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Nontraditional Factors Influencing Cardiovascular Disease Risk: Correlation Among Framingham Risk Score, Body Composition Index, and Sleep-Breathing Monitoring Index

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Keywords: body composition | cardiovascular disease | ECW/TBW | Framingham risk score | sleep-breathing monitoring

ABSTRACT

To examine the correlation among body composition, sleep-breathing indicators, and Framingham risk score (FRS) to identify and amplify nontraditional factors that influence the risk of CVD in males, A total of 195 male participants underwent examinations for body composition and sleep-breathing monitoring. We compared the differences in individual factors across various FRS groups. We further conducted multiple linear regression analysis. A cutoff value of FRS ≥ 14 was utilized, and potential influencing factors were examined by logistic regression analysis. Statistical differences were observed in the levels of fasting blood glucose (FBG), CO_2, serum ferritin, hemoglobin (HB), and ECT/TBW among the FRS tripartite groups. However, no significant differences were found in AHI and $MSpO_2$. The multiple linear regression analysis revealed positive correlations between ECW/TBW and FBG with FRS ($\beta = 0.324$ and 0.324, $p < 0.001$), while HB and muscle/fat mass exhibited negative correlations with the score ($\beta = -0.185$ and -0.169, $p < 0.01$). These five factors—ECW/TBW, FBG, HB, serum ferritin, and muscle/fat mass—collectively accounted for 28.6% of the variation in FRS. A higher ECW/TBW was significantly associated with FRS ≥ 14 (OR = 2.208, 95% CI: 1.503–3.244). Conversely, reduced levels of muscle/fat mass, HB, and basal metabolic rate (BMR) were significantly linked to moderate-to-high CVD risk ($OR_{ratio} = 0.532$, 95% CI: 0.284–0.996; $OR_{HB} = 0.961$, 95% CI: 0.932–0.991; $OR_{BMR} = 0.997$, 95% CI: 0.995–1.000). This study revealed correlations among ECW/TBW, HB, FBG, and muscle-to-fat mass ratio with the risk of CVD predicted using FRSs.

JEL Classification: Integrity Check

LiBo Zhao, Xin Xue, and Yinghui Gao contributed equally to this work.

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Summary

- What is the current knowledge on the topic?
  - Framingham's research is critical to the risk assessment and prevention of cardiovascular disease (CVD). With the progress of science and technology, the items of health examination are more and more complete. It makes sense to correlate new examinations and new indicators with cardiovascular risk.
- What question did this study address?
  - The previous Framingham study included only traditional factors such as blood pressure and lipids. This study adds to the evidence that body composition and other indicators are associated with CVD risk in male Chinese.
- What Does This Study Add to Our Knowledge?
  - These five factors—ECW/TBW (extracellular water/total body water), fasting blood glucose, hemoglobin, serum ferritin, and muscle/fat mass—collectively account for 28.6% of the variation in FRS. Analysis with CVD risk of $\geq$ 18.4% suggested that ECW/TBW is a risk predictor, while muscle/fat mass, hemoglobin, and basal metabolic rate are protective predictors. These provide a more comprehensive reference for the individualized prevention of CVD.
- How might this change clinical pharmacology or translational science?
  - In the prevention and treatment strategy of CVD, in addition to traditional factors such as blood pressure and lipids, attention should also be paid to nonconventional indicators such as body composition and sleep-breathing status in order to more effectively and accurately help prevent and control CVD.

1 | Introduction

As living standards continually improve, cardiovascular disease (CVD) emerges as a paramount health concern, significantly threatening health and life. The Global Burden of Disease Study estimates that the global age-standardized CVD mortality rate averages 235 cases per 100,000 population [1]. At present, the number of people suffering from cardiovascular diseases in China has reached 330 million, including 13 million strokes and 11.39 million coronary heart disease (CHD) [2]. Therefore, it is of great significance to study the influencing factors and risk prediction of CVDs.

Currently, prioritizing CVD risk assessment is crucial for prevention and treatment. Framingham's study stands as a cornerstone in American medicine epidemiological research, making it a pivotal moment in global CVD prevention. It yields substantial evidence supporting primary prevention strategies for CHD [3]. The Framingham risk score (FRS), derived from factors such as blood pressure, smoking, diabetes, blood lipids, and age, predicts the risk of CVD for an individual over the following decade [4]. While FRS lacks certain factors, such as family history of CVD, BMI, exercise habits [5], and other information, it maintains high sensitivity and specificity in predicting the degree of risk of CVD [6]. Since the late 1970s, the death rate from CVDs in the United States has exhibited a steady and even declining trend. The emergence of this "inflection point" is directly linked to the Framingham study, underscoring the effectiveness and significance of FRS in preventing and treating CVD. FRS is widely acknowledged as a vital tool for predicting individual CVD in domestic and international settings within the field of chronic disease.

Besides conventional factors such as age, blood pressure, and blood lipids, which are known to influence CVD, studies exploring the correlation between FRS and emerging indicators during newly developed physical examinations in recent years remain limited. These include body composition analysis and sleep-breathing monitoring. Bioelectrical impedance analysis (BIA) is a simple and noninvasive method that offers reliable information on bioelectric parameters, reflecting nutritional status and body composition data [7]. The test not only enables measurement of BMI but also facilitates analysis of muscle content, fat percentage, and fluid storage. The study by Bond et al. [8] showed that increased body fat mass strongly correlates with an elevated resting heart rate and diastolic blood pressure. Skin fold measurements were employed in the study above to estimate fat mass, a method potentially less accurate than the BIA employed in our study.

Good sleep quality is identified as one of the American Heart Association's (AHA) Life's Essential 8 (LE8) [9]. Considering the significant link between sleep health and CVD, the New York Heart Association suggests that a formal sleep evaluation is reasonable for patients with CVD or excessive daytime sleepiness [10]. Polysomnography (PSG) monitoring can help objectively and accurately detect apnea and hypoxia levels during sleep. Repeated occurrences of complete and/or partial upper airway obstruction in the body can result in intermittent hypoxemia, autonomic fluctuations, and sleep fragmentation, which are physiological disturbances linked to heightened CVD risk [11].

However, the imbalance in the sex ratio among study participants and recognition of sex differences influencing CVD and body composition remain unclear [12]. Therefore, this study aimed to examine the correlation between nontraditional clinical measures such as sleep apnea and body composition and FRS risk stratification in men exclusively. Extensive exploration of potential factors influencing CVD could offer a more comprehensive understanding of the features contributing to the occurrence or progression of CVD.

2 | Materials and Methods

2.1 | Study Population

This cross-sectional observational study was conducted at the Department of International Medicine of the Chinese People's Liberation Army General Hospital (PLAGH). Male hospitalized individuals who experienced PSG between September 2019 and October 2022 were included. This study was conducted in strict accordance with the Declaration of Helsinki and had been approved by the Ethics Committee of the Chinese PLAGH (S2022-366-01). Basic information and clinical monitoring data about participants were strictly managed and kept confidential.

This study investigated the correlation among body composition, sleep-breathing status, and predicted CVD risk solely within a male population. The exclusion criteria included individuals with water imbalance, such as patients with oliguria, cardiac, or renal insufficiency. In addition, patients unable to participate in the examination, such as those with malignant tumors, cachexia, or mental disorders, were further excluded. Since BIA was included in the research protocol, individuals with pacemakers or defibrillators were excluded. Furthermore, for sleep-breathing analysis, patients with central sleep apnea–hypopnea frequency exceeding half of the total sleep apnea–hypopnea frequency due to central depression or other causes, and individuals with resting pulse oxygen saturation ($SpO_2 < 90\%$) were excluded. Therefore, the samples for the final analysis were collected from 195 men.

2.2 | Data Collection

BIA: The instrument used to measure the impedance value of the human body was sourced from InBody Co. Ltd., Shanghai, China. This modern BIA technology facilitates easy, rapid, and accurate acquisition of body composition data without subjecting individuals to X-ray exposure [13]. We conducted periodic checks on the instrument using fixed resistors and capacitors. Participants were instructed to avoid strenuous physical activity on the day preceding the test. On the morning of the test, individuals were required to have an empty stomach and bladder. The testing procedures were conducted under strict standardized conditions, ensuring consistent measurement of all body composition-related parameters by a designated professional technician and utilizing the same equipment. The patients were instructed to wear light clothing, stand barefoot on the instrument, keep their arms extended without touching their bodies, and ensure that their inner thighs did not touch.

Clinical indexes: The age, height, and weight of participants were recorded within 12 h of admission, along with prevalent comorbidities and history of tobacco and alcohol use. Participants were instructed to abstain from staying up late or consuming alcohol within 3 days before blood sampling. Subsequently, blood was drawn in the morning after fasting to measure blood-related indicators, such as total cholesterol and creatinine. Two senior laboratory technicians examined the blood test results. Diabetes diagnosis was based on a fasting blood glucose (FBG) level $\geq$ 126 mg/dL, glycosylated hemoglobin (HB) A1c level $\geq$ 6.5%, or the use of any form of hypoglycemic treatment [14]. Smoking and tea consumption were prohibited 30 min before blood pressure measurement, and patients were instructed to rest quietly and empty their bladders before measurement. Blood pressure was then measured on the right upper arm using a calibrated electronic sphygmomanometer by an experienced caregiver while the participant was seated quietly.

Polysomnography (PSG): Participants avoided tea, coffee, alcohol, and sedatives prior to PSG monitoring. Monitoring was conducted overnight using Compumedics equipment (Melbourne, Australia), recording electroencephalogram, sleeping posture, airflow, pulse oxygen saturation, etc. All indexes from PSG were automatically analyzed and manually calibrated by two professional sleep technologists, which were then collated again by a senior sleep medicine physician. Respiratory events were assessed per the American Academy of Sleep Medicine criteria [15]. When the peak value of the airflow intensity signal decreased by $\geq$ 90% and lasted for more than 10 s, it was scored as sleep apnea. Sleep hypopnea was rated if the airflow intensity reduced by $\geq$ 30% for more than 10 s and SpO_2 decreased by $\geq$ 3%. The apnea–hypopnea index (AHI, defined as the number of apnea and hypopnea per hour during sleep), the lowest pulse oxygen saturation ($LSpO_2$), the mean pulse oxygen saturation ($MSpO_2$), and the length of time the SpO_2 was below 90% (T90) were recorded.

FRS: The scores were calculated based on the method proposed by the Framingham Heart Study for predicting CVD risk. Specifically, it was the cumulative sum of scores for age, total cholesterol, HDL-C, and systolic blood pressure levels, as well as whether they smoked and had diabetes. Moreover, the Framingham Heart Study directly and clearly demonstrated that each FRS score corresponded to a probability of CVD risk and predicted heart age [3]. Additionally, heart age is an index that can represent the heart's physiological function.

2.3 | Statistical Analyses

Statistical analysis was conducted using SPSS software, version 25. Initially, the research data were categorized into three groups based on the FRS tripartite. Before analyzing the measurement data, tests were conducted to assess homogeneity of variance (Levene's test) and normality (Kolmogorov–Smirnov test). Variables with a normal distribution were reported as mean $\pm$ standard deviation, and the One-Way ANOVA test was utilized to compare between groups. Skew variables were expressed as median (interquartile distance) [M(Q1, Q3)], and the nonparametric Kruskal–Wallis H test was employed to compare the differences between the three groups. Fisher's precise test and chi-square test were used for unordered results in categorical data. Since FRS was found to be skewed in this study, the Spearman method was employed to analyze its correlation with other indicators. Additionally, to explore the relationship between FRS and various parameters such as body composition and $MSpO_2$, statistically significant data from the pairwise correlation analysis were further examined using multiple linear regression analysis. A $p < 0.1$ not only took into account statistically significant trends but also allowed for more comprehensive inclusion of clinical variables that may be associated. Before we performed multiple linear regression and logistic regression analysis, we performed sensitivity analyses such as collinear correlation on the included variables. Next, Binary Logistic regression was conducted with FRS $\geq$ 14 (this score corresponded to a male medium-high risk category of CVD $\geq$ 18.4% [3]) as the dependent variable to analyze factors influencing the risk of developing CVD. In addition, since many previous studies had proved that obstructive sleep apnea (OSA) was a risk factor for CVD and also significantly affected body fluid accumulation and distribution, subgroup analyses were performed based on internationally accepted severity groups of OSA, that is, AHI $\geq$ 15 times/h was diagnosed as moderate-to-severe OSA [16]. Analysis results with corresponding $p < 0.05$ were considered statistically significant.

3 | Results

3.1 | Descriptive Statistics of the Participants via FRS Stratification

All participants were categorized into three groups based on the FRS tripartite (Table 1). Since the FRS was determined based on age ($p < 0.001$), total cholesterol ($p = 0.024$), HDL-C ($p = 0.608$), systolic blood pressure ($p < 0.001$), smoking ($p < 0.001$), and diabetes mellitus ($p < 0.001$), almost all these factors exhibited significant variations between groups. However, no statistically significant difference was observed in HDL-C levels among the groups. In addition, other blood indicators, such as serum ferritin ($p = 0.024$) and HB ($p = 0.006$), showed variations between the groups. The concentration of carbon dioxide (CO_2) in the blood was higher in the third group ($p = 0.044$). However, no significant differences were observed among the three groups regarding BMI ($p = 0.588$), total bilirubin ($p = 0.597$), creatinine ($p = 0.439$), uric acid ($p = 0.590$), homocysteine ($p = 0.685$), and alcohol consumption ($p = 0.981$).

Among the body composition and sleep-breathing measures considered, statistically significant differences were observed only in extracellular water/total body water (ECW/TBW, $p < 0.001$) and basal metabolic rate (BMR, $p < 0.001$) between the three groups. The results showed that $MSpO_2$ was suspected to be declining in the Tripartite 3 group; however, no significant differences were observed in $MSpO_2$ size between groups ($p = 0.093$). Similarly, muscle mass index, muscle mass/fat mass, protein content, and AHI did not exhibit significant differences between groups (all $p > 0.05$).

3.2 | Correlation Analysis Between FRS and Clinical Indicators

Table 2 shows that the FRS exhibited positive correlations with age, systolic blood pressure (SBP), mean arterial pressure (MAP), FBG, glycosylated hemoglobin, and ECW/TBW (r, respectively = 0.697, 0.452, 0.396, 0.316, 0.319, and 0.373, all $p < 0.001$). In contrast, the score exhibited negative correlations with serum ferritin ($r = -0.159$, $p = 0.027$) and HB ($r = -0.221$, $p = 0.002$). No significant relationships were observed between FRS and AHI, BMI, $MSpO_2$, CO_2, or BMR (all $p > 0.05$).

In the subgroup classified by obstructive sleep apnea severity, the four indicators that exhibited positive correlations with FRS in all participant analyses remained positively associated with this score (all $p < 0.01$). In Table 2, although there were no significant statistical associations between FRS and muscle mass/fat mass, there was a trend towards a correlation between FRS and muscle mass/fat mass in patients with AHI < 15 ($r = -0.181$, $p = 0.077$). Also, there was a trend towards a correlation between FRS and serum ferritin in patients with AHI < 15 ($r = -0.196$, $p = 0.054$). For patients with AHI < 15, FRS was positively correlated with AHI ($r = 0.201$, $p = 0.048$), while it showed an inverse association with BMR ($r = -0.279$, $p = 0.006$). Conversely, in the group with AHI ≥ 15, we also observed an inverse correlation between HB and FRS ($r = -0.330$, $p = 0.001$). Figure 1 displays the relationships between examination indexes and FRS.

3.3 | Multiple Linear Regression Analysis

In the above part, indicators with P-values < 0.1 corresponding to the FRS correlation analysis were incorporated into the multiple linear regression. However, age and blood pressure, which are components of the FRS, were not included as separate variables. The results showed that ECW/TBW and FBG exhibited positive correlations with FRS ($\beta = 0.324$ and 0.324, $p < 0.001$), while HB and muscle mass/fat mass showed negative correlations with the score ($\beta = -0.185$ and -0.169, $p < 0.01$). Table 3 shows the influencing factors related to the difference between predicted heart age and actual age, which were largely consistent with those of FRS.

These five factors—ECW/TBW, FBG, hemoglobin, serum ferritin, and muscle/fat mass—collectively accounted for 28.6% of the variance in FRS and predicted 21.4% of the difference between predicted heart and actual age. The indicators analyzed in the subgroup were consistent with those in the whole subjects. In subgroup analysis categorized using OSA severity, FRS was significantly correlated with ECW/TBW and FBG in each subgroup ($p < 0.05$). However, the associations of HB and muscle-to-fat mass ratio to FRS were different in participants with different OSA severity, and HB in the AHI ≥ 15 subgroup and muscle/fat mass proportion in the AHI < 15 subgroup were negatively correlated with FRS.

3.4 | Binary Logistic Regression Analysis

In the initial part of the results, the differences in FRS tripartite parameters between the groups (corresponding to $p < 0.025$) and the body composition index of muscle mass/fat mass were included in the binary Logistic regression analysis. This analysis did not incorporate the clinical indicators necessary in the FRS system. If F scores of ≥ 14 were selected as the dependent variable, it corresponded to a male CVD risk of ≥ 18.4%. The analysis results demonstrated that a higher ECW/TBW was significantly associated with this moderate-to-high level of CVD risk (OR = 2.208, 95% CI: 1.503–3.244). Conversely, lower levels of muscle mass/fat mass, HB, and BMR were significantly associated with an increased 10-year risk of CVD ($OR_{ratio} = 0.532$, 95% CI: 0.284–0.996; $OR_{HB} = 0.961$, 95% CI: 0.932–0.991; $OR_{BMR} = 0.997$, 95% CI: 0.995–1.000). For men with a CVD risk greater than or equal to 18.4%, no significant effect or association of serum ferritin was observed ($p > 0.05$, Table 4).

4 | Discussion

Identifying moderate-to-high-risk groups in the absence of typical symptoms and implementing measures to control and prevent associated risk factors, followed by active and precise intervention, can effectively decrease the incidence and mortality rates of CVD. This principle, which was pivotal in the Framingham study, continues to inspire global efforts. This study examined the correlations between nonconventional indicators, such as body composition parameters and sleep-breathing indicators, with CVD risks among Chinese men.

The participants were recruited from a first-class hospital exclusively in mainland China, with the majority originating from the

TABLE 1 | Comparison of clinical indicators of subjects with different FRS grades.

		Tripartite 1 ($n=61$)	Tripartite 2 ($n=73$)	Tripartite 3 ($n=61$)	p
FRS[a,b,c]		8.0 (7.0, 10.0)	14.0 (13.0, 15.0)	19.0 (18.0, 21.0)	0.000
General indicators					
Age (year)[a,b,c]		43.52 ± 6.76	50.97 ± 6.44	56.74 ± 6.31	0.000
Waist circumstance (cm)		95.0 (89.0, 100.0)	94.0 (89.0, 99.0)	94.0 (90.0, 101.0)	0.867
Waist–hip ratio (%)		93.88 (90.10, 97.09)	94.44 (90.48, 97.14)	93.94 (90.48, 97.22)	0.850
BMI (kg/m^2)		27.67 ± 3.60	27.12 ± 2.38	27.28 ± 3.44	0.588
SBP (mmHg)[a,b,c]		121.4 ± 11.2	129.3 ± 13.7	136.5 ± 16.6	0.000
DBP (mmHg)[a,c]		80.8 ± 9.5	86.5 ± 9.7	87.7 ± 11.9	0.001
PP (mmHg)[b,c]		40.6 ± 7.4	42.8 ± 10.8	48.8 ± 11.4	0.000
MAP (mmHg)[a,c]		94.3 ± 9.5	100.8 ± 9.9	104.0 ± 12.6	0.000
Diabetes, n (%)[a,b,c]		4 (6.6)	23 (31.5)	44 (72.1)	0.000
Smoking, n (%)[a,b,c]	never	46 (75.4)	39 (53.4)	15 (24.6)	0.000
	once or always	15 (24.6)	34 (46.6)	46 (75.4)	
Drinking, n (%)	never	22 (36.1)	26 (35.6)	21 (34.4)	0.981
	once or always	39 (63.9)	47 (64.4)	40 (65.6)	
Biochemical indicators					
HDL-C (mmol/L)		1.03 ± 0.21	1.06 ± 0.25	1.08 ± 0.28	0.608
TC (mmol/L)[b]		4.83 (4.35, 5.38)	4.83 (4.34, 5.67)	4.39 (3.71, 5.16)	0.024
TBiL (μmol/L)		11.7 (9.1, 15.8)	11.6 (8.6, 14.3)	12.1 (9.4, 15.2)	0.597
Serum ferritin (μg/L)[b,c]		311.9 (180.2, 494.2)	304.5 (174.2, 478.0)	247.4 (140.0, 318.3)	0.024
Uric acid (μmol/L)		380.0 (349.0, 448.0)	409.0 (336.0, 450.0)	381.0 (334.0, 425.0)	0.590
Creatinine (μmol/L)		79.0 (71.0, 87.0)	76.0 (67.0, 88.0)	76.0 (69.0, 82.0)	0.439
FBG (mmol/L)[a,b,c]		5.49 (5.04, 5.96)	5.90 (5.43, 6.73)	6.60 (5.88, 7.76)	0.000
Glycosylated HB (%)[b,c]		5.60 (5.50, 5.90)	5.70 (5.50, 6.50)	6.20 (5.90, 7.00)	0.000
CO_2 (mmol/L)[b]		25.40 ± 2.45	24.99 ± 2.48	26.06 ± 2.46	0.044
HB (g/L)[a,c]		157.0 (149.0, 163.0)	152.0 (145.0, 159.0)	150.0 (143.0, 156.0)	0.006

(Continues)

TABLE 1 | (Continued)

	Tripartite 1 ($n=61$)	Tripartite 2 ($n=73$)	Tripartite 3 ($n=61$)	p
CRP (mg/dL)	0.10 (0.04, 0.24)	0.07 (0.02, 0.12)	0.07 (0.02, 0.21)	0.124
Homocysteine (μmol/L)	16.15 (12.52, 18.63)	15.86 (13.70, 19.30)	17.22 (13.66, 20.46)	0.685
Body composition indexes				
ECW (L)	16.5 (15.4, 17.9)	16.2 (15.5, 17.6)	16.8 (16.0, 18.2)	0.269
TBW (L)	43.95 ± 5.77	42.58 ± 3.95	42.99 ± 4.73	0.255
ECW/TBW (%)[a,b,c]	38.34 (37.56, 39.01)	38.66 (38.30, 39.15)	39.34 (38.76, 39.76)	0.000
Basal metabolic rate (Kcal)[a,c]	1474.0 (1406.0, 1576.0)	1416.0 (1330.0, 1485.0)	1371.0 (1301.0, 1471.0)	0.000
Minerals (kg)	4.7 (4.3, 5.1)	4.6 (4.3, 4.9)	4.6 (4.4, 4.9)	0.318
Protein (kg)	12.0 (11.3, 13.0)	11.8 (11.1, 12.8)	12.1 (11.2, 12.9)	0.487
Fat mass (kg)	21.3 (18.1, 25.4)	21.0 (18.5, 23.5)	20.3 (17.6, 23.3)	0.556
Fat percentage (%)	26.13 ± 5.01	26.24 ± 3.27	25.86 ± 3.97	0.866
Muscle mass (kg)	56.11 ± 6.89	54.53 ± 5.06	55.12 ± 6.02	0.312
Muscle percentage (%)	68.22 ± 5.09	67.87 ± 3.80	68.12 ± 4.77	0.899
Muscle mass index (kg/m^2)	18.75 ± 1.86	18.35 ± 1.29	18.47 ± 1.70	0.347
Muscle mass/BMI (m^2)	2.05 (1.91, 2.14)	1.97 (1.91, 2.11)	2.04 (1.92, 2.13)	0.454
Muscle mass/Fat mass (%)	2.56 (2.30, 3.02)	2.56 (2.35, 2.87)	2.69 (2.26, 3.01)	0.678
ECW/Fat mass (L/kg)	77.72 (67.32, 89.63)	78.17 (70.42, 86.14)	81.86 (70.21, 91.89)	0.309
Fat mass/Muscle mass of both lower limbs (%)	106.78 ± 25.46	106.52 ± 18.37	104.18 ± 22.08	0.767
Sleep-breathing indicators				
AHI (events/h)	12.70 (3.80, 36.20)	13.80 (5.40, 36.30)	16.90 (8.70, 30.10)	0.734
Total sleep time (h)	6.89 ± 1.25	7.19 ± 1.50	7.14 ± 1.26	0.437
$MSpO_2$ (%)	94.0 (92.0, 94.0)	94.0 (93.0, 95.0)	93.0 (92.0, 94.0)	0.093
$LSpO_2$ (%)	81.0 (79.0, 86.0)	81.0 (76.0, 85.0)	83.0 (76.0, 86.0)	0.738
T90 (min)	4.76 (0.71, 12.96)	2.70 (0.71, 11.40)	6.85 (0.88, 13.89)	0.506

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; CO_2, carbon dioxide; CRP, C-reactive protein; DBP, diastolic blood pressure; ECW, extracellular water; FBG, fasting blood glucose; FRS, Framingham risk score; HB, hemoglobin; HDL-C, high-density lipoprotein cholesterol; $LSpO_2$, lowest pulse oxygen saturation; MAP, mean arterial pressure; $MSpO_2$, mean pulse oxygen saturation; PP, pulse pressure; SBP, systolic blood pressure; T90, the length of time the SpO_2 below 90%; TBiL, total bilirubin; TBW, total body water; TC, total cholesterol.

[a]The difference was statistically significant between Group 1 and Group 2.

[b]Group 2 and Group 3.

[c]Group 1 and Group 3.

TABLE 2 | Correlation between Framingham risk score and clinical indices.

	Total		*AHI* < 15 (*n* = 97)		*AHI* ≥ 15 (*n* = 98)	
Clinical indices	***r***	***p***	***r***	***p***	***r***	***p***
Age	0.697	< 0.001	0.690	< 0.001	0.706	< 0.001
BMI	−0.018	0.803	−0.120	0.241	0.056	0.583
SBP	0.452	< 0.001	0.518	< 0.001	0.392	< 0.001
MAP	0.396	< 0.001	0.463	< 0.001	0.327	0.001
AHI	0.031	0.669	0.201	0.048	−0.030	0.769
$MSpO_2$	−0.015	0.837	−0.011	0.918	−0.004	0.971
Serum ferritin	−0.159	0.027	−0.196	0.054	−0.106	0.299
CO_2	0.100	0.163	0.075	0.468	0.126	0.215
FBG	0.316	< 0.001	0.360	< 0.001	0.286	0.004
Glycosylated hemoglobin	0.319	< 0.001	0.395	< 0.001	0.271	0.007
HB	−0.221	0.002	−0.127	0.217	−0.330	0.001
ECW/TBW	0.373	< 0.001	0.457	< 0.001	0.343	0.001
Basal metabolic rate	−0.071	0.325	−0.279	0.006	−0.067	0.512
Muscle mass/Fat mass	−0.119	0.096	−0.181	0.077	0.006	0.953
Predicting heart age	0.993	< 0.001	0.994	< 0.001	0.993	< 0.001

Note: $p < 0.05$, The correlation between the two variables was statistically significant.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; CO_2, carbon dioxide; ECW, extracellular water; FBG, fasting blood glucose; HB, hemoglobin; MAP, mean arterial pressure; $MSpO_2$, mean pulse oxygen saturation; SBP, systolic blood pressure; TBW, total body water.

central and northern regions of the country. Therefore, despite the single-center selection of the participants, the research individuals were relatively universal and representative. Moreover, the comparative analysis among groups with varying levels of FRS revealed no significant differences in BMI, drinking status, or total sleep time ($p > 0.05$). However, these indicators were well-documented risk factors for CVD. The reasons why no differences between groups were found may be that the sample size was small, the subjects were almost urban males with relatively concentrated ages, and their similar living habits. Hence, paying more attention to the influence of other indicators, such as body composition and blood biochemistry, on FRS is crucial. Since HDL-C is a key component of FRS, it would be reasonable to expect differences in HDL-C levels among groups with high, medium, and low FRS scores. However, this study found no statistical difference in HDL-C among these groups. We hypothesized that the individuals in our study exhibited a relatively narrow range of HDL-C (< 40 mg/dL), within the corresponding range for extra points in the FRS system. Hasan et al. [17] observed increased use of lipid-regulating statins across all risk groups following FRS assessment, potentially contributing to certain reports suggesting an overestimated CVD risk [18]. However, the effectiveness and significance of FRS for assessing CVD risk remain undeniable.

No significant differences were observed in the primary sleep-breathing indexes across the varying FRS scores. However, among other groups, the high-risk CVD group (the Tripartite 3, namely FRS ≥ 17) exhibited a declining trend in $MSpO_2$ and an increase in carbon dioxide levels ($P_{MSpO2} < 0.10$, $P_{CO2} < 0.05$). As the focus on sleep health grows, several studies have highlighted the prevalence of OSA in patients with CVD. In a retrospective study spanning 7 years [19], patients with OSA were found to exhibit a 57% increased risk of cardiac events (HR: 1.57, 95% CI: 1.04–2.39, $p = 0.034$) compared to patients without it. Similarly, in a study conducted by Zhang et al. involving 169 men, individuals at moderate-to-high risk of CVD were observed to exhibit a higher AHI, along with lower mean oxygen saturation [20]. In contrast, this study showed that CVD risk appears to be more closely linked to the severity of hypoxia rather than significant differences in AHI between groups. This finding lends support to the notion that emerging indicators such as hypoxic burden associated with sleep apnea [21] may serve as predictors of adverse cardiovascular outcomes associated with OSA. Hypoxia can trigger an increase in inflammatory cytokines and reactive oxygen species, inhibit the production of adenosine triphosphate, alter circulating exosomal vector, induce vascular endothelial dysfunction, and enhance the permeability of endothelial cells [22]. Additionally, oxygen deprivation leads to telomere shortening and accelerates aging in blood vessels and organs, potentially contributing to CVD [23]. Clinicians should not solely concentrate on the size of AHI during sleep monitoring but also identify OSA phenotypes. This approach is crucial for recommending optimal individualized treatment strategies aimed at minimizing cardiovascular damage.

FRS ≥ 14 utilized in this study falls within the medium-high risk category for predicting CVD [24]. Multiple linear and Logistic regression analyses revealed significant correlations among ECW/TBW, HB, FBG, and muscle mass/fat mass with FRS. The

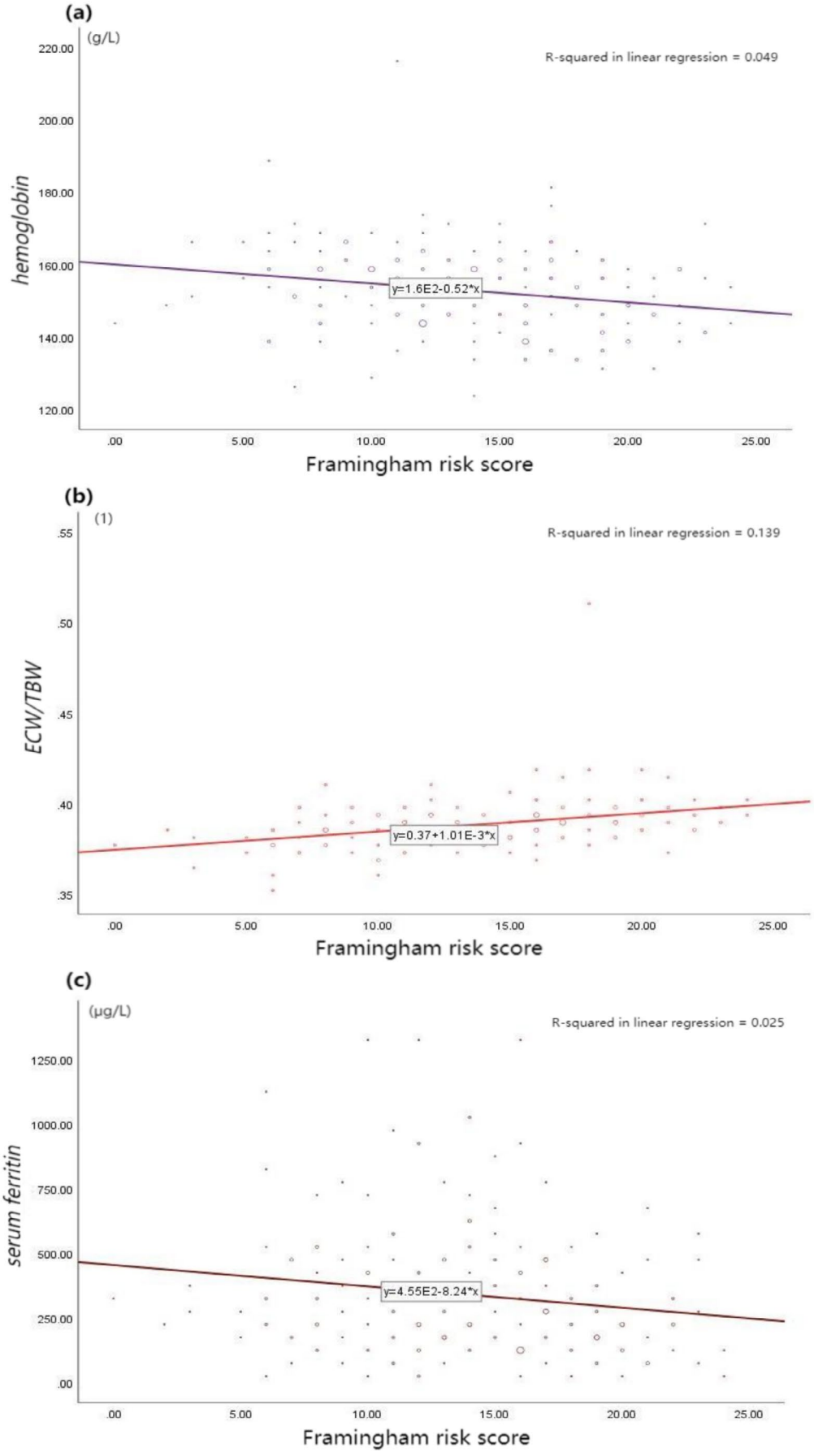

FIGURE 1 | Legend on next page.

FIGURE 1 | The relationships between examination indexes and FRS. ECW: Extracellular water; TBW: Total body water. In each coordinate system, the X-axis is the FRS score and the Y-axis is the level of clinical indicators. (a) Negative correlation between hemoglobin and FRS; (b) positive correlation between ECW/TBW and FRS; and (c) negative correlation between serum ferritin and FRS.

ratio of ECW/TBW is a common measure for assessing fluid retention in the body [25]. A study involving 307 patients on dialysis [26] revealed that individuals with fluid overload (defined by ECW/TBW ≥ 0.40) exhibited a significantly higher rate of cerebrovascular events (3.9 vs. 1.1 events/100 patient-years, $p = 0.024$) than normal persons. The ECW/TBW ratio is likely influenced by fluid retention, glomerular filtration rate, and atrial natriuretic peptide [27]. An increase in this ratio results in increased strain on the circulatory system, potentially leading to cardiovascular dysfunction such as high blood pressure. A rise in this ratio may also suggest a decline in renal excretion function [28]. Mendelian randomized analysis for CHD revealed a significant association among participants with eGFR < 60 mL/min*1.73m^2. Specifically, the risk of CHD increased by 14% (95% CI: 3%–27%) for every 5 mL/min*1.73m^2 reduction [29]. Since the creatinine and uric acid levels among the participants in this study did not differ across the three FRS groups, they did not directly elucidate the connection between kidney function and CVD risk. These results primarily underscored the correlation between ECW/TBW and FRS. Meanwhile, our results still demonstrate that lower HB levels may correlate with higher FRS scores. Conversely, a large nationwide retrospective cohort study from South Korea [30] suggested an increase in HB variability was associated with a heightened risk of CVD among Koreans [aHR (95% CI): 1.07 (1.02–1.12)]. However, within the subgroup exhibiting HB reduction, it was observed that HB variability might influence the CVD trend [aHR (95% CI): 1.04 (0.99–1.10)]. The inconsistent results between the two studies could be attributed to variations in sample size, race, assay method, and HB range (140.0 g/L vs. 152.8 g/L). For example, our study exclusively included males, and HB levels were predominantly within the higher normal range [153.0 (145.0, 160.0)], with few instances of levels being too high or too low. Increased HB could lead to blood thickening, potentially causing left ventricular hypertrophy [31], consequently resulting in heart failure. Conversely, a decrease in HB might stimulate the growth of heart muscle cells and enhance cardiac output to compensate for reduced oxygen transport capacity. Persistent and repetitive stimulation over time can ultimately lead to ventricular hypertrophy or enlargement. Moreover, HB levels tend to decline with aging, especially in men [32]. Age is a direct FRS-related factor. A decrease in HB might coincide with an active inflammatory response, wherein inflammatory factors disrupt erythrogenic differentiation and erythropoietin secretion, thereby limiting iron utilization by red blood cells. Furthermore, inflammation plays a crucial role in all stages of atherosclerosis [33]. Foreign research findings have shown a negative correlation between HB and ECW/TBW [34, 35], which could be linked to overall protein levels and nutritional status within the body. Elevated blood glucose levels are widely recognized as significant risk factors for CVD. High blood sugar levels trigger oxidative stress and inflammation in blood vessels, heightening arterial stiffness [36]. The biological mechanisms underlying elevated blood glucose involve insulin resistance and hyperinsulinemia, which can directly strain the cardiovascular system by promoting water and sodium retention [37] and enhanced sympathetic nerve activity. Hyperglycemia often coexists with poor dietary habits and lack of exercise, which are linked to a heightened risk of CVD. Hence, focusing on managing daily behaviors and cultivating healthier habits is essential.

A correlation between an increase in muscle-to-fat mass ratio and a decrease in FRS score is found. It is plausible to anticipate the natural physiological trend of age-related decline in muscle mass and function. Additionally, a study revealed that with aging, fat mass in the upper limbs increased in men but not in women [38]. A study utilizing Mendelian randomization design revealed a positive association between fat mass index and various cardiovascular outcomes, such as a 46% elevated risk of aortic stenosis per 1 kg/m^2 increase in fat mass index [39]. Conversely, evidence suggests that an increase in fat-free mass index may lower the risk of atrial fibrillation, aortic aneurysm, and ischemic stroke. Research conducted on the Dutch general population yielded similar findings, suggesting that adjustments for total muscle mass strengthened the association between relative fat mass and all-cause mortality [40]. In practice, rather than solely focusing on muscle or fat mass, we concentrated on the importance of the muscle-to-fat mass ratio. It was reasonable to avoid using BMI or body weight as the sole reference for assessing muscle and fat mass. This approach finds support in a recent study, which highlights that anthropometric indices excluding "body weight" showed less evidence for the obesity survival paradox in model calculations [41]. A Korean nationwide, population-based cohort study [42] further supported the notion that increased predicted muscle mass or decreased predicted fat mass may lower the risk of CVD. The underlying physiological mechanism is: on the one hand, excess fat can lead to hypertension through dyslipidemia-mediated activation of the renin–angiotensin–aldosterone system and sympathetic nervous system [43]. Moreover, adipose tissue secretes adipokines and various proinflammatory cytokines, contributing to insulin resistance and endothelial dysfunction [44], thereby promoting atherosclerosis. On the other hand, the maintenance and growth of muscle mass are closely related to effective exercise and regular rest, serving as protective factors against CVD. In addition, myokines secreted by muscle cells exhibit an anti-inflammatory effect, crucially combating insulin resistance and maintaining metabolic homeostasis [45]. Therefore, these findings underscore the importance of addressing excessive muscle loss during weight loss efforts. Considering other factors such as muscle-to-fat mass ratio, ECW/TBW, and other anthropometric indices may be essential when predicting the risk of developing CVD.

Furthermore, considering the influence of BMR on CVD is essential. A Mendelian randomization study conducted with European databases revealed a significant positive association between genetically predicted BMR and the risk of heart failure (OR: 1.53, 95% CI: 1.39–1.67) and atrial fibrillation (OR: 2.12, 95% CI: 1.87–2.40) [46]. However, this is contrary to the effect of BMR on predicting CVD risk ≥ 18.4% in our study. Possible explanations

TABLE 3 | The influencing factors of FRS obtained by multiple linear regression analysis.

	Framingham risk score			Predicted heart age minus actual age		
Total	***β***	***p***	**R^2%**	***β***	***p***	***R^2%***
ECW/TBW	0.324	<0.001	28.6	0.198	0.003	21.4
HB	−0.185	0.004		−0.161	0.017	
FBG	0.272	<0.001		0.344	<0.001	
Serum ferritin	−0.113	0.075		−0.022	0.738	
Muscle mass/Fat mass	−0.169	0.008		−0.095	0.152	
AHI ≥ 15 (*n* = 98)						
ECW/TBW	0.311	0.001	29.6	0.218	0.019	29.1
HB	−0.314	0.001		−0.276	0.003	
FBG	0.280	0.003		0.392	<0.001	
Serum ferritin	−0.059	0.530		0.020	0.833	
Muscle mass/Fat mass	−0.080	0.383		−0.096	0.299	
AHI < 15 (*n* = 97)						
ECW/TBW	0.400	<0.001	35.0	0.215	0.031	17.1
HB	−0.065	0.469		−0.052	0.608	
FBG	0.266	0.003		0.287	0.004	
Serum ferritin	−0.139	0.108		−0.054	0.581	
Muscle mass/Fat mass	−0.201	0.024		−0.080	0.422	

Note: Adjusted for these five variables in the table. R^2%: These five variables combine to explain how much FRS scores change and predict how much the difference between heart age and actual age has changed.
Abbreviations: ECW, extracellular water; TBW, total body water; HB, hemoglobin; FBG, fasting blood glucose.

TABLE 4 | The influencing factors of FRS ≥ 14 obtained by logistic regression analysis.

	Multivariate analysis			
Variable	***β***	***w***	**OR (95% CI)**	***p***
ECW/TBW	0.792	16.287	2.208 (1.503–3.244)	<0.001
HB	−0.040	6.325	0.961 (0.932–0.991)	0.012
BMR	−0.003	5.424	0.997 (0.995–1.000)	0.020
Serum ferritin	0.000	0.010	1.000 (0.999–1.001)	0.920
Muscle mass/ Fat mass	−0.632	3.885	0.532 (0.284–0.996)	0.049

Note: The five variables in the table were included in the logistic regression analysis together.
Abbreviations: BMR, basal metabolic rate; ECW, extracellular water; HB, hemoglobin; TBW, total body water.

for this discrepancy include the following: 1. BMR was associated with height, weight, and age, and no significant difference was observed in BMI distribution among the FRS groups. Therefore, as far as the subjects of this study were concerned, the influence of age on BMR might be highlighted. Simultaneously, aging was factored into FRS scoring and is negatively correlated with BMR; 2. It could be attributed to the relatively small sample size and the use of a threshold FRS ≥ 14 points. Thus, with an expanded sample size and adjustment of the statistical calculation for the critical value, the association between BMR and CVD risk might change. However, in reality, several studies have suggested that elevated BMR could be a potential risk factor for developing CVD. This is associated with high arterial blood pressure, leading to increased myocardial oxygen consumption, consequently placing a burden on the heart [47]. A higher BMR encompasses increased energy and protein consumption, along with an expected rise in glycolytic activity and correspondingly higher levels of reactive oxygen species. This could potentially affect the normal function of mitochondria throughout the body [48]. Besides, the elevation in BMR might influence and trigger CVD through mechanisms involving immune activation, insulin resistance, and the promotion of an inflammatory state [49]. BMR plays a significant role in maintaining the physical energy balance. Elevated BMR levels appear to indicate higher energy intake and more frequent eating [50]. The resulting bioenergetic imbalance could potentially damage the cardiac circulatory system.

In summary, this study underscores the significant role of body composition index and sleep oxygen deficiency in CVD, highlighting the feasibility and significance of similar research endeavors. However, this study has some limitations. First, this

study was conducted as a single-center observational study. Second, the sample size was relatively small, and all participants were male. Third, the results of a one-time sleep monitoring may not accurately reflect long-term habitual sleep patterns, necessitating consideration of the first-night effect. Fourth, the interaction between these relevant variables that had an impact on FRS in this study has not been analyzed clearly. Therefore, the conclusion drawn exclusively highlights the significance of the FRS to nontraditional indicators. These findings may serve as a supplementary insight and reference for predicting CVD risk in Chinese men over the next decade. However, confirmation of these findings would require larger sample sizes and clinical cohort studies encompassing all ages and sexes.

5 | Conclusion

The findings of this study revealed correlations among ECW/TBW, HB, FBG, and muscle-to-fat mass ratio with the risk of CVD predicted via FRS. This suggests that a comprehensive understanding of the combined effects of body composition and sleep-breathing index may aid clinicians in accurately assessing CVD risk. Enhanced comprehensive screening and monitoring of factors influencing CVD, coupled with individualized preventive measure strategies, can effectively reduce CVD incidence and associated mortality risk.

Author Contributions

L.Z. and Y.G. wrote the manuscript; L.F., C.M., and L.L. designed the research; Z.Z., D.R., T.N., and T.L. performed the research; and L.Z., W.C., and X.X. analyzed the data. All authors gave final approval and agreed to be accountable for all aspects of this work.

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Ethics Statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Chinese PLA General Hospital (S2022-366-01).

Consent

The patients provided their informed consent to participate in this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author or the first author. The data are not publicly available due to privacy or ethical restrictions.

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