Research Square

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Lifestyle, metabolic, and gut microbial determinants of hypertension onset according to metabolic dysfunction status: insights from the population-based FoCus study

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Abstract

Background: Hypertension is closely associated with metabolic dysfunction; however, whether the determinants of hypertension onset differ according to metabolic status remains unknown. We aimed to investigate the lifestyle, metabolic, and gut microbial signatures associated with hypertension prevalence and onset according to metabolic phenotypes.

Methods: We used comprehensive data from the German population-based Food Chain Plus (FoCus) cohort. Participants were classified according to their metabolic dysfunction status. Cox proportional hazards and restricted cubic spline (RCS) regression analyses were performed to evaluate the associations between metabolic biomarkers, lifestyle factors, gut microbiota diversity, and age-at-hypertension-onset.

Results: Among individuals with metabolic dysfunction, elevated WHtR (HR = 1.876,95%CI, 1.411–2.495; P = 0.0003), TyG index (HR = 1.313, 95% CI: 1.024-1.684; P = 0.0317), and HOMA-β (HR = 1.319, 95% CI: 0.974-1.786; P = 0.0389) were significantly associated with an earlier onset of hypertension. Conversely, higher relative handgrip strength of the right hand (HR = 1.025, 95% CI: 1.006-1.044; P = 0.0105), greater microbial diversitymeasured using the Chao1 index(HR = 0.672, 95% CI: 0.495-0.913; P = 0.0076), and observed index (HR = 0.667, 95% CI: 0.492-0.906; P = 0.008) were associated with delayed hypertension onset. Among individuals without metabolic dysfunction, only sports and television watching were associated with the timing of hypertension onset, whereas biomedical and gut microbial markers were not significantly associated.

Conclusions: Hypertension exhibits substantial metabolic heterogeneity. Metabolic dysfunction is accompanied by distinct metabolic and gut microbial signatures associated with earlier hypertension onset, whereas lifestyle factors appear to play a greater role in individuals without metabolic dysfunction. These findings support the importance of metabolic stratification for the precision prevention and targeted management of hypertension.

Research insights

What is currently known about this topic?

Hypertension frequently coexists with metabolic dysfunction; however, whether the determinants of hypertension onset differ according to metabolic status remains unknown.

What is the key research question?

Do lifestyle, metabolic, and gut microbial factors associated with hypertension onset differ between individuals with and without metabolic dysfunction?

What is new?

- Metabolic dysfunction markedly modifies the determinants of hypertension onset.
- Central adiposity, insulin resistance, lower relative handgrip strength, and reduced gut microbial diversity were associated with earlier hypertension onset only among individuals with metabolic dysfunction.
- Among individuals without metabolic dysfunction, the onset of hypertension was primarily associated with lifestyle behaviours rather than metabolic or microbial characteristics.

What are the implications of this study for clinical practice?

Metabolic stratification may facilitate personalized hypertension prevention by identifying distinct intervention targets for different metabolic backgrounds.

Introduction

Hypertension is one of the leading causes of cardiovascular disease (CVD) morbidity and mortality, affecting more than 1.4 billion individuals worldwide. Its burden continues to increase alongside a rapidly aging population and the escalating prevalence of metabolic disorders [1]. Hypertension frequently coexists with metabolic dysfunction, sharing intertwined pathophysiological mechanisms, including insulin resistance, chronic low-grade inflammation, visceral adiposity, dyslipidemia, and endothelial dysfunction [2–4]. Accordingly, surrogate markers of insulin resistance and visceral adiposity, such as the triglyceride–glucose (TyG) index and waist-to-height ratio (WHtR), have emerged as accessible and reliable biomarkers for assessing cardiometabolic risk [5–8]. However, hypertension can also occur in individuals without overt metabolic abnormalities. This clinical divergence strongly underscores the profound pathogenesis heterogeneity underlying blood pressure elevation, suggesting that the driving forces of hypertension may fundamentally differ depending on an individual's baseline metabolic status.

Although numerous studies have investigated the risk factors for prevalent hypertension, less attention has been paid to the determinants of the timing of hypertension onset. Identifying factors associated with earlier disease onset is important because early onset hypertension is associated with a longer cumulative exposure to elevated blood pressure and a substantially greater lifetime risk of developing cardiovascular complications.

Increasing evidence indicates that metabolic dysfunction substantially modifies the risk of hypertension and its associated cardiovascular consequences [9, 10]. However, most epidemiological studies have treated hypertension as a homogeneous condition without considering whether the determinants of hypertension differ according to metabolic status. Consequently, it remains unclear whether lifestyle behaviours, metabolic biomarkers, and anthropometric characteristics contribute equally to hypertension in metabolically healthy and metabolically dysfunctional individuals.

In addition to metabolic dysfunction, gut microbiota has emerged as an important contributor to blood pressure regulation. Alterations in microbial diversity and composition have been linked to hypertension through mechanisms involving host metabolism, immune regulation, inflammation, and microbial metabolites, such as short-chain fatty acids (SCFAs) [12–14]. As the gut microbiota is closely linked to host metabolic homeostasis, hypertension-associated microbial signatures may also differ according to metabolic status.

However, few population-based studies have simultaneously evaluated metabolic, lifestyle, and gut microbial factors in relation to hypertension within distinct metabolic strata groups. Clarifying these differences may provide important insights into disease pathogenesis and facilitate more precise risk stratification. To address these limitations, the present study comprehensively characterized the lifestyle, metabolic, and gut microbial landscapes associated with hypertension according to metabolic dysfunction status, utilizing the deeply phenotyped, population-based German Food Chain Plus (FoCus) cohort study. By employing rigorous age-, sex-, and BMI-matched analyses, we sought to identify the specific factors for both hypertension prevalence and the timing of its clinical onset.

Methods

Study design and population

This study utilized data from the German population-based Food Chain Plus (FoCus) cohort, a comprehensive and ongoing study established between 2011 and 2015. The FoCus cohort was previously reported by Geisler et al.[14]. In brief, approximately 1,811 adults aged 18–83 years were recruited through registration offices in the Kiel area in Northern Germany or in a case-specific manner through the obesity clinic of the University Medical Center Schleswig–Holstein (USKH) in Kiel, where people with a BMI ≥ 30 kg/m^2 and obesity-associated comorbidities are treated. Participants underwent extensive phenotyping, including anthropometric measurements, blood pressure assessment, metabolic and inflammatory laboratory analyses, lifestyle and dietary questionnaires, and gut microbiota profiling using stool samples.

To investigate hypertension under different metabolic conditions, two analytical cohorts were constructed. Participants without hypertension or any predefined metabolic abnormalities were first identified and served as metabolically healthy controls. Individuals with isolated hypertension, defined as hypertension in the absence of any other predefined metabolic abnormality, were selected and individually matched (1:1) to healthy controls according to age, sex, and BMI, thereby constituting the non-metabolic dysfunction (non-MD) cohort (N = 128; 80 female and 48 male). The non-metabolic dysfunction (non-MD) cohort consisted of metabolically healthy controls and participants with isolated hypertension. All remaining participants exhibited at least one predefined metabolic abnormality and were classified as having metabolic dysfunction (MD). Within this population, participants with hypertension were individually matched (1:1) to normotensive participants according to age, sex, and BMI, forming the MD cohort (N = 710, 430 female, 280 male). A flowchart illustrating the construction of the analytical cohorts is shown in Fig. 1. This two-stage matching strategy enabled the comparison of hypertension in the absence of metabolic dysfunction, while separately investigating hypertension within a metabolically dysfunctional background, thereby minimizing confounding factors such as age, sex, and BMI. These two matched cohorts were subsequently used for an exploratory analysis of the association between biomedical and lifestyle factors and prevalent hypertension, as well as survival analyses evaluating their associations with the age-at-hypertension-onset.

Definition of hypertension and metabolic health

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, self-reported physician-diagnosed hypertension, or current use of antihypertensive medication. To identify metabolically healthy controls for the construction of the non-metabolic dysfunction (non-MD) cohort, participants were required to meet all of the following criteria at baseline: (1) no history of major metabolic or cardiovascular diseases, including diabetes mellitus, heart failure, myocardial infarction, coronary heart disease, or stroke; (2) no diagnosis of hypertension and no history of dyslipidemia; (3) body mass index (BMI) between 18.5 and < 30 kg/m^2;(4) HOMA-IR < 2; (5) C-reactive protein (CRP) < 10 mg/L and interleukin-6 (IL-6) < 7 pg/mL; and (6) total cholesterol concentration < 5.2 mmol/L. Participants with missing information for an individual criterion were assumed to not meet the corresponding abnormality criterion.

Statistical analysis

Baseline characteristics were compared across groups using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Continuous variables were described as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical variables were presented as numbers and percentages. Multivariable binary logistic regression models were fitted to evaluate the associations between each biomedical or lifestyle factor (independent variable) and prevalent hypertension (dependent variable). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All models

were adjusted for age, sex, and body mass index (BMI). Forest plots were generated to visualize the statistically significant associations ($P < 0.05$). To explore associations with age-at-hypertension-onset within this cross-sectional framework, we conducted Cox proportional hazards regression analyses (Cox-PH regression) for each biomedical and lifestyle factor. Age-at-hypertension-onset (for cases) or current age-at-baseline (age-at-examination for normotensive controls) served as the time scale, hypertension status was considered as a censoring indicator, and the model was adjusted for sex and BMI class. Using a likelihood ratio test, biomedical and lifestyle factors that significantly improved the model fit were determined by comparing the full model, including the biomedical or lifestyle factor, with a reduced model, excluding the biomedical or lifestyle factor.

Kaplan–Meier curves were generated to visualize cumulative hypertension incidence for biomedical and lifestyle factors that showed p-values < 0.05. All continuous variables were categorized into tertiles for graphical visualization and hazard ratio calculation, using the lowest tertile as the reference category. The R survival package (version 3.8.6) and coxph function were used for this analysis.

To further characterize potential dose–response relationships and assess departures from linearity, four-knot restricted cubic spline (RCS) regression models were fitted for continuous variables, adjusting for sex and BMI class. Overall and non-linear associations were evaluated using the Wald test.

Given the substantial heterogeneity in missing data across variables, particularly for dietary and gut microbiota measurements, complete case analyses were performed separately for each variable. Therefore, the number of participants included in each Cox, Kaplan–Meier, and RCS analyses varied according to the availability of data for the variable under investigation. Because both disease status and explanatory variables were collected at baseline, the analyses were intended to assess associations rather than infer causality or estimate prospective incidence risk. Statistical analyses and data visualization were conducted using R software 4.4.3 and RStudio with the survival, rms, survminer, and related packages. Two-sided P-values < 0.05 were considered statistically significant.

Statistical analysis of the gut microbiota

Stool samples for 16 S rRNA gene sequencing were stored at -80°C until further processing by the Institute for Clinical Molecular Biology (IKMB) of the UKSH in Kiel. Intestinal microbiota analysis was performed as previously described by Heinsen et al.[15] and was based on amplicon sequence variants (ASV) [16]. Statistical analysis of the gut microbiota was performed using the R packages phyloseq (version 1.50.0), microbiome (version 1.28.0), vegan (version 2.7.3), pscl (version 1.5.9) and selbal (version 0.1.0). ASVs with zero abundance in all samples and those that lacked microbiota data were excluded.

Alpha diversity was assessed using the Chao1 richness and Simpson diversity indices. Overall differences between groups were evaluated using the Kruskal–Wallis test, followed by pairwise Wilcoxon rank-sum tests with false discovery rate (FDR) correction for multiple comparisons, where appropriate. Microbial β-diversity was assessed using Bray–Curtis dissimilarity and Jaccard distance. Differences in the overall microbial community composition were evaluated using permutational multivariate analysis of variance (PERMANOVA) with 1,000 permutations implemented in the adonis2 function of the vegan package.

Relative abundances of bacterial taxa were compared between groups using the Wilcoxon rank-sum test with FDR correction for multiple testing. To identify microbial signatures associated with hypertension, compositional balance analysis was performed using the Selbal algorithm. The optimal microbial balance was selected by cross-validation

and evaluated for its ability to discriminate participants with and without hypertension within each metabolic subgroup. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 128 participants without metabolic dysfunction (non-MD) and 710 participants with metabolic dysfunction (MD) were analyzed. The baseline characteristics stratified by hypertension status and sex are summarized in Table 1.

Within the non-MD cohort, no significant differences in anthropometric, metabolic, or lifestyle factors were observed between hypertensive and normotensive individuals of either biological sex(Table 1A).

In contrast, within the MD cohort, individuals with hypertension of both sexes exhibited significantly higher waist-to-hip ratios (WHR), elevated triglyceride-glucose (TyG) indices, and a higher prevalence of diabetes mellitus (Table 1B). Among men, participants with hypertension demonstrated significantly higher lipid accumulation product (LAP) values, elevated triglyceride levels, higher prevalence of dyslipidemia, and lower relative handgrip strength (RHGS, right hand) than men without hypertension. Among women, participants with hypertension presented with higher levels of fasting blood glucose, fasting insulin, and homeostatic model assessment of insulin resistance (HOMA-IR), along with lower self-reported life satisfaction. No significant differences were observed between the participants with and without hypertension among either men or women in terms of waist circumference (WC), waist-to-height ratio (WHtR), educational level, lifestyle behaviors, or inflammatory markers. Comprehensive baseline characteristics of the entire study population are provided in Supplementary Tables S1A and S1B.

Table 1
Baseline characteristic stratified by gender and hypertension status of two cohorts.

	Female			Male		
	Normotension	**Hypertension**	**p**	**Normotension**	**Hypertension**	**p**
A. INDIVIDUALS WITHOUT METABOLIC DYSFUNCTION						
Subject,n	40	40		24	24	
Age,years	58.50 [48.75, 67.00]	59.00 [48.75, 67.00]	0.912	60.50 [45.25, 69.25]	60.00 [44.75, 68.50]	0.836
Age-at-disease-onset (average cases), years	-	50.00[45.50,55.50]	-		47.50[30.00,59.75]	-
Diastolic blood pressure, mmHg	80.00 [70.00, 80.00]	80.00 [80.00, 80.00]	0.449	80.00 [80.00, 80.00]	80.00 [80.00, 90.00]	0.154
Systolic blood pressure, mmHg	127.50 [120.00, 130.00]	130.00 [120.00, 140.00]	0.093	130.00 [120.00, 131.25]	140.00 [125.00, 140.00]	0.023
Anthropometry						
Height, m	1.66 (0.07)	1.69 (0.07)	0.146	1.80 (0.06)	1.80 (0.05)	0.89
Weight, kg	67.02 (9.10)	68.33 (7.92)	0.493	81.16 (7.89)	81.67 (8.28)	0.829
BMI,kg/m2	24.15 (2.55)	24.06 (2.65)	0.882	25.08 (2.11)	25.04 (2.11)	0.943
Waist-hip-ratio, WHR	0.80 (0.06)	0.81 (0.07)	0.797	0.90 (0.06)	0.92 (0.06)	0.343
rel. HGS, right hand	1.01 (0.23)	0.99 (0.25)	0.664	1.79 (0.34)	1.65 (0.30)	0.14
rel. HGS, left hand	0.88 (0.22)	0.87 (0.19)	0.792	1.60 (0.29)	1.49 (0.28)	0.205
Biomedical						
HOMA-IR	24.33 (7.77)	24.46 (5.67)	0.932	25.98 [20.58, 30.15]	24.50 [17.83, 28.22]	0.303
Triglycerides, mmol/L	80.12 (24.75)	84.28 (26.42)	0.471	93.92 (30.49)	81.38 (22.56)	0.112
TyG, mg/dl	8.16 (0.35)	8.22 (0.36)	0.48	8.33 (0.34)	8.22 (0.30)	0.25
CRP, mg/L	1.40 [1.30, 1.42]	1.40 [1.40, 1.50]	0.395	1.60 [1.60, 1.60]	1.60 [1.60, 1.63]	0.806
IL-6, pg/L	2.65 [2.50, 2.82]	2.65 [2.48, 3.02]	0.511	3.05 [2.84, 3.90]	3.05 [2.68, 3.09]	0.282
Lifestyle						

	Female			Male		
	Normotension	**Hypertension**	**p**	**Normotension**	**Hypertension**	**p**
Total energy intake, kJ/day	8344 [7528–9449]	8036 [6882–9750]	0.735	10061.30 [7877.00, 11573.40]	11017.05 [8891.62, 14946.95]	0.26
MDS score	5.00 [4.00, 6.00]	5.00 [4.00, 6.00]	0.951	5.00 [3.00, 5.00]	4.50 [3.75, 6.00]	0.568
DASH score	25.00 [21.00, 29.25]	26.50 [21.00, 29.00]	0.952	20.00 [18.00, 22.00]	21.50 [19.75, 24.25]	0.19
Alcohol, g EtOH/day	2.64 [1.17, 4.42]	4.84 [2.25, 7.25]	0.136	3.64 [1.74, 4.93]	4.22 [2.20, 6.22]	0.334
Smoker, prevalence (95% CI)	4 (10.5)	8 (20.0)	0.398	6 (26.1)	3 (12.5)	0.416
Intensity (average smokers), n cigarettes/day	6.00[5.00, 10.00]	11.00[6.50, 19.75]	0.150	10.50 [5.00, 20.00]	15.00 [10.00, 20.00]	0.47
Sleep daytime, h	0.00 [0.00, 0.50]	0.00 [0.00, 0.44]	0.395	0.00 [0.00, 0.50]	0.50 [0.00, 1.00]	0.141
Sleep night, h	7.00 [7.00, 8.00]	7.00 [7.00, 8.00]	0.791	7.00 [7.00, 8.00]	7.00 [6.00, 8.25]	0.776
TV watching, h/week	2.00[1.38, 3.00]	2.00[1.50, 3.00]	0.734	3.00[2.00, 3.00]	2.50 [1.50, 4.00]	0.63
Everyday activity, h/week	20.62 [13.50, 34.12]	21.06 [12.75, 29.75]	0.701	14.50 [9.75, 18.00]	12.81 [7.31, 18.50]	0.557
Sports, h/week	4.00 [2.75, 8.00]	3.06 [1.31, 6.00]	0.098	5.50 [1.75, 9.00]	4.38 [1.03, 7.12]	0.361
Gut microbiota						
Shannon index	4.51[3.85, 4.86]	4.34[3.91, 4.55]	0.436	4.38 [3.93, 4.62]	4.20 [3.93, 4.47]	0.64
Chao1 Index	290.00[239.93, 367.60]	275.00[218.58, 346.69]	0.362	308.00 [232.33, 354.00]	290.50 [216.75, 334.50]	0.35
B. INDIVIDUALS WITH METABOLIC DYSFUNCTION						
Subject, n	215	215		140	140	
Age at examination, years	53.00 [42.25, 65.00]	54.00 [43.50, 63.00]	0.829	58.50 [48.00, 68.00]	58.50 [49.00, 68.00]	0.974
Age-at-disease-onset (average cases), years	-	45.00 [32.00, 52.00]	-	-	48.00 [38.50, 55.50]	-

	Female			Male		
	Normotension	**Hypertension**	**p**	**Normotension**	**Hypertension**	**p**
Diastolic blood pressure, mmHg	80.00 [80.00, 85.00]	80.00 [80.00, 90.00]	0.095	80.00 [80.00, 81.25]	80.00 [80.00, 90.00]	0.657
Systolic blood pressure, mmHg	130.00 [120.00, 135.00]	130.00 [125.00, 140.00]	< 0.001	130.00 [128.75, 140.00]	140.00 [130.00, 140.00]	0.001
Anthropometry						
Height, m	1.68 [1.63, 1.71]	1.67 [1.63, 1.71]	0.478	1.80 [1.76, 1.84]	1.80 [1.75, 1.84]	0.161
Weight, kg	86.45 [72.93, 111.35]	87.05 [74.90, 117.40]	0.479	92.00 [83.21, 101.53]	91.18 [82.80, 103.41]	0.937
BMI,kg/m^2	31.28 [26.55, 40.05]	31.48 [26.84, 39.83]	0.509	27.82 [25.78, 31.21]	28.69 [26.20, 31.37]	0.231
Waist-hip-ratio, WHR	0.88 [0.82, 0.92]	0.89 [0.85, 0.94]	0.031	0.95 [0.92, 0.99]	0.97 [0.93, 1.01]	0.025
rel. HGS, right hand	0.73 [0.59, 0.90]	0.71 [0.54, 0.88]	0.227	1.44 [1.24, 1.64]	1.36 [1.15, 1.57]	0.036
rel. HGS, left hand	0.62 [0.53, 0.79]	0.64 [0.49, 0.76]	0.716	1.30 [1.12, 1.47]	1.28 [1.02, 1.43]	0.197
Biomedical						
HOMA-IR	46.54 [33.92, 76.10]	54.40 [40.15, 93.37]	0.002	50.60 [36.99, 88.06]	62.12 [39.63, 99.07]	0.132
Triglycerides, mmol/L	120.00 [85.00, 160.00]	128.00 [89.50, 177.50]	0.141	118.00 [84.75, 165.50]	151.00 [105.00, 214.00]	< 0.001
TyG, mg/dl	8.63 (0.48)	8.76 (0.51)	0.007	8.70 (0.51)	8.92 (0.51)	< 0.001
CRP, mg/L	3.80 [2.10, 5.80]	3.80 [2.65, 6.60]	0.053	2.50 [1.87, 3.80]	2.50 [1.70, 3.23]	0.648
IL-6, pg/L	4.10 [3.00, 5.30]	4.10 [3.25, 5.60]	0.141	3.75 [2.98, 4.90]	3.75 [2.90, 5.32]	0.857
Lifestyle						
Total energy intake, kJ/day	7790[6310, 9320]	7970 (6759, 9362)	0.3	9,465 (7,972, 11,620)	9910[8540, 11780]	0.2
MDS score	4.00 [3.00, 6.00]	5.00 [4.00, 6.00]	0.04	4.00 [3.50, 5.00]	5.00 [4.00, 6.00]	0.105
DASH score	23.00 [21.00, 27.00]	24.00 [21.00, 27.00]	0.415	23.00 [21.00, 27.00]	24.00 [21.25, 27.00]	0.217
Alcohol, g EtOH/day	1.16 [0.53, 2.78]	1.19 [0.47, 3.22]	0.834	2.96 [1.14, 4.61]	3.13 [1.21, 6.14]	0.402

	Female			Male		
	Normotension	**Hypertension**	**p**	**Normotension**	**Hypertension**	**p**
Smoker, prevalence (95% CI)	49 (23.8)	39 (18.6)	0.237	27 (19.3)	24 (17.4)	0.8
Intensity (average smokers), n cigarettes/day	15.00[10.00, 20.00]	13.00 [8.00, 20.00]	0.4	17 [10.00, 20.00]	20[13.00, 30.00]	0.2
Sleep daytime, h	0.00 [0.00, 0.50]	0.00 [0.00, 0.50]	0.682	0.00 [0.00, 0.75]	0.25 [0.00, 1.00]	0.48
Sleep night, h	7.00 [6.00, 8.00]	7.00 [6.00, 8.00]	0.536	7.00 [7.00, 8.00]	7.00 [6.00, 8.00]	0.875
TV watching, h/week	3.00 [2.00, 4.00]	3.00 (2.00, 4.00)	0.2	3.00 (2.00, 3.00)	3.00 [2.00, 4.00]	0.6
Everyday activity, h/week	18.75 [11.00, 27.50]	20.25 [11.25, 28.00]	0.519	13.00 [8.00, 21.50]	13.50 [8.31, 20.00]	0.973
Sports, h/week	3.00 [1.00, 5.50]	2.75 [0.50, 5.50]	0.786	4.50 [2.00, 7.38]	3.94 [0.75, 6.00]	0.131
Microbiota						
Shannon index	4.12 [3.73, 4.49]	4.10 (3.75, 4.39)	0.3	4.28 (3.88, 4.65)	4.24 [3.80, 4.55]	0.3
Chao1 Index	278 [196, 329]	245 (187, 323)	0.051	271 (206, 347)	248 [208, 324]	0.2

(A)Individuals without metabolic dysfunction(B)Individuals with metabolic dysfunction.

Continuous variables are presented as median [IQR]or mean (SD). Categorical variables are presented as n (%). P-values were calculated using the Chi-square test for categorical variables and Mann–Whitney U test for non-normally distributed continuous variables. A p-value < 0.05 is considered statistically significant. Abbreviations: BMI, Body Mass Index; WHR, Waist-Hip Ratio; rel. HGS, relative Hand Grip Strength; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; TyG, Triglyceride-Glucose index; CRP, C-Reactive Protein; IL-6, Interleukin-6; MDS, Mediterranean Diet Score; DASH, Dietary Approaches to Stop Hypertension.

Associations of biomedical characteristics, lifestyle factors, and gut microbial diversity with prevalent hypertension according to metabolic dysfunction status

Multivariable logistic regression analyses were conducted to investigate the associations between biomedical characteristics, lifestyle factors, and gut microbial diversity with prevalent hypertension according to metabolic dysfunction status. Model 1 represents the unadjusted univariate analysis, whereas Model 2 was adjusted for age, sex, and BMI. The results for the MD cohort are summarized in Fig. 2, and the complete regression results for both the MD and non-MD cohorts are presented in Supplementary Tables S2A and S2B.

Non-Metabolic Dysfunction (non-MD) Cohort

After adjusting for age, sex, and BMI, none of the anthropometric characteristics, metabolic biomarkers, lifestyle factors, or gut microbial diversity indices were significantly associated with prevalent hypertension, except for life satisfaction. Participants who reported being very content with life had lower odds of hypertension than those who reported being content (Supplementary Table S2A).

Metabolic Dysfunction (MD) Cohort

In contrast, multiple anthropometric, metabolic, and microbial characteristics remained independently associated with prevalent hypertension after multivariable adjustment in the MD cohort (Fig. 2).

Anthropometric characteristics. A higher waist-to-hip ratio (WHR) (OR = 12.419, 95% CI: 1.710–94.667, P = 0.014) was independently associated with increased odds of hypertension. Conversely, a larger hip circumference (OR = 0.978, 95% CI: 0.961–0.994, P = 0.008) and greater relative handgrip strength of the right hand (RHGS: OR = 0.465, 95% CI: 0.249–0.859, P = 0.015) were associated with lower odds of hypertension.

Metabolic biomarkers. A higher TyG index (OR = 1.956, 95% CI: 1.436–2.682, P < 0.001), HOMA-IR (OR = 1.004, 95% CI: 1.001–1.007, P = 0.005), fasting insulin (OR = 1.021, 95% CI: 1.006–1.036, P = 0.007), fasting glucose (OR = 1.017, 95% CI: 1.007–1.028, P = 0.001), and serum triglyceride (OR = 1.005, 95% CI: 1.002–1.007, P < 0.001) levels were each independently associated with increased odds of prevalent hypertension.

Lifestyle factors. Participants who reported being very content with life had significantly lower odds of hypertension than those who reported being content (OR = 0.56, 95% CI: 0.38–0.84, P = 0.005). No significant associations were observed between smoking status, healthy lifestyle score, physical activity, or sleep duration after adjustment (Supplementary Table S2B).

Gut microbial diversity. Greater microbial richness, as measured by Observed richness (OR = 0.998, 95% CI: 0.996–1.000, P = 0.018) and Chao1 index (OR = 0.998, 95% CI: 0.996–1.000, P = 0.018), was independently associated with lower odds of prevalent hypertension. In contrast, the Shannon and Inverse Simpson diversity indices were not significantly associated with hypertension.

Lifestyle determinants of age-at-hypertension-onset differ according to metabolic dysfunction status

Multivariable Cox proportional hazards regression analyses were performed to investigate the associations between lifestyle factors and age-at-hypertension-onset, according to metabolic dysfunction status. Hazard ratios (HRs) were adjusted for sex and BMI class, and overall associations were evaluated using likelihood ratio tests. The complete results are presented in Supplementary Tables S3A and S3B, and the significant lifestyle-related associations are illustrated in Fig. 3.

Within the non-MD cohort, sports activity and television watching remained associated with age-at-hypertension-onset after sex and BMI class adjustment (overall likelihood ratio test: P = 0.031 and P = 0.050, respectively). Participants in the highest-intensity sports activity category tended to develop hypertension at a later age (low-high HR = 0.572, 95% CI: 0.278–1.175). Likewise, participants who reported the highest television watching duration showed a lower hazard of hypertension onset than those in the lowest category (HR = 0.614, 95% CI: 0.270–1.394). The corresponding cumulative incidence curves are shown in Fig. 3a and b.

In contrast, a broader range of lifestyle factors was associated with age-at-hypertension-onset in the MD cohort. Greater life satisfaction demonstrated the strongest association with delayed hypertension onset (overall likelihood ratio test: P < 0.001). Compared with participants who reported being content, those who reported being very content exhibited a substantially lower hazard of hypertension onset (HR = 0.531, 95% CI: 0.382–0.738), whereas participants who reported being not content had a higher hazard (HR = 1.457, 95% CI: 1.081–1.964) (Fig. 3c).

Television watching was also associated with age-at-hypertension-onset (overall likelihood ratio test: *P* = 0.026). Although the highest television-watching category showed a lower hazard than the reference category (HR = 0.884, 95% CI: 0.665–1.175), individual category comparisons were modest, and the overall association was primarily supported by the likelihood ratio test (Fig. 3d).

A higher total daily energy intake was associated with an earlier age-at-hypertension-onset (overall likelihood ratio test: *P* = 0.009), with participants in the highest tertile showing a significantly higher hazard than those in the lowest tertile (HR = 1.397, 95% CI: 1.022–1.910) (Fig. 3e).

No significant associations were observed between sleep duration, smoking status, physical activity, educational attainment, or healthy lifestyle score in either metabolic subgroup.

Biomedical characteristics and microbial diversity associated with age-at-hypertension-onset among individuals with metabolic dysfunction

Additional biomedical characteristics and gut microbial diversity indices were associated with age-at-hypertension-onset, exclusively in individuals with metabolic dysfunction. The multivariable-adjusted Cox regression results are summarized in Table 2, and the corresponding cumulative incidence curves are presented in Fig. 4.

Anthropometric and metabolic biomarkers. A higher waist-to-height ratio (WHtR) was significantly associated with earlier hypertension onset (overall likelihood ratio test: P = 0.045). Participants in the highest WHtR tertile had a higher hazard of hypertension onset than those in the lowest tertile (HR = 1.036, 95% CI: 0.650–1.649), although the overall association was primarily supported by the likelihood ratio test. Relative handgrip strength was associated with age-at-hypertension-onset (P = 0.049), with greater handgrip strength associated with delayed onset.

Metabolic biomarkers. A higher TyG index demonstrated the strongest association with earlier hypertension onset (P = 0.004). Participants in the highest TyG tertile had a significantly greater risk of hypertension onset than those in the lowest tertile (HR = 1.568, 95% CI: 1.177–2.088). Significant overall associations were also observed for HOMA-β (P = 0.039) and serum triglyceride concentrations (P < 0.001), with higher tertiles generally associated with an earlier age-of-hypertension-onset (Table 2; Fig. 4c, d).

Gut microbial diversity. Gut microbial richness was inversely associated with the onset of hypertension. Participants in the highest tertile of Observed richness exhibited a lower hazard of hypertension onset than those in the lowest tertile (HR = 0.672, 95% CI: 0.495–0.913; overall P = 0.008). Similar findings were observed for the Chao1 richness index (HR = 0.667, 95% CI: 0.492–0.906; overall P = 0.008), indicating that greater microbial richness was associated with a later age-at-hypertension-onset (Fig. 4e and f).

Restricted cubic spline analyses further demonstrated predominantly linear associations between significant continuous biomedical variables, gut microbial richness, and age-at-hypertension-onset (Fig. 5).

Table 2
Associations of biomedical, lifestyle, and gut microbial factors with age-at-hypertension-onset in the metabolic dysfunctional (MD) cohort.

Variable	N	Events	level	Thresholds	HR (95%CI)	P_LRT
Anthropometry						
WHtR	670	315	Moderate	(0.564,0.633]	1.247 (0.858–1.811)	0.0451
			High	(0.633,0.951]	1.036 (0.650–1.649)	
rel. HGS, left	661	312	Moderate	(0.659,1.08]	1.331 (0.976–1.817)	0.0485
			High	(1.08,2.26]	1.125 (0.696–1.820)	
Biomedical						
HOMA-Beta	670	315	Moderate	(2.1,3.49]	1.303 (0.977–1.736)	0.0389
			High	(3.49,12.7]	1.319 (0.974–1.786)	
TyG	670	315	Moderate	(8.48,8.96]	1.174 (0.878–1.570)	0.0043
			High	(8.96,9.88]	1.568 (1.177–2.088)	
Triglycerides	670	315	Moderate	(101,157]	0.973 (0.729–1.298)	0.0006
			High	(157,276]	1.363 (1.034–1.796)	
Lifestyle						
Energy intake	591	275	Moderate	(7.62e + 03,9.67e + 03]	1.232 (0.911–1.666)	0.0086
			High	(9.67e + 03,1.76e + 04]	1.397 (1.022–1.910)	
Watch tv	591	275	Moderate	v_t(2,3]	0.919 (0.682–1.238)	0.0259
			High	v_t(3,24]	0.884 (0.665–1.175)	
Content life	662	311	not at all content		0.908 (0.519–1.589)	0
			not so content		1.457 (1.081–1.964)	
			very content		0.531 (0.382–0.738)	
Microbiota						
Observed	559	272	Moderate	(216,310]	0.966 (0.724–1.289)	0.0076
			High	(310,626]	0.672 (0.495–0.913)	
Chao1	559	272	Moderate	(216,310]	0.974 (0.730–1.300)	0.008
			High	(310,626]	0.667 (0.492–0.906)	

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models adjusted for sex and BMI class. Continuous variables were categorized into tertiles, with the lowest tertile serving as the reference group. Likelihood ratio tests were used to evaluate overall associations. Complete results are presented in Supplementary Table S3B.

Gut microbial signatures associated with hypertension differ according to metabolic dysfunction status

To identify gut microbial signatures associated with hypertension under different metabolic conditions, gut microbial profiles were compared between participants with and without hypertension within the MD and non-MD cohorts. Neither α-diversity nor β-diversity analyses demonstrated significant differences in the overall microbial diversity or community composition between participants with and without hypertension in either metabolic subgroup (Supplementary Figure S2). Given the absence of community-level differences, selbal analysis was performed to identify taxonomic balances associated with hypertension.

Among women without metabolic dysfunction, the optimal microbial balance consisted of *Clostridium cluster IV* in the numerator and *Sutterella* and *Anaerotruncus* in the denominator (Fig. 6a). This balance discriminated participants with hypertension from those without hypertension, with an AUC of 0.847. Among men without metabolic dysfunction, the optimal balance was characterized by *Capnococcus* in the numerator and *Parabacteroides*, *Romboutsia*, *Coprobacillus*, *Blautia*, and an unclassified genus from the Erysipelotrichaceae in the denominator (Fig. 6b), yielding an AUC of 0.946.

In women with metabolic dysfunction, the optimal microbial balance comprised *Blautia*, *Faecalibacterium*, *Streptococcus*, *Alistipes*, *Flavonifractor*, and *Coprobacter* in the numerator and *Parasutterella*, *Odoribacter*, *Oscillibacter* and *Sutterella* in the denominator (Fig. 6c). The corresponding balance achieved an AUC of 0.778. In men with metabolic dysfunction, the numerator included *Escherichia/Shigella*, whereas the denominator included *Odoribacter* and *Oscillibacter* (Fig. 6d). The model achieved an AUC of 0.756.

Overall, the selbal analysis identified distinct microbial balances associated with hypertension across metabolic and sex strata, despite the absence of significant differences in global microbial diversity.

Discussion

Hypertension has undergone a marked epidemiological transition in recent decades, largely driven by profound changes in lifestyle and dietary habits. Traditionally regarded as a disease of older adults, hypertension is increasingly diagnosed at younger ages and frequently coexists with metabolic abnormalities, including obesity, dyslipidemia, insulin resistance, and diabetes[17–19]. Consequently, hypertension is increasingly recognized as a heterogeneous cardiometabolic disorder rather than an isolated increase in blood pressure. This evolving disease profile presents new challenges for hypertension prevention and underscores the importance of identifying the determinants of hypertension across different metabolic phenotypes.

In this population-based FoCus study, we established two analytical cohorts according to metabolic dysfunction status and comprehensively evaluated the biomedical, lifestyle, and gut microbial factors associated with both hypertension prevalence and timing of hypertension onset. Our findings demonstrate that metabolic dysfunction substantially reshapes the hypertension-associated risk profiles. Notably, in individuals without metabolic dysfunction, hypertension was predominantly associated with lifestyle-related factors, whereas those with metabolic dysfunction exhibited a broader pattern involving adverse metabolic characteristics, behavioral factors, and gut microbial diversity. These findings indicate that metabolic dysfunction is not merely a coexisting condition but an important modifier of the biological and behavioural pathways underlying hypertension development and further highlight the heterogeneity of hypertension across different metabolic backgrounds.

To our knowledge, this is one of the first population-based studies to simultaneously investigate the prevalence of hypertension and age-at-hypertension-onset across different metabolic backgrounds while integrating biomedical, lifestyle, and gut microbial characteristics within the same analytical framework. These findings provide new insights into the biological heterogeneity of hypertension and support the development of metabolically tailored prevention strategies.

Lifestyle factors

Our findings indicate that the influence of lifestyle on hypertension onset differs substantially according to metabolic status. Among individuals without metabolic dysfunction, only sports activity and television watching were associated with age-at-hypertension-onset, emphasizing the importance of maintaining an active lifestyle before metabolic abnormalities develop. In contrast, individuals with metabolic dysfunction exhibited considerably broader lifestyle-related associations. In addition to television watching, both greater life satisfaction and appropriate energy intake were associated with a later age-at-hypertension-onset. These findings suggest that once metabolic homeostasis is disrupted, the development of hypertension is increasingly influenced by the combined effects of behavioural and psychosocial factors rather than physical activity alone.

The beneficial effects of regular physical activity on blood pressure regulation are well established. Regular physical activity has been shown to improve endothelial function, vascular compliance, autonomic balance, insulin sensitivity, and systemic inflammation, all of which contribute to lower blood pressure and reduced cardiovascular risk [20–22]. Although television watching showed an overall association in the Cox model, this finding was modest and not consistently supported across complementary analyses. Previous work by Zhang *et al.* further demonstrated that individuals with hypertension who limited their sedentary time to ≤ 6 h/day while engaging in moderate-intensity physical activity experienced a 64% lower risk of cardiovascular mortality [23]. Extending these observations, our study suggests that physical activity and sedentary behaviour may influence not only hypertension prevalence but also the timing of hypertension onset, particularly among individuals without metabolic dysfunction.

Interestingly, the total energy intake was associated with hypertension onset only in individuals with metabolic dysfunction. This observation supports the concept that dietary factors may become increasingly important after metabolic regulation has already been impaired. Previous prospective studies have reported a U-shaped association between energy intake, particularly carbohydrate-derived energy intake, and incident hypertension, suggesting that both insufficient and excessive energy intake may adversely affect blood pressure regulation [24]. Given that metabolic dysfunction is characterized by insulin resistance, altered substrate utilization, and chronic low-grade inflammation, maintaining an appropriate energy balance may become increasingly important for delaying hypertension progression in this population.

Another notable finding was the differential role of psychosocial well-being. Although greater life satisfaction was associated with lower hypertension prevalence in both metabolic groups, it was associated with a later age-at-hypertension-onset only among individuals with metabolic dysfunction. Previous studies have suggested that higher life satisfaction is independently associated with lower cardiovascular risk through reduced chronic stress, more favourable neuroendocrine regulation, and healthier lifestyle behaviours [25–27]. Our findings extend this evidence by suggesting that psychosocial well-being may become particularly important once metabolic abnormalities are established, potentially buffering the additional physiological burden imposed by metabolic dysfunction, thereby delaying the clinical manifestation of hypertension.

Biomedical factors

Compared with lifestyle factors, metabolic biomarkers exhibited stronger and more consistent associations with both hypertension prevalence and the timing of disease onset among individuals with metabolic dysfunction, underscoring the central role of metabolic impairment in the development of hypertension.

WHtR is widely recognized as a sensitive marker of visceral adiposity and has consistently been shown to outperform BMI in predicting hypertension and cardiometabolic risk [28–30]. Consistent with previous evidence, we found that an elevated WHtR was associated with both a higher prevalence of hypertension and an earlier age-at-hypertension-onset among individuals with metabolic dysfunction, whereas this relationship was not observed in participants without metabolic dysfunction. This difference may partly reflect the distinct WHtR distributions between the two metabolic groups. Compared with metabolically healthy individuals, participants with metabolic dysfunction generally exhibited substantially higher WHtR values, indicating a greater burden of visceral adiposity. Accordingly, WHtR may better reflect the pathological consequences of excess abdominal fat accumulation in this population. Visceral adiposity promotes insulin resistance, chronic low-grade inflammation, endothelial dysfunction, and neurohormonal activation, all of which contribute to elevated blood pressure and vascular dysfunction [31]. Therefore, its contribution to the development of hypertension may become increasingly pronounced as metabolic abnormalities accumulate.

In addition to visceral adiposity, disturbances in glucose homeostasis also appeared to play an important role in hypertension among individuals with metabolic dysfunction. Both TyG index and HOMA-β were independently associated with hypertension, suggesting that abnormalities in insulin sensitivity and pancreatic β-cell function may jointly contribute to the development of hypertension. The TyG index demonstrated one of the strongest associations with both hypertension prevalence and timing of hypertension onset in the metabolically dysfunctional cohort. This finding is consistent with the accumulating evidence identifying TyG as a robust surrogate marker of insulin resistance and an important predictor of metabolic syndrome, type 2 diabetes, cardiovascular disease, and incident hypertension [7, 32, 33].While previous studies have primarily focused on hypertension risk [34, 35], our findings further suggest that TyG is also associated with the timing of disease onset. Individuals with higher TyG values tend to develop hypertension at a younger age, indicating that progressive insulin resistance may not only increase susceptibility to hypertension but also accelerate its clinical manifestation.

Consistent with the role of impaired glucose homeostasis, HOMA-β was also independently associated with hypertension. While the TyG index primarily reflects insulin resistance, HOMA-β provides complementary information on pancreatic β-cell function. These findings suggest that abnormalities across multiple stages of glucose homeostasis, rather than insulin resistance alone, may contribute to the development of hypertension in individuals with metabolic dysfunction.

The biological plausibility of these associations is supported by the central role of impaired glucose homeostasis in the pathogenesis of hypertension. Insulin resistance and compensatory hyperinsulinaemia contribute to endothelial dysfunction, chronic low-grade inflammation, sympathetic nervous system activation, activation of the renin–angiotensin–aldosterone system, and renal sodium retention, collectively promoting vascular dysfunction and sustained blood pressure elevation [36].Therefore, the deterioration of both insulin sensitivity and β-cell function may accelerate the development of hypertension, particularly in individuals with established metabolic dysfunction.

Another notable finding was the inverse association between relative handgrip strength and the risk of hypertension. Relative handgrip strength has emerged as an integrated marker of muscle quality and overall metabolic health and has been associated with lower risks of hypertension, diabetes, and cardiovascular disease in several population-based studies [37, 38]. Skeletal muscle is the primary site of insulin-mediated glucose disposal, and reduced muscle

function may exacerbate insulin resistance, systemic inflammation, and metabolic dysfunction [39–41]. The association observed in our study further suggests that preserving muscle quality may contribute not only to a lower hypertension risk but also to delaying disease onset among metabolically unhealthy individuals.

Collectively, these findings indicate that hypertension occurring in the presence of metabolic dysfunction is characterized by interconnected disturbances in visceral adiposity, glucose homeostasis, and skeletal muscle health. Rather than acting independently, these metabolic abnormalities likely interact to accelerate vascular dysfunction and the development of hypertension. These observations further support the concept that metabolic dysfunction is not merely a coexisting condition but represents a key biological substrate underlying earlier hypertension onset, highlighting the potential value of early metabolic optimization in delaying disease progression.

Gut microbiota

One of the most notable findings of this study was that gut microbial richness was associated with a delayed onset of hypertension only in individuals with metabolic dysfunction. This specific association may help explain the inconsistent findings of previous studies investigating the relationship between gut microbial diversity and hypertension [12]. By stratifying participants according to their metabolic status, our results suggest that metabolic dysfunction represents an important modifier of host–microbiota interactions during hypertension development, rather than gut microbial diversity acting as an independent determinant of disease.

A biologically plausible explanation for this is that metabolic dysfunction creates a physiological environment in which microbial alterations exert greater cardiovascular consequences. Chronic insulin resistance, low-grade inflammation, and impaired metabolic homeostasis may increase host susceptibility to microbiota-derived metabolic and inflammatory signals, thereby amplifying their effects on blood pressure regulation [42]. In contrast, preserved metabolic homeostasis may buffer these effects, reducing the contribution of gut microbial variation to hypertension in metabolically healthy individuals.

Collectively, these findings suggest that the clinical relevance of gut microbial diversity may largely depend on the host metabolic background. This observation further highlights the importance of incorporating metabolic stratification into future microbiome studies and may partly explain why previous studies that did not account for metabolic heterogeneity have reported inconsistent associations between gut microbial diversity and hypertension.

Strengths and limitations

To our knowledge, this is one of the first population-based studies to comprehensively characterize the biomedical, behavioural, and gut microbial determinants of hypertension after stratifying individuals according to metabolic dysfunction status. By simultaneously evaluating both the prevalence of hypertension and the age-at-hypertension-onset, our study provides a life-course perspective on hypertension development across different metabolic backgrounds. Furthermore, integrating host metabolic characteristics, lifestyle factors, and gut microbiota within the same analytical framework offers novel insights into the biological heterogeneity of hypertension and highlights the importance of metabolic stratification for individualized cardiovascular risk assessment and prevention.

However, several limitations of this study should be acknowledged. First, the case–control design does not allow for the estimation of age-specific hypertension prevalence and limits the interpretation of relative disease risks. Although time-to-event analyses based on age-at-hypertension-onset were performed, the retrospective ascertainment of disease onset and case–control sampling strategy may have introduced recruitment bias and potentially violated the assumption of independent censoring. Consequently, the hazard ratios should be interpreted cautiously and are primarily applicable to the present study population. Nevertheless, this analytical approach has

been widely applied in previous epidemiological studies [43, 44] and represents a practical strategy when prospective longitudinal data are unavailable. Second, although the participants were stratified according to metabolic dysfunction status, the analyses were conducted independently within each metabolic subgroup rather than directly comparing hypertensive individuals with and without metabolic dysfunction. This approach was primarily determined by the study design and substantial imbalance in the sample size between the two metabolic groups. Therefore, caution is warranted when interpreting the differences between metabolic strata, and future studies with larger and more balanced populations are needed to directly compare these hypertension phenotypes. In addition, the potential effects of lipid-lowering and glucose-lowering medications were not considered in the present analyses. As these therapies may influence metabolic parameters and cardiovascular risk, their potential confounding effects cannot be excluded. Future studies incorporating detailed medication information are warranted. Finally, despite identifying significant associations between metabolic dysfunction, gut microbiota, and hypertension, the cross-sectional nature of the baseline analysis precludes causal inference. Future prospective cohort studies integrating repeated measurements, multi-omics profiling, and functional microbiome analyses are warranted to validate these findings and further elucidate the biological mechanisms underlying hypertension development across different metabolic contexts.

Conclusion

In conclusion, our findings demonstrate that hypertension exhibits substantial biological heterogeneity according to metabolic dysfunction status. Lifestyle-related factors predominated among individuals without metabolic dysfunction, whereas hypertension in individuals with metabolic dysfunction was characterized by a broader pattern involving adverse metabolic characteristics, behavioural factors, and gut microbial diversity. These findings indicate that metabolic dysfunction fundamentally reshapes both the biological determinants of hypertension and the timing of disease onset, supporting the concept that hypertension develops through distinct pathophysiological pathways across different metabolic contexts. From a clinical perspective, metabolic stratification may represent a promising framework for improving hypertension risk assessment, identifying individuals at risk of earlier disease onset, and developing personalized prevention strategies. Future longitudinal studies integrating multi-omics approaches, functional microbiome analyses, and mechanistic investigations are needed to clarify the causal interplay between metabolic dysfunction, gut microbiota, and hypertension, ultimately facilitating precision prevention and intervention strategies for hypertension.

Abbreviations

CVD	Cardiovascular disease
TyG	Triglyceride–glucose index
WHtR	Waist-to-height ratio
SCFAs	Short-chain fatty acids
FoCus	Food Chain Plus
BMI	Body mass index
non-MD	Non-metabolic dysfunction
MD	Metabolic dysfunction
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
CRP	C-reactive protein
IL-6	Interleukin-6
ANOVA	Analysis of Variance
SD	Standard deviation
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval
Cox-PH	Cox proportional hazards
HR	Hazard ratio
RCS	Restricted cubic spline
ASV	Amplicon sequence variant
IKMB	Institute for Clinical Molecular Biology
FDR	False discovery rate
PERMANOVA	Permutational multivariate analysis of variance
WHR	Waist-to-hip ratio
RHGS	Relative handgrip strength
LAP	Lipid accumulation product
HOMA-β	Homeostasis Model Assessment of β-cell function
WC	Waist circumference
MDS	Mediterranean Diet Score
DASH	Dietary Approaches to Stop Hypertension
AUC	Area under the curve

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from each included participant. Study protocols conform to the ethical guidelines of the 1975 Declaration of Helsinki and have been priorly approved by the local ethics committee of the Medical Faculty at Kiel University, Germany (FoCus: A156/03).

Consent for publication

Not applicable.

Availability of data and materials

All data are available upon request from the P2N biobank. P2N is a controlled-access human data repository subject to European data protection laws. Therefore, data access is subject to an application, ethics approval by the applicant's ethics board and a data access agreement.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

C.G. conceived and designed the study. W.W. and C.G. performed the exploratory data analysis and statistical analyses, with support from A.J.C., and N.R. W.W. drafted the manuscript. C.G. and M.L. supervised the study and critically revised the manuscript. K.H., L.K., and K.T. contributed to cohort recruitment and data preparation. C.B. and A.F. performed gut microbiota sequencing and provided expertise in data handling and interpretation. All authors reviewed the manuscript, provided critical comments, and approved the final version.

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Figures

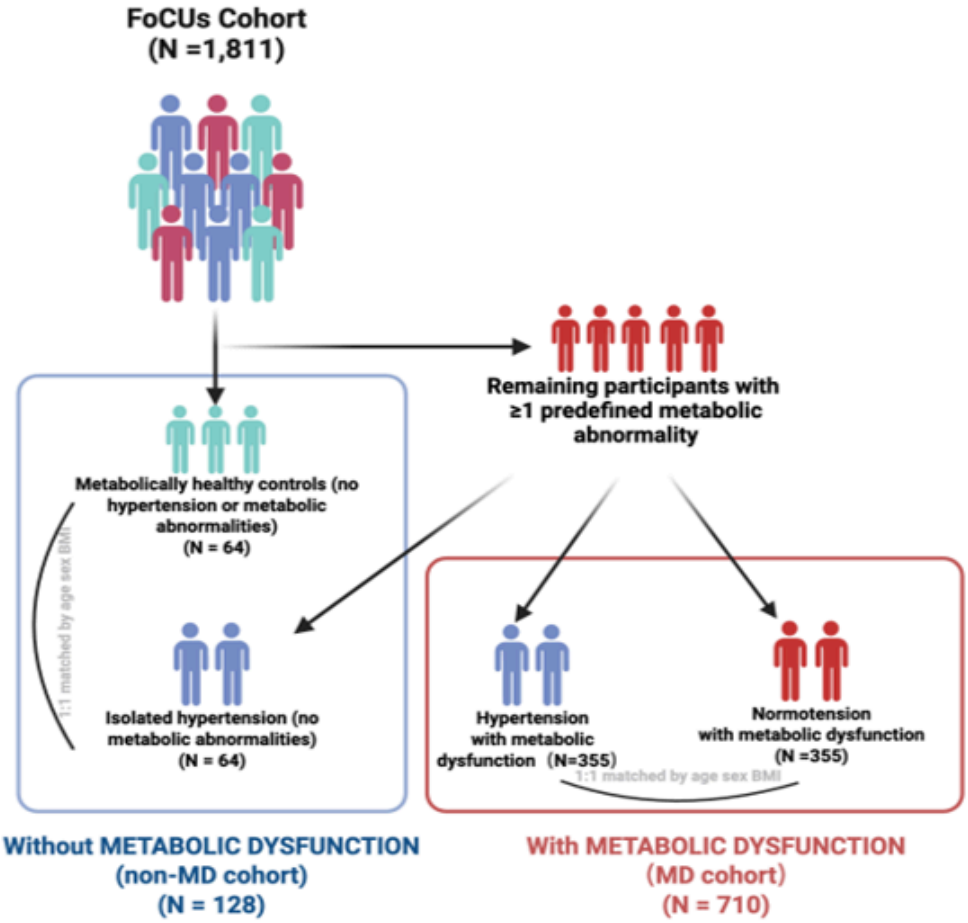


Figure 1

Flowchart illustrating participant selection and the construction of the non-metabolic dysfunction (non-MD) and metabolic dysfunction (MD) analytical cohorts from the FoCus study. Numbers of participants included in each group are shown in the figure.

Variable	Adjusted OR (95% CI)	Forest	P value
Hip circumference	0.978 (0.961–0.994)		0.008
Relative grip strength, right	0.465 (0.249–0.859)		0.015
HOMA–IR	1.004 (1.001–1.007)		0.005
Fasting glucose	1.017 (1.007–1.028)		<0.001
Fasting insulin	1.021 (1.006–1.036)		0.007
Triglycerides	1.005 (1.002–1.007)		<0.001
TyG index	1.956 (1.436–2.682)		<0.001
Observed richness	0.998 (0.996–1.000)		0.018
Chao1 richness	0.998 (0.996–1.000)		0.018

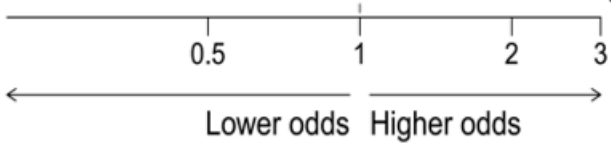


Figure 2

Multivariable-adjusted associations of biomedical characteristics and gut microbial richness with prevalent hypertension in the metabolic dysfunction (MD) cohort. Odds ratios(OR) and 95% confidence intervals(CI) were estimated using logistic regression models adjusted for age, sex, and BMI. Only statistically significant continuous variables are displayed. Waist-to-hip ratio was not included because of its substantially wider confidence interval, and life satisfaction was not displayed because it was analysed as a categorical variable. Complete results are provided in Supplementary Table S2B.

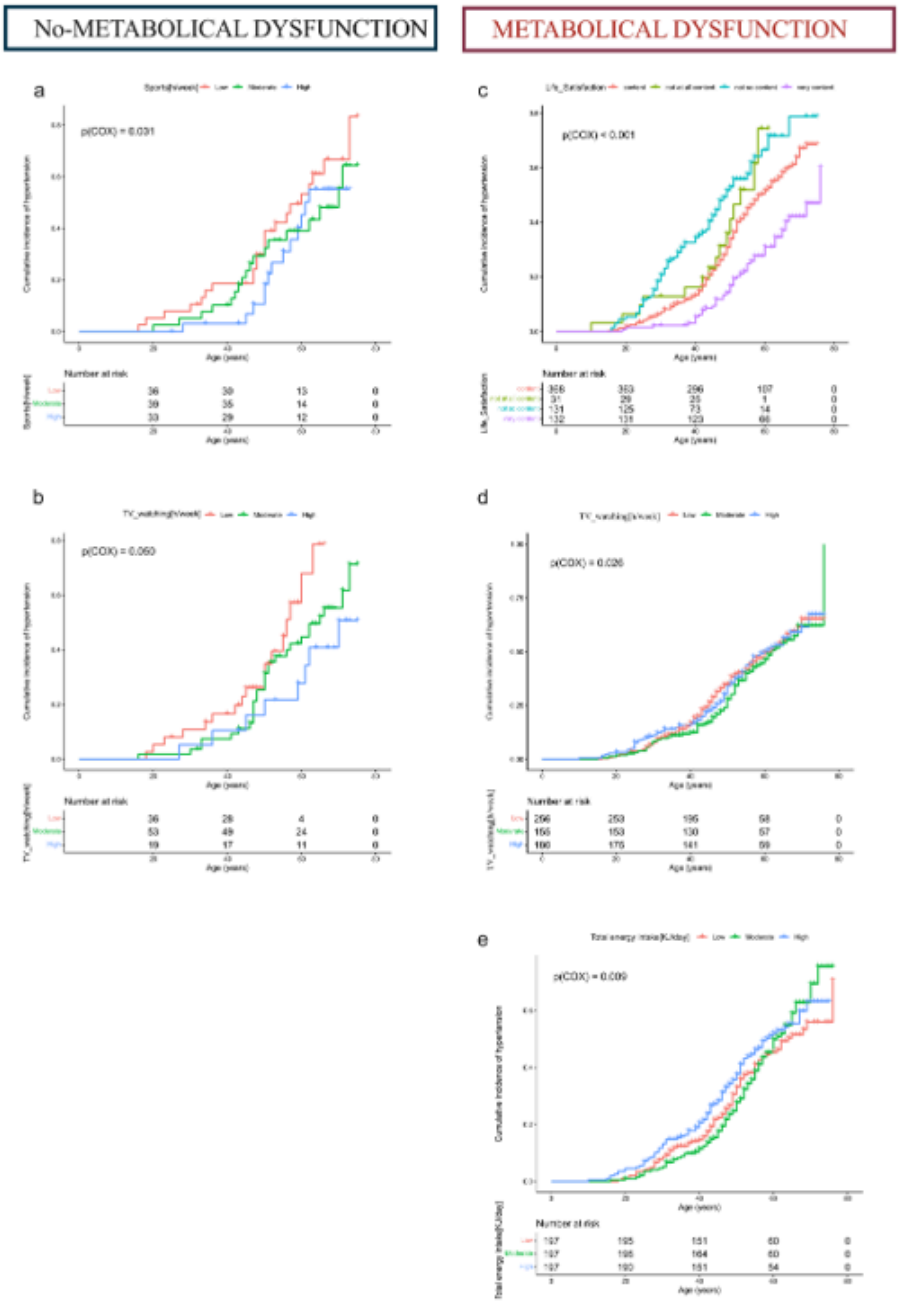


Figure 3

Kaplan–Meier curves illustrating the associations between lifestyle factors and age-at-hypertension-onset according to metabolic dysfunction status. (a) Sports activity and (b) television watching in the non-MD cohort; (c) life satisfaction, (d) television watching, and (e) total energy intake in the MD cohort. Associations were evaluated using Cox proportional hazards regression models adjusted for sex and BMI class. P values were obtained from likelihood ratio tests of the corresponding Cox models.

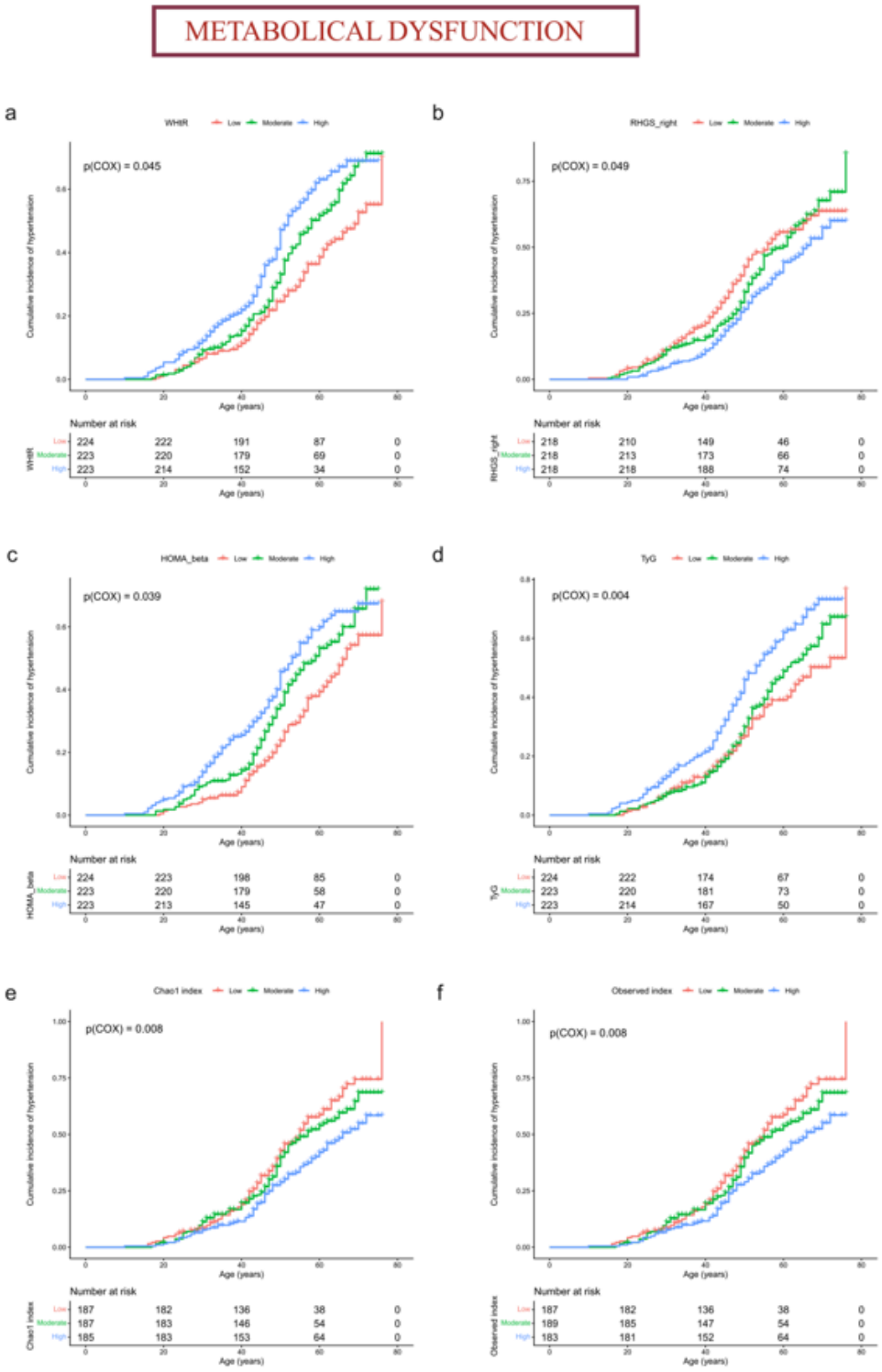


Figure 4

Kaplan–Meier curves showing associations between biomedical characteristics and gut microbial richness with age-at-hypertension-onset in the metabolic dysfunction (MD) cohort. This figure displays (a) WHtR, (b) relative handgrip strength, (c) HOMA-β, (d) TyG index, (e) Chao1 richness, and (f) Observed richness. Associations were evaluated using Cox proportional hazards regression models adjusted for sex and BMI class. P values were obtained from likelihood ratio tests of the corresponding Cox models.

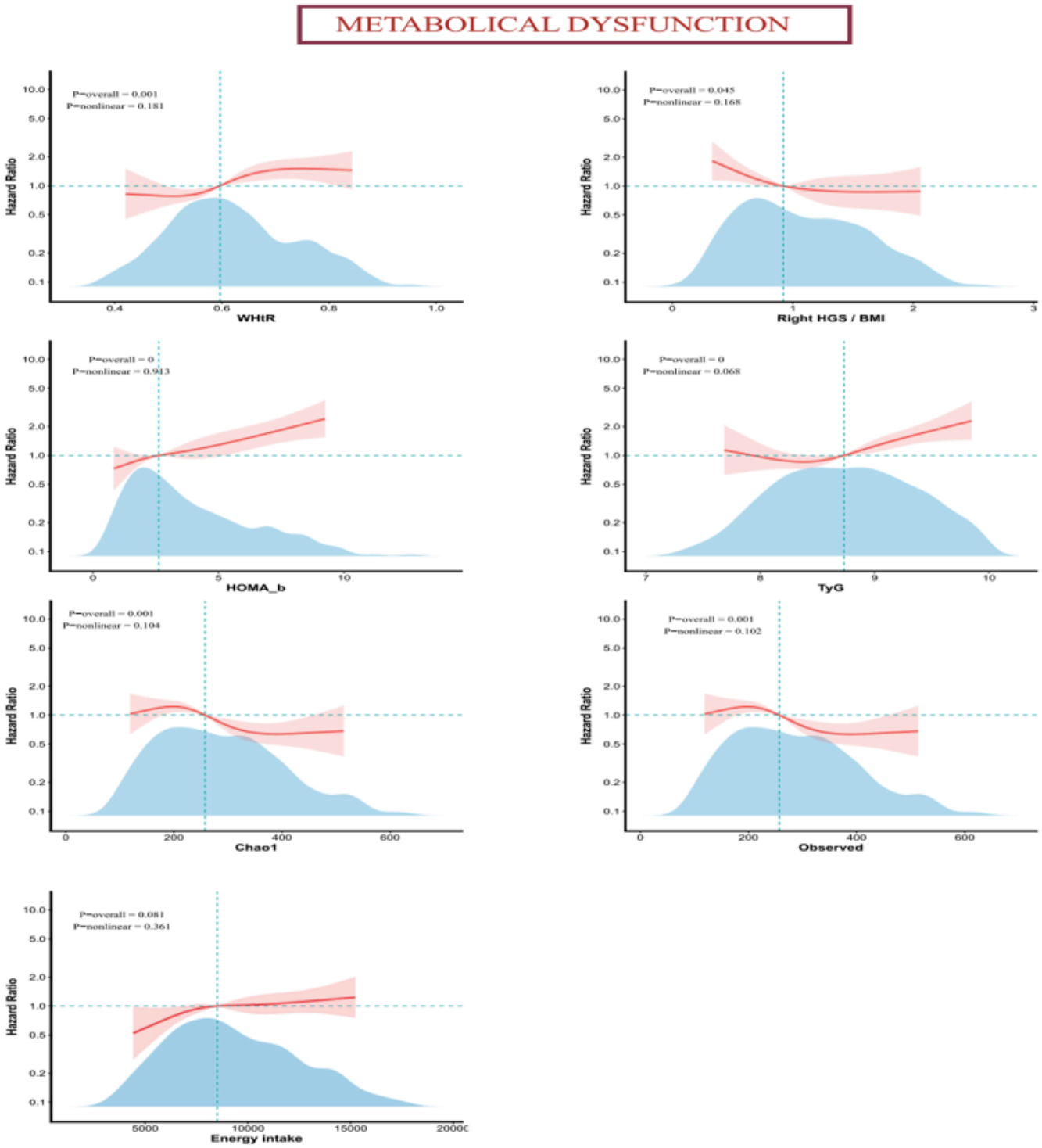


Figure 5

Restricted cubic spline analyses of continuous biomedical and gut microbial variables associated with age-at-hypertension-onset in the metabolic dysfunction cohort. Curves represent adjusted hazard ratios with 95% confidence intervals estimated from Cox proportional hazards regression models. Histograms illustrate the distribution of each variable. Restricted cubic spline analyses were adjusted for sex and BMI class.

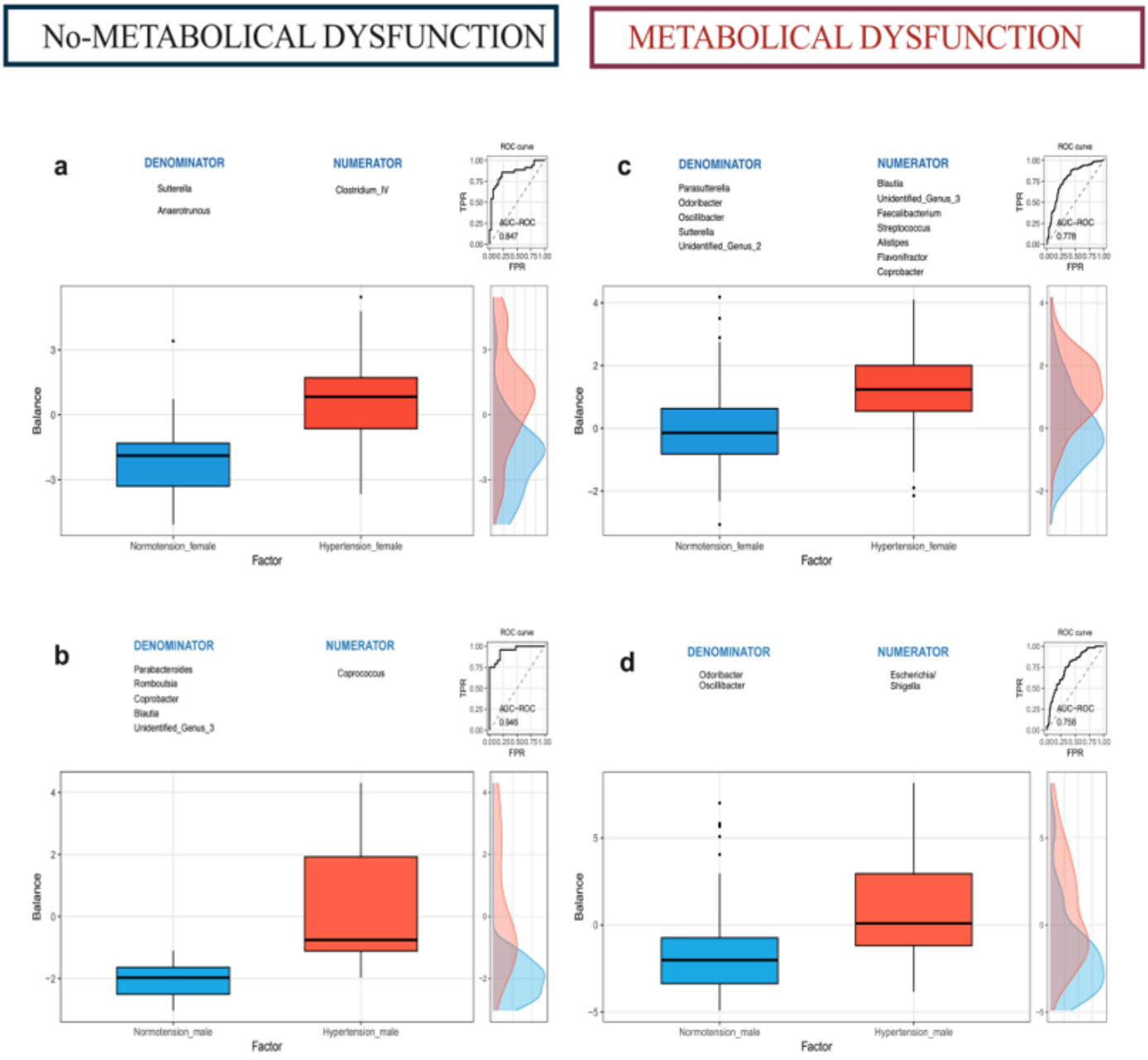


Figure 6

Gut microbial signatures identified by selbal analysis for discriminating hypertension according to sex and metabolic dysfunction status. Panels (a–d) present the microbial balances selected by selbal, including numerator and denominator taxa. Boxplots illustrate the distribution of balance scores between hypertension and normotension groups, whereas the right panels show ROC curves with the AUC values(top) and density distributions(bottom), demonstrating the discriminatory performance of each microbial signature.

Supplementary Files

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- Graphicalabstract.png