8%]) [39]. (iv) Diabetes-related microvascular complications were categorized as 'without complication' and 'with complication(s)' (supplementary methods). In the OGTT subsample, participants were classified into the following groups: prevalent normoglycemia (reference group), prediabetes, and newly detected diabetes, using the 1999/2006 World Health Organization criteria [40] (supplementary methods).

2.4. Covariates

Age (continuous, years), sex (men/women), education (continuous, years), fasting status (yes/no), smoking status (never/former/current), alcohol consumption status (no/previous/current), physical activity intensity (high/middle/low), intake of lipid-lowering medication (no/yes), cancer treatment within the past 12 months (no/yes), and parental history of diabetes (no/yes) were collected through pre-designed questionnaires, mainly via touchscreen, or with face-to-face interviews when necessary [34]. To ensure a larger overall sample size, we created a "missing" category for participants with missing values on smoking status (2.6%), alcohol consumption (3.7%), physical activity (7.4%), and parental history of diabetes (22.7%), respectively. Waist circumference (continuous, cm), height (continuous, cm), and weight (continuous, kg) were measured using standard methods [36]. BMI (continuous, kg/m^2) was calculated from weight divided by height squared. Body fat percentage (BFP, continuous, %) was calculated based on Kyle's equation [41]. Skeletal muscle mass (SMM, continuous, kg) was estimated using equations developed by Janssen et al. [42] and was further normalized by height squared as SMMI (continuous, kg/m^2). Hypertension (no/yes) was assessed by self-report in combination with blood pressure measurement. Laboratory biomarkers included triglycerides (continuous, mmol/L), high-density lipoprotein cholesterol (HDL-C, continuous, mmol/L), low-density lipoprotein cholesterol (LDL-C, continuous, mmol/l), uric acid (continuous, μmol/L), and estimated glomerular filtration rate (eGFR) (continuous, ml/min/1.73 m^2) (supplementary methods).

2.5. Statistical analysis

All analyses were stratified by sex due to published literature indicating sex differences in the PhA [26]. Baseline characteristics are shown as means (standard deviations) or medians (interquartile intervals) as appropriate for continuous variables and absolute numbers (relative frequencies, %) for categorical variables. One-way ANOVA and the Kruskal–Wallis tests were used to compare normally distributed and skewed continuous variables, respectively, while nominal categorical variables were compared using the Chi-square tests across different groups. Pearson correlation analysis was used to assess correlations between the PhA and normally distributed continuous variables.

We calculated three models for men and women separately. Covariates were selected according to previous literature and data availability. Model 1 was adjusted for study center, age, and fasting status (for the main sample only). Model 2 was adjusted for variables in Model 1 plus waist circumference, education, smoking status, alcohol consumption, and physical activity intensity. Model 3 was further adjusted for HDL-C, eGFR, uric acid, hypertension, intake of lipid-lowering medication, and parental history of diabetes. Multicollinearity of covariates was examined using variance inflation factors.

First, multinomial logistic regression models were used to assess the sex-specific associations of the PhA (and its components Xc/H and R/H) with types of known diabetes compared to no diabetes in the main sample. Second, multinomial logistic regression models were used to evaluate the sex-specific associations of the PhA with subgroups of individuals with known type 2 diabetes, compared to those without known diabetes. Additionally, multinomial logistic regression models were used to explore sex-specific associations between the PhA (and Xc/H and R/H) and early stages of glucose dysregulation compared to normoglycemia in the OGTT subsample. Relative risk ratios (RRRs) and 95% confidence intervals (CIs) were calculated.

Moreover, the following analyses for advanced dysglycemia were limited to known type 2 diabetes (ref. no diabetes) due to smaller sample sizes for known type 1 diabetes. Restricted cubic splines (3–5 knots) were used to test for potential nonlinearity, with three knots selected based on the Bayesian information criterion. Nonlinearity was then evaluated using Wald tests. Moreover, the associations of the PhA fifths with known type 2 diabetes were examined using sex-specific PhA cut-off values. Interaction analyses with multiplicative interaction terms were conducted to test the modifying effect of sex, age groups, and BMI groups. Subsequently, pre-specified stratified analyses by age (< 50 and ≥ 50 years) and BMI (normal weight: 18.5–24.9 kg/m^2, overweight: 25–29.9 kg/m^2, and obese: ≥ 30 kg/m^2) groups were performed for known type 2 diabetes separately in men and women using binary logistic regression. Odds ratios (ORs) and 95% CIs were calculated.

Additionally, among women with a history of gestational diabetes, stratified analyses by the interval between initial diagnosis (≤ 10 and > 10 years) and BIA measurement were performed using binary logistic regression. Sensitivity analyses were performed in both samples by excluding individuals who had received cancer treatment or had missing data on cancer treatment in the previous 12 months, as cancer treatment may influence the PhA. Exclusions comprised 2792 men and 3479 women from the main sample, and 228 men and 252 women from the OGTT subsample. We further excluded 178 women with a history of gestational diabetes who later progressed to type 2 diabetes from the known type 2 diabetes group. We also repeated the analyses after excluding 324 men and 149 women taking sodium–glucose cotransporter 2 (SGLT2) inhibitors, 192 men and 142 women taking glucagon-like peptide-1 (GLP-1) receptor agonists, or 489 men and 267 women who were taking either SGLT2 inhibitors or GLP-1 receptor agonists. Moreover, alternative adjustments were performed to assess the impact of obesity (BMI and BFP), muscle mass (SMM and SMMI). Lastly, we explored the effects of triglycerides and LDL-C despite considerable missingness in these variables.

All analyses were performed using the statistical software R version 4.4.3 [43], a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Description and correlation

The main sample (Fig. S1 & Table S1) consisted of 178,097 participants (mean age: 49.5 years; 50.1% men), of whom 9587 individuals (5.4%) reported having known diabetes. In men, 180

individuals had type 1 diabetes (0.2%), and 5074 had type 2 diabetes (5.7%). In women, 129 individuals had type 1 diabetes (0.1%), 3160 had type 2 diabetes (3.6%), and 1044 had a history of gestational diabetes (1.2%). The whole-body PhA ranged from 2.3° to 8.9° in men, and 2.3°–7.1° in women, with men having a higher mean value than women. Unadjusted PhA values (Table 1) were lower in persons with type 1 diabetes and type 2 diabetes, but higher in women with a history of gestational diabetes compared to participants without diabetes. The distribution of study participants by study centers is provided in Table S2.

In the OGTT subsample (Fig. S2), 16,153 participants (mean age: 48.5 years; 8622 men and 7531 women) were included, comprising 2662 individuals with prevalent prediabetes (1697 men and 965 women), and 534 individuals with newly detected diabetes (357 men and 177 women). Unadjusted PhA values (Table S3) were slightly lower in men with prediabetes and newly

Table 1
Characteristics of the study participants in the main sample (N = 178,097).

	Men				Women				
	No diabetes	Type 1 diabetes	Type 2 diabetes	*p*	No diabetes	Type 1 diabetes	Type 2 diabetes	History of gestational diabetes[a]	*p*
N	83,946	180	5074		84,564	129	3160	1044	
Age, years	48.8 (12.7)	45.6 (12.4)	60.5 (7.6)	<0.001	49.3 (12.6)	43.1 (13.0)	60.0 (8.2)	43.8 (8.5)	<0.001
Fasting status, yes	13,717 (16.3)	6 (3.3)	340 (6.7)	<0.001	1,1654 (13.8)	5 (3.9)	143 (4.5)	123 (11.8)	<0.001
Education, years	15.2 (3.4)	14.9 (3.5)	14.8 (2.6)	<0.001	14.8 (3.3)	14.3 (3.6)	13.7 (2.9)	15.4 (2.7)	<0.001
Waist circumference, cm	95.6 (12.3)	94.2 (12.3)	109.0 (13.5)	<0.001	84.8 (12.9)	86.9 (13.1)	102.5 (14.7)	87.0 (13.6)	<0.001
BMI, kg/m^2	26.9 (4.2)	26.4 (3.7)	31.0 (5.2)	<0.001	25.7 (5.2)	26.7 (5.6)	32.2 (6.5)	26.6 (5.7)	<0.001
BFP, %	31.4 (5.0)	30.9 (5.1)	35.5 (4.8)	<0.001	39.9 (5.2)	40.8 (5.5)	45.2 (4.5)	40.3 (5.4)	<0.001
SMM, kg	29.9 (3.3)	30.4 (3.2)	30.1 (3.7)	0.003	18.8 (2.5)	20.1 (2.7)	19.3 (3.0)	19.5 (2.6)	<0.001
SMMI, kg/m^2	9.3 (0.9)	9.4 (0.8)	9.7 (1.0)	<0.001	6.8 (0.7)	7.2 (0.8)	7.3 (1.0)	7.1 (0.8)	<0.001
Smoking status				<0.001					<0.001
Non-smoker	34,873 (41.5)	75 (41.7)	1340 (26.4)		41,595 (49.2)	68 (52.7)	1391 (44.0)	499 (47.8)	
Former smoker	27,658 (32.9)	55 (30.6)	2330 (45.9)		24,061 (28.5)	27 (20.9)	957 (30.3)	329 (31.5)	
Current smoker	19,625 (23.4)	44 (24.4)	1112 (21.9)		16,602 (19.6)	30 (23.3)	568 (18.0)	195 (18.7)	
Missing	1790 (2.1)	6 (3.3)	292 (5.8)		2306 (2.7)	4 (3.1)	244 (7.7)	21 (2.0)	
Alcohol consumption status				<0.001					<0.001
No	2380 (2.8)	5 (2.8)	200 (3.9)		4081 (4.8)	11 (8.5)	357 (11.3)	73 (7.0)	
Previous	3270 (3.9)	4 (2.2)	440 (8.7)		2858 (3.4)	7 (5.4)	231 (7.3)	46 (4.4)	
Current	75,567 (90.0)	163 (90.6)	4026 (79.3)		74,521 (88.1)	104 (80.6)	2258 (71.5)	897 (85.9)	
Missing	2729 (3.3)	8 (4.4)	408 (8.0)		3104 (3.7)	7 (5.4)	314 (9.9)	28 (2.7)	
Physical activity intensity				<0.001					<0.001
High	25,836 (30.8)	47 (26.1)	1739 (34.3)		25,883 (30.6)	41 (31.8)	1089 (34.5)	319 (30.6)	
Middle	25,930 (30.9)	56 (31.1)	1321 (26.0)		26,561 (31.4)	42 (32.6)	855 (27.1)	291 (27.9)	
Low	25,720 (30.6)	62 (34.4)	1449 (28.6)		26,334 (31.1)	38 (29.5)	877 (27.8)	368 (35.2)	
Missing	6460 (7.7)	15 (8.3)	565 (11.1)		5786 (6.8)	8 (6.2)	339 (10.7)	66 (6.3)	
Triglyceride, mmol/L	1.6 [1.1, 2.3]	1.1 [0.8, 1.6]	2.2 [1.5, 3.2]	<0.001	1.2 [0.9, 1.7]	1.0 [0.8, 1.3]	2.0 [1.4, 2.8]	1.2 [0.8, 1.8]	<0.001
HDL-C, mmol/L	1.4 (0.3)	1.5 (0.4)	1.2 (0.3)	<0.001	1.7 (0.4)	1.9 (0.4)	1.5 (0.4)	1.6 (0.4)	<0.001
LDL-C, mmol/L	3.4 (0.9)	3.0 (0.9)	3.0 (0.9)	<0.001	3.3 (0.9)	2.9 (0.9)	3.3 (0.9)	3.1 (0.8)	<0.001
Uric acid, μmol/L	334.5 (68.7)	279.2 (69.0)	342.6 (80.6)	<0.001	244.3 (61.2)	213.9 (60.9)	303.8 (80.5)	242.7 (56.5)	<0.001
eGFR, ml/min/1.73m^2	100.2 (14.5)	102.5 (19.6)	91.9 (16.3)	<0.001	98.5 (15.1)	102.1 (18.5)	90.6 (16.8)	103.6 (13.2)	<0.001
Hypertension, yes	37,634 (44.8)	96 (53.3)	4090 (80.6)	<0.001	27,330 (32.3)	41 (31.8)	2501 (79.1)	259 (24.8)	<0.001
Intake of lipid-lowering medication, yes	7082 (8.4)	45 (25.0)	2221 (43.8)	<0.001	4480 (5.3)	18 (14.0)	1027 (32.5)	23 (2.2)	<0.001
Parental history of diabetes				<0.001					<0.001
No	49,299 (58.7)	102 (56.7)	1253 (24.7)		46,531 (55.0)	65 (50.4)	624 (19.7)	481 (46.1)	
Yes	16,302 (19.4)	52 (28.9)	1997 (39.4)		19,305 (22.8)	37 (28.7)	1340 (42.4)	363 (34.8)	
Missing	18,345 (21.9)	26 (14.4)	1824 (35.9)		18,728 (22.1)	27 (20.9)	1196 (37.8)	200 (19.2)	
Bioimpedance components									
PhA, ° mean (SD)	5.7 (0.6)	5.4 (0.7)	5.3 (0.6)	<0.001	5.0 (0.5)	4.9 (0.6)	4.9 (0.5)	5.2 (0.5)	<0.001
PhA, °, median [IQR]	5.7 [5.3, 6.1]	5.5 [4.9, 5.9]	5.3 [4.9, 5.7]	<0.001	5.0 [4.6, 5.3]	4.9 [4.5, 5.3]	4.9 [4.5, 5.2]	5.2 [4.8, 5.5]	<0.001
R/H, Ω/m	297.7 (34.8)	295.4 (34.5)	281.9 (35.4)	<0.001	392.3 (45.3)	376.2 (47.0)	360.0 (49.4)	386.2 (47.4)	<0.001
Xc/H, Ω/m	29.7 (4.5)	28.0 (5.1)	26.3 (4.3)	<0.001	34.1 (4.8)	32.0 (5.2)	30.7 (5.0)	34.9 (4.8)	<0.001

Abbreviations: BMI: body mass index; BFP: body fat percentage; SMM: skeletal muscle mass; SMMI: skeletal muscle mass index; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; PhA: phase angle; R/H: resistance by height; Xc/H: reactance by height; SD: standard deviation; IQR: interquartile range.

Data are presented as n (%) for categorical variables and mean (SD) or median [IQR] for continuous variables, as appropriate.

One-way ANOVA and the Kruskal–Wallis tests were used to compare normally distributed and skewed continuous variables, respectively, while nominal categorical variables were compared using the Chi-square test across different groups.

[a] Women with gestational diabetes only included those with a history of gestational diabetes and did not develop type 2 diabetes afterward.

detected diabetes compared to normoglycemia; however, no significant differences were observed in women ($p = 0.210$).

In the main sample (Fig. S3), the PhA showed a moderate positive correlation with Xc/H ($r_{men} = 0.65$; $r_{women} = 0.57$) and a weak positive correlation with BMI ($r_{men} = 0.08$; $r_{women} = 0.16$). In contrast, the PhA had a weak negative correlation with R/H ($r_{men} = -0.07$; $r_{women} = -0.16$) and a moderate negative correlation with age ($r_{men} = -0.50$; $r_{women} = -0.35$).

3.2. Association of the PhA with known diabetes

In the main sample, significant interactions between the PhA and sex were observed for known type 2 diabetes ($p_{interaction} < 0.001$ in all three models). Among men (Fig. 1A), the PhA (per 1°) was inversely associated with both known type 1 (RRR [95% CIs]: 0.33 [0.27, 0.40]) and type 2 diabetes (RRR [95% CIs]: 0.72 [0.69, 0.76]) after full adjustment. Among women (Fig. 1B), the PhA showed a similar inverse association with known type 1 diabetes (RRR [95% CIs]: 0.39 [0.29, 0.52]) but a weaker inverse association with known type 2 diabetes (RRR [95% CIs]: 0.88 [0.81, 0.96]) compared with men. In contrast, a positive association was observed for women with a history of gestational diabetes (RRR [95% CIs]: 1.69 [1.51, 1.88]). Results of all models are shown in Table S4. The Xc/H showed associations similar in direction and magnitude to those observed for the PhA across early and advanced stages of dysglycemia in both men and women (Table S5). In contrast, the R/H showed associations in opposite directions for known type 1 and type 2 diabetes, as well as prediabetes (with no statistically significant association for newly detected diabetes) among men, while no clear associations were observed among women, except for gestational diabetes, where a strong inverse association was observed.

Moreover, inverse nonlinear associations were observed for known type 2 diabetes (men: $p_{non\text{-}linear} < 0.001$, women: $p_{non\text{-}linear} = 0.009$) for both sexes. In men (Fig. 2A), the splines showed a more pronounced nonlinear association than in women, with a higher risk of known type 2 diabetes observed among individuals with PhA values below the median, and a flatter association (men) or no association (women) for PhA values above the median. Compared to the middle group (Fig. S4A), men in the lowest fifth of the PhA had the highest odds (OR [95% CIs]: 1.30 [1.18, 1.43]), while those in the highest fifth had the lowest odds (OR [95% CIs]: 0.85 [0.74, 0.99]). In women, a similar shape was observed at lower PhA values (Fig. 2B); however, the associations were attenuated in both the lowest and highest fifths (Fig. S4B). No significant interactions were detected for age groups or BMI groups (all $p_{interaction} > 0.05$). For men (Fig. S5A), inverse associations of the PhA with known type 2 diabetes were robust across age and BMI groups. For women (Fig. S5B), these associations remained significant in those older than 50 years and in obese individuals.

In sensitivity analyses, the inverse association of the PhA with known type 2 diabetes persisted and remained stronger in men (Fig. S6A) than in women (Fig. S6B). Additionally, the association between the PhA and a history of gestational diabetes was consistent across strata (≤ 10 vs. > 10 years: OR = 1.76 vs. 1.75) defined by the interval between the initial diagnosis and the BIA measurement (Fig. S7).

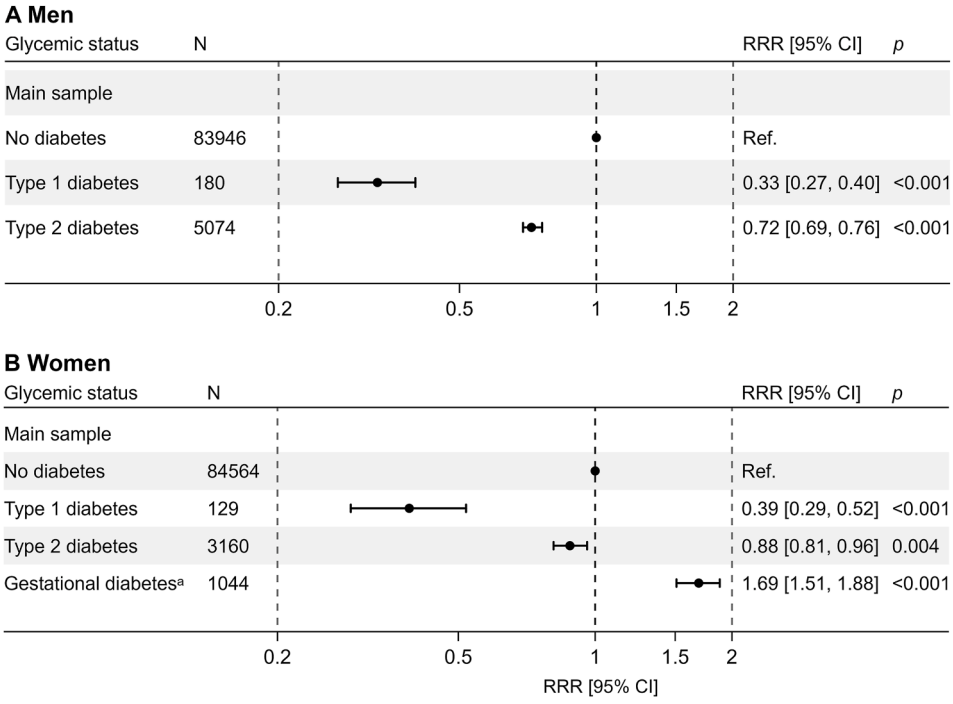

Fig. 1. Associations of the phase angle (PhA) with advanced stages of glucose dysregulation and history of gestational diabetes in the main sample for A) men and B) women
Figure legends:
Abbreviations: RRR: relative risk ratio; CI: confidence interval.
The RRR and 95% CI are per 1-degree increase of the PhA estimated from multinomial logistic regression models.
The reference group refers to participants without diabetes.
Model adjustment (Model 3): adjusted for study center, age, fasting status, education, waist circumference, smoking status, alcohol consumption, physical activity intensity, high-density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, hypertension, intake of lipid-lowering medication, and parental history of diabetes.
[a] Women with gestational diabetes included only those with a history of gestational diabetes who did not develop type 2 diabetes afterwards.

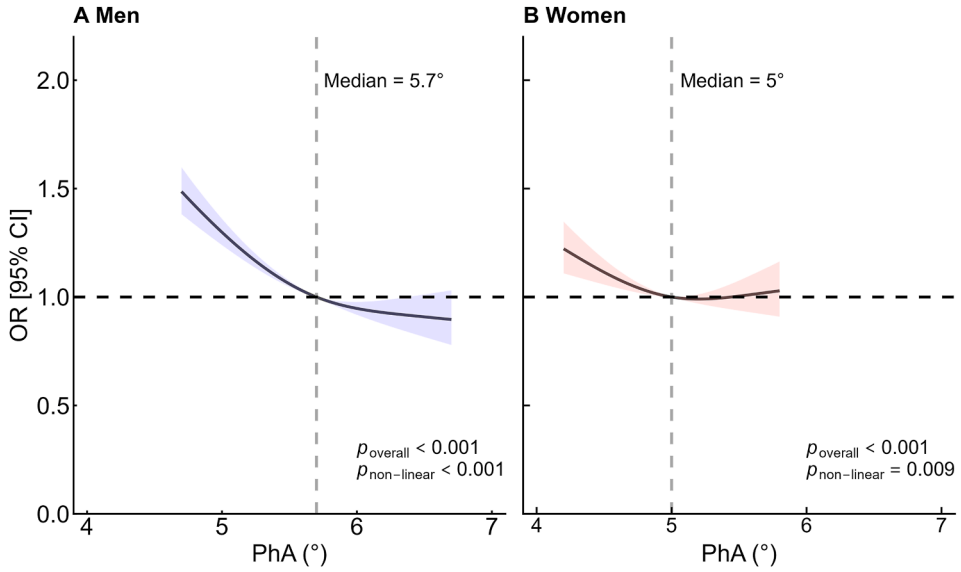

Fig. 2. Nonlinear associations of the phase angle (PhA) with known type 2 diabetes in the main sample for A) men and B) women
Figure legends:
Abbreviations: OR: odds ratio; CI: confidence interval.
Restricted cubic splines were applied to assess the association of the PhA with known type 2 diabetes in the main sample. The upper and lower 5% PhA values were excluded, and the median PhA values were used as reference points. The OR and 95% CI are per 1-degree increase of the PhA.
Model adjustment (Model 3): adjusted for study center, age, fasting status, education, waist circumference, smoking status, alcohol consumption, physical activity intensity, high-density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, hypertension, intake of lipid-lowering medication, and parental history of diabetes.

3.3. Association of the PhA with subgroups of known type 2 diabetes

Inverse associations of the PhA with known type 2 diabetes persisted among most subgroups compared to individuals without known diabetes (Fig. 3). Overall, the inverse associations were stronger in men than in women (all $p_{interaction} < 0.001$). In men (Fig. 3A), compared to those without diabetes, a 1° increase in the PhA was associated with moderately lower odds for the less severe subgroups, and with notably lower odds for the most severe subgroups, including those with long-term diabetes duration (> 10 years), advanced-stage treatment (insulin only), poor glycemic control (HbA1c $\geq$ 64 mmol/mol), and microvascular complications. In contrast, the inverse associations of the PhA with known type 2 diabetes were generally attenuated in women (Fig. 3B), whereas a significant positive association was observed among those who received dietary management only (RRR [95% CIs]: 1.22 [1.06, 1.40]).

3.4. Association of the PhA with prediabetes and newly detected diabetes

In the OGTT subsample (Fig. 4; Table S4), higher PhA values (per 1°) were positively associated with prevalent prediabetes (RRR [95% CIs]: men: 1.45 [1.32, 1.59]; women: 1.34 [1.13, 1.58]) and newly detected diabetes (RRR [95% CIs]: men: 1.33 [1.11, 1.60]; women: 1.37 [1.05, 1.79]) after full adjustments. Higher Xc/H was positively associated with prediabetes in both sexes and with newly detected diabetes in men, while R/H did not show significant associations with newly detected diabetes in both sexes and was inversely associated with prediabetes in men (Table S5). In sensitivity analyses (Fig. S8), the positive associations seen for the PhA were generally consistent for prediabetes; however, a few associations for newly detected diabetes lost statistical significance after adjustments for BMI, SMMI, and triglycerides in men, and triglycerides in women.

4. Discussion

This large-scale, population-based cross-sectional study examined the association between the whole-body PhA at 50 kHz and dysglycemia at various stages. At advanced stages, higher PhA values were associated with lower odds of known type 1 and type 2 diabetes. Men showed more pronounced inverse associations than women. Particularly, across advanced stages of dysglycemia, higher PhA values were associated with a lower odds for type 2 diabetes with a longer disease duration, advanced-stage treatment, poorer glycemic control, and more microvascular complications. In contrast, at early stages, higher PhA values were associated with higher odds of prediabetes, newly detected diabetes, and with a history of gestational diabetes.

4.1. Comparison with prior studies

Evidence on the associations of the PhA with dysglycemia, especially at early stages, remains very limited. We are unaware of any previous study that investigated the association of the PhA with prediabetes or newly detected diabetes. Two prior studies comparing PhA values between women with and without gestational diabetes have reported inconsistent findings. López-Plaza et al. [44] observed no difference in the PhA between 124 women with a history of gestational diabetes and 480 without, whereas Wang et al. [45] reported higher PhA values during early pregnancy in 59 women who later developed gestational diabetes compared with 243 normoglycemic women. Both studies were limited by small sample sizes and a lack of confounder adjustment.

At advanced stages, most existing studies involving fewer participants than ours have linked lower whole-body PhA values to a higher likelihood of established type 1 and/or type 2 diabetes compared to those without [22–28], which aligns with our results. For example, Dittmar et al. [23] observed lower PhA values at 50 kHz in 182 men and women with type 2 diabetes compared with 107 age- and BMI-matched healthy controls. Lower PhA

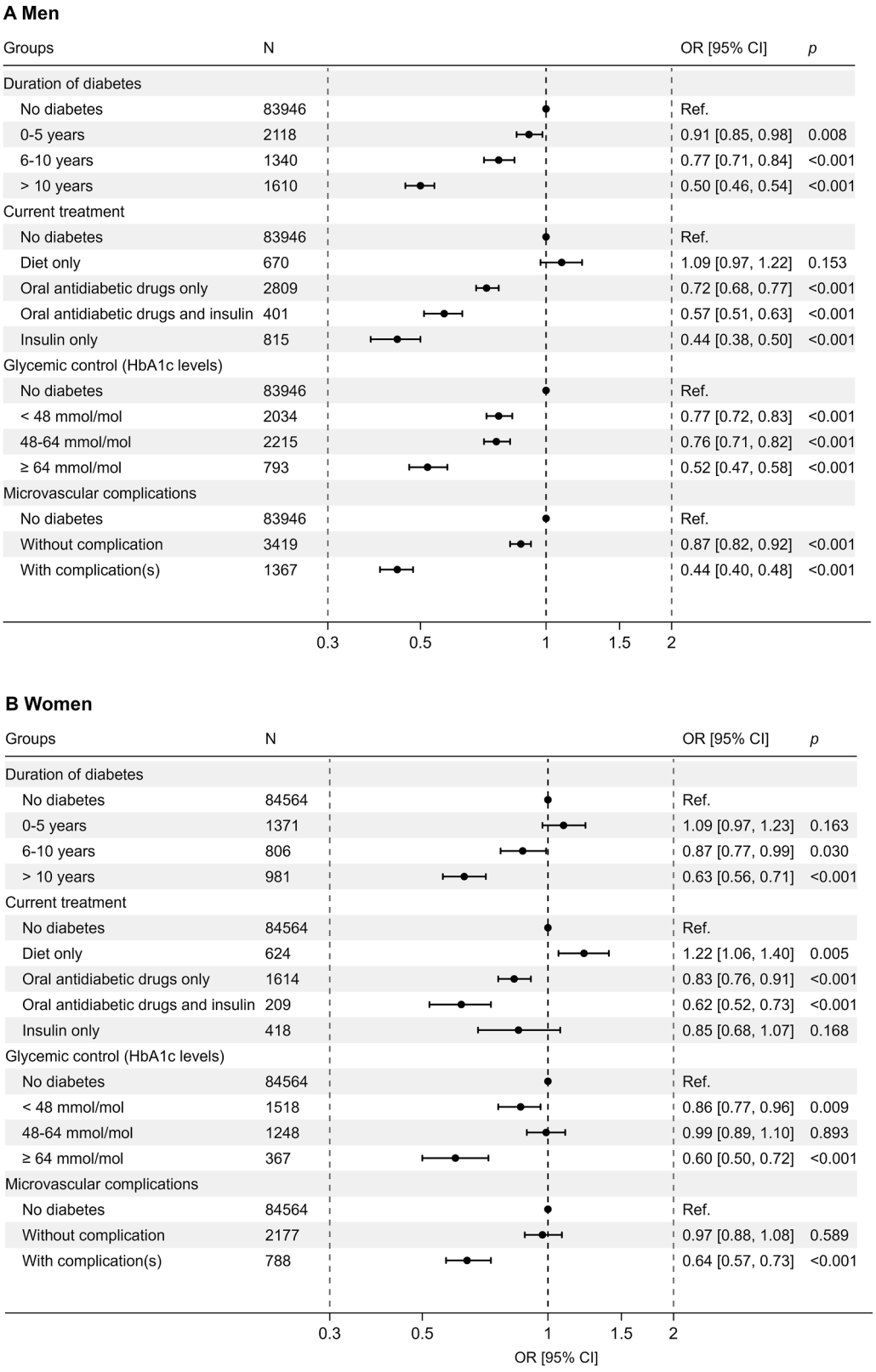

Fig. 3. Associations of the phase angle (PhA) with known type 2 diabetes subgroups defined by duration of diabetes, treatment, glycemic control, and microvascular complications in the main sample, for A) men and B) women
Figure legends:
Abbreviations: RRR: odds ratio; CI: confidence interval; HbA1c: hemoglobin A1C.
The RRR and 95% CI are per 1-degree increase of the PhA estimated from multinomial logistic regression models. The reference group refers to participants without known diabetes, and the comparison group refers to participants with known type 2 diabetes. For each subgroup analysis, participants in the comparison group with missing data on duration of diabetes, current treatment, HbA1c values, or complications were excluded separately.

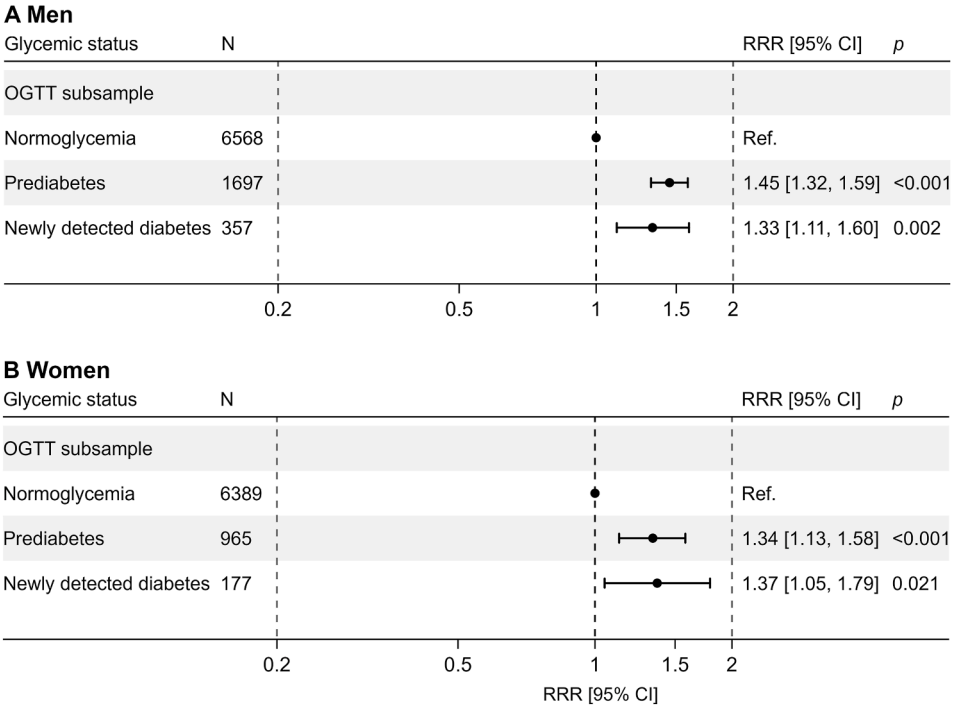

Fig. 4. Associations of the phase angle (PhA) with early stages of glucose dysregulation in the OGTT subsample for A) men and B) women
Figure legends:
Abbreviations: RRR: relative risk ratio; CI: confidence interval; OGTT: oral glucose tolerance test.
The RRR and 95% CI are per 1-degree increase of the PhA estimated from multinomial logistic regression models. The reference group refers to participants with normoglycemia. Model adjustment (Model 3): adjusted for study center, age, education, waist circumference, smoking status, alcohol consumption, physical activity intensity, high-density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, hypertension, intake of lipid-lowering medication, and parental history of diabetes.

values have been associated with longer duration of diabetes [23,25], poor glycemic control as reflected by HbA1c levels [46], and various diabetes-related complications such as diabetic polyneuropathy [47,48], diabetic chronic kidney disease [49], microalbuminuria [50], and diabetic foot ulcers [51]. However, prior findings on the role of treatment modalities in relation to the PhA are inconsistent. For example, Dittmar et al. [23] found no significant differences in PhA values among 54 participants without treatment, 57 participants receiving oral glucose-lowering medication, and 58 participants receiving insulin treatment. Mancinetti et al. [52] observed that the PhA increased significantly after insulin treatment among 36 adults aged $\geq$ 65 years with type 2 diabetes. We observed the strongest inverse association of the PhA with known type 2 diabetes in men receiving insulin-only treatment compared to participants without known diabetes, while no significant associations were observed in women. These discrepancies may be explained by small sample sizes, differences in reference groups, or sex. Men generally have higher PhA values than women throughout the lifespan [32]. However, sex-specific associations between the PhA and diabetes have been rarely reported before, likely due to limited sample sizes in previous studies. Only one study with a relatively large sample size [26] reported sex differences, with an inverse association of the PhA with prevalent type 2 diabetes in men but not in women. They also reported that men receiving oral glucose-lowering medications showed significantly lower PhA values compared with those without diabetes, but no significant differences were found in women [26]. In the present study, men showed stronger inverse associations of the PhA with known type 2 diabetes than women. Unlike prior studies indicating no differences between type 1 and type 2 diabetes [22,53], we found stronger inverse associations of the PhA with type 1 diabetes compared to type 2 diabetes. This discrepancy may be due to the larger sample sizes in our study compared to previous studies, which provided greater statistical power. Notably, contrary to the present results and other previous studies, two other studies observed higher PhA values among individuals with type 1 or type 2 diabetes. Buffa et al. [31] observed higher PhA values among individuals with type 2 diabetes who were not on insulin treatment compared to those without diabetes, and Salis et al. [30] found that individuals with both controlled and uncontrolled diabetes had higher PhA values than those without diabetes. These discrepancies could be potentially explained by variations in disease stages, population heterogeneity in ethnicity, insufficient adjustment for potential confounders (age, sex, obesity, etc.), or differences in bioimpedance measurement methods.

4.2. Potential mechanisms across stages of dysglycemia

At advanced stages, stronger inverse associations of the PhA and established type 1 or type 2 diabetes were observed among individuals with longer disease durations, microvascular complications, or more advanced treatment regimens. These patterns may be associated with underlying cellular metabolic disturbances. Jun et al. [25] suggested that the lower PhA among persons with diabetes may be induced by chronic hyperglycemia or

Model adjustment (Model 3): adjusted for study center, age, fasting status, education, waist circumference, smoking status, alcohol consumption, physical activity intensity, high-density lipoprotein cholesterol, estimated glomerular filtration rate, uric acid, hypertension, intake of lipid-lowering medication, and parental history of diabetes.

glycemic variability, which might induce an osmotic effect, followed by a water shift from the intracellular to the extracellular space. Dittmar et al. [23] suggested that lower PhA values in persons with poorly controlled type 1 diabetes indicated a catabolic state and a longer duration, in which prolonged insulin deficiency increases protein breakdown and leads to metabolically active BCM loss. Prior knowledge has linked a lower PhA to inflammation and oxidative stress [11], which can damage the cell membrane and lead to a functional loss of cell number and altered intra- and extracellular water distribution [54]. Based on in vitro experiments, Lukaski et al. [10] suggested that a greater decrease in the PhA at 50 kHz resulted from the destruction of cell membrane integrity, accompanied by the simultaneous movement of fluid from the intracellular to the extracellular space. Decreased PhA values have been predominantly associated with a decrease in Xc (reduced cell integrity and extracellular water expansion) and only smaller reductions in R (slight increases in total body water) [10]. Aligned with this, in the present study, higher Xc/H was robustly associated with lower odds of known type 1 and type 2 diabetes in both sexes, whereas R/H showed opposite associations among men, but no significant associations among women. Furthermore, our previous study found that the PhA was inversely associated with insulin-like growth factor binding protein 2 [13], further supporting the link between the PhA and BCM. Therefore, lower PhA values observed in individuals with known type 1 or type 2 diabetes may be associated with accumulative metabolic disturbances at the cellular level, including reduced BCM, impaired cell membrane integrity, and intra- and extracellular water redistributions. Importantly, a positive association was observed among women receiving diet-only management, with effect estimates comparable to those for newly detected diabetes, suggesting a less severe dysglycemic stage corresponding to the early-stage pattern.

Notably, sex differences in the associations between PhA and dysglycemia became more pronounced at more severe stages of dysglycemia. In our study, men with type 2 diabetes typically had longer diabetes duration, higher proportions of insulin-only treatment, poorer glycemic control, and more complications than women, which may partially explain the stronger inverse associations observed for overall type 2 diabetes in men. Additionally, the observed sex differences may be related to differences in body composition and metabolic profiles. Men generally have higher SMM and tend to rely more on glucose metabolism (e.g., increased glycolytic enzyme expression), whereas women tend to have a higher adiposity and a more efficient fat metabolism, especially before menopause [55,56]. As the PhA is primarily determined by BCM, particularly SMM, rather than adipose tissue [57], muscle-related alterations may be more likely captured by the PhA in men, potentially explaining the more pronounced associations observed in men. In contrast, higher body fat in women may attenuate the relationship between PhA and dysglycemia. Other sex-specific factors, such as hormones, menopausal status, reproductive factors, differences in risk factor burden, and treatment adherence [33] may also contribute to the observed sex differences.

In contrast, the positive associations of the PhA with early stages of glucose dysregulation remain largely unexplored. Higher PhA values could be associated with several compensatory metabolic adaptations in individuals at early stages of dysglycemia. At the cellular level, one possible explanation is that higher PhA values are linked with greater BCM, particularly in metabolically active tissues such as skeletal muscle. Consistently, we found that when incorporating Xc/H and R/H in the same model, Xc/H (mainly related to BCM) showed associations in the same direction and magnitude as those observed for the PhA. As discussed by Rosa et al. [57], in obesity-related conditions, although increased adiposity may impair electrical conductivity, greater BCM may compensate by increasing cellular capacitance, potentially contributing to higher PhA values. Moreover, as the PhA partially reflects cell membrane integrity and body water distribution, higher values may also indicate preserved or even upregulated cellular functional status, possibly related to increased intracellular water proportion (e.g., cell swelling) and enhanced cellular activity (e.g., protein synthesis) during early adaptive responses [57,58]. At the tissue level, higher PhA values in early dysglycemia may be related to insulin resistance-related muscle changes (e.g., increased intramuscular water, altered membrane permeability) [58], following increased muscle mass. Aligned with this, we observed that individuals with early dysglycemia had higher SMMI than those with normoglycemia. However, differences in muscle mass may only partly explain the observed associations of the PhA with early dysglycemia, which remained similar after adjustment for SMMI among women, while some attenuation was observed among men. In addition, the observed positive association of the PhA with a history of gestational diabetes may relate to persistent metabolic alterations (e.g., insulin resistance and β-cell dysfunction) [59,60] or metabolic memory [61]. Such alterations among women with a prior diagnosis of gestational diabetes are likely to persist over time, as the positive association of the PhA with a history of gestational diabetes was consistent across shorter and longer intervals between the occurrence of gestational diabetes and PhA measurements. Interestingly, Xc/H (positive) and R/H (inverse) demonstrated opposite associations with a history of gestational diabetes, further strengthening the combined influence of long-term metabolic alterations post-pregnancy, such as larger BCM and increased cellular hydration. Nonetheless, these hypothesized biological mechanisms linking the PhA to early dysglycemia and gestational diabetes remain inadequately understood.

4.3. Clinical implications and future directions

Although the PhA is a simple, non-invasive, and widely accessible BIA-derived parameter, current evidence is insufficient to support its routine use for diabetes screening or management. While the PhA may provide complementary information on metabolic and body composition changes, its incremental value for diabetes management beyond established markers such as HbA1c remains to be investigated. Given the relatively low cost and portability of BIA devices, PhA assessment is feasible in resource-limited settings and therefore warrants future investigation as a potential screening tool. Future research is required to establish the relationship between the PhA and glucose metabolism across different stages of disease and to elucidate the pathophysiological mechanisms. In addition, further studies in diverse ethnic or geographic populations are needed to confirm the generalizability of our findings and to establish population- and device-specific cut-offs for future clinical use.

4.4. Strengths and limitations

The large sample size and in-depth phenotyping of this population-based cohort enabled us to adjust for several potential confounders, whereas prior studies were limited to hospital or specific community-based settings and primarily reported univariate or minimally adjusted results. Using the largest population-based data available from Germany, this study had sufficient statistical power to examine different types of known diabetes and to investigate subgroup differences within the same population. The large sample size also enabled sex-specific analyses, overcoming a key limitation of prior studies with insufficient power to examine sex differences. Importantly, the availability of

OGTT data allowed us, for the first time, to assess the PhA at early stages of glucose dysregulation. In addition, our study contributes to the limited research on the PhA in women with a history of gestational diabetes within a large population-based sample.

The present study has several limitations. First, the present study is cross-sectional, which hinders the investigation of longitudinal changes within participants during glycemic deterioration. Furthermore, reverse causation cannot be ruled out, for instance, diabetes-related treatments or complications may influence the PhA rather than changes in the PhA preceding disease progression. Second, prevalent diabetes was self-reported, which might have introduced recall bias. Third, our diabetes classification approach may have introduced misclassification. Type 1 diabetes was, for example, defined using age at diagnosis $\leq$ 30 years in combination with current insulin therapy started within one year after diagnosis. Due to the age restriction, some individuals with latent autoimmune diabetes in adults may have been missed. Furthermore, diabetes may be underestimated due to a 45-year age cutoff. In the OGTT subsample, newly detected diabetes presumably reflects shorter disease duration, although longer-standing undiagnosed diabetes cannot be fully excluded. Fourth, time-of-day variations and menstrual cycle phase in women which may influence hydration status and therefore BIA-derived PhA, were not considered. Fifth, despite extensive adjustment for many potential confounders, residual confounding from unmeasured factors cannot be ruled out. Sixth, including waist circumference in the models might introduce overadjustment and remove part of the effect by which the PhA relates to dysglycemia. However, results were consistent when removing obesity markers, supporting the robustness of our results. Seventh, body composition parameters such as BFP were derived from the same bioimpedance components as the PhA, representing a potential source of common bias.

5. Conclusion

This large-scale population-based study demonstrated cross-sectional associations of the whole-body PhA with dysglycemia. Specifically, the PhA was inversely associated with advanced dysglycemia, including known type 1 and type 2 diabetes, with stronger inverse associations among individuals with long-term and poorly controlled type 2 diabetes, and more pronounced associations in men than in women. In contrast, the PhA was positively associated with early dysglycemia, including prediabetes and newly detected diabetes. However, given the cross-sectional design, reverse causation and diabetes-related changes in body composition cannot be excluded. Further longitudinal studies are warranted to assess the temporal relationship of the PhA with diabetes development or progression.

Data availability

Access to and use of NAKO data can be requested via the online application portal (https://transfer.nako.de/transfer/index).

Author contributions

Conceptualization, BT and MH; Data curation, BF, VP; Formal analysis, FA; Investigation, All authors except FA, MH, and MD; Methodology, BT, MH, AP, MD, FA; Project administration, BT and MH; Supervision, BT, AP, MD, and MH; Writing - original draft, FA; Writing - review & editing, all authors.

FA and BT are responsible for the final content and data integrity, with full access to all study data and oversight of the accuracy of the data analysis.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2026.106729.

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