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Adiposity indicators exhibit depot- and sex-specific associations with multimorbidity onset: A cohort study of the UK Biobank

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Abstract

Aim: This study investigated the depot- and sex-specific associations of adiposity indicators with incident multimorbidity and comorbidity pairs.

Materials and Methods: We selected 382 678 adults without multimorbidity (≥2 chronic diseases) at baseline from the UK Biobank. General obesity, abdominal obesity and body fat percentage indices were measured.

Results: Cox proportional hazard regression analyses of general obesity indices revealed that for every one-unit increase in body mass index, the risk of incident multimorbidity increased by 5.2% (95% confidence interval 5.0%-5.4%). A dose-response relationship was observed between general obesity degrees and incident multimorbidity. The analysis of abdominal obesity indices showed that for every 0.1 increment in waist-to-height ratio and waist-to-hip ratio, the risk of incident multimorbidity increased by 42.0% (37.9%-46.2%) and 27.9% (25.7%-30.0%), respectively. Central obesity, as defined by waist circumference, contributed to a 23.2% increased risk of incident multimorbidity. Hip circumference and hip-to-height ratio had protective effects on multimorbidity onset. Consistent findings were observed for males and females. Body fat percentage elevated 3% (0.2%-5.9%) and 5.3% (1.1%-9.7%) risks of incident multimorbidity in all adults and females, respectively. Arm fat percentages elevated 5.3% (0.8%-9.9%) and 19.4% (11.0%-28.5%) risks of incident multimorbidity in all adults and males, respectively. The general obesity indices, waist circumference,

waist-to-height ratio, waist-to-hip ratio and central obesity increased the onset of comorbidity pairs, whereas hip circumference and hip-to-height ratio decreased the onset of comorbidity pairs. These adiposity indicators mainly affect diabetes mellitus-related comorbidity onset in males and hypertensive-related comorbidity onset in females.

Conclusions: Adiposity indicators are predictors of multimorbidity and comorbidity pairs and represent a promising approach for intervention.

KEYWORDS

adults, body fat percentage, central obesity, general obesity, multimorbidity

1 | INTRODUCTION

The concurrent existence of chronic diseases, commonly known as multimorbidity,[1] has become a pressing public health issue on a global scale.[2] Multimorbidity affects approximately 33.1% of the global population, with high-income countries bearing a substantially higher disease burden than low- and middle-income countries (37.9% vs. 29.7%).[3] Multimorbidity contributes to unfavourable health complications and has significantly elevated the risk of mortality.[4] The multimorbidity epidemic has emerged as a major challenge faced by health care systems worldwide.[2] With the ever-expanding ageing and overweight/obese populations worldwide, the prevalence of multimorbidity is projected to rise from 42.4% in 2020 to 57% in 2050.[5,6] In response to the global issue of multimorbidity, the World Health Organization (WHO) has published the first diagnosis and management guidelines for multimorbidity (2016) to advocate for a systems-based approach to address the determinants of multimorbidity, including biomedical and individual factors, health behaviours, socioeconomic characteristics, and social and environmental factors.[1,7]

Numerous studies have underscored the pivotal role of adiposity indicators in the initiation of multimorbidity.[8–10] However, the existing literature predominantly focuses on the impact of general obesity indices, such as body mass index (BMI).[9] However, the appropriateness of the sole use of BMI as an indicator of adiposity has been subject to scrutiny.[11] The limitations of BMI lie in its inability to reflect regional body fat distribution and distinguish between lean and fat body mass.[12,13] An extensive body of evidence has suggested that indices of abdominal obesity[14] and body fat distribution[15–17] exhibit stronger associations with the risk of chronic diseases. Furthermore, adipose tissue has sex-[18] and location-specific[19,20] biological functions. Adipose tissue deposition and function differ by sex.[21] The upper- and lower-body fat deposits have detrimental and beneficial effects on disease outcomes, respectively.[19,20] Considering this evidence, abdominal obesity indices and body fat percentage indices may offer greater accuracy than BMI in identifying adiposity and, consequently, may provide more precise predictions regarding the onset of multimorbidity. Although waist circumference-related abdominal obesity indices and hip circumference-related indices exhibit different associations with chronic diseases,[22] the existing studies only examined the associations between waist circumference-related indices and incident multimorbidity.[23–25] We did not find any studies examining the effects of hip circumference-related indices on incident multimorbidity. Furthermore, only one cross-sectional study examined the association between body fat percentage and the prevalence of multimorbidity[26]; however, the causal associations could not be implied because of the study design. Moreover, the effects of location-specific adipose tissue have not yet been investigated. Besides, although curvilinear associations between BMI and cause-specific mortality have been established,[27] it remains unclear whether similar associations exist between adiposity indicators and multimorbidity. Furthermore, understanding how various adiposity indicators contribute to the onset of specific comorbidity pairs may provide important evidence for interventions to reduce the burden of multimorbidity.

The UK Biobank presents an unparalleled opportunity to address these existing knowledge gaps. By utilizing a retrospective design, our study aims to examine the associations between adiposity indicators, including indices of general obesity, abdominal obesity and body fat percentage, and incident multimorbidity (≥2 chronic conditions) in a middle-aged and older-aged population. We also further expanded the analysis to specific comorbidity pairs and in both males and females. Our investigation has the potential to offer valuable insights to inform public health policies and lead to changes in clinical practices for multimorbidity interventions.

2 | METHODS

2.1 | Study design and participants

The UK Biobank is a prospective longitudinal study that enrolled 502 640 participants aged 38-73 years across England, Scotland and Wales from 2006 to 2010. A detailed description of enrolment procedures, data collection and follow-up has been previously published.[28]

In the current study, multimorbidity was defined as the coexistence of two or more chronic conditions, where each must be a non-communicable disease, a mental health disorder, or an infectious disease of long duration. The list of chronic diseases included was taken

from eight chapters of chronic diseases (Table S1), which were coded according to the International Classification of Diseases 10th Revision (ICD-10) based on their hospital inpatient records in either the primary or secondary position (Data-field: 41270).[29] The date of chronic disease diagnosis was the date of each ICD-10 diagnosis code on record in either the primary or secondary position in the participant's hospital inpatient records (Data-field: 41280). We excluded participants who had two or more pre-existing chronic diseases at baseline to minimize reverse causality (multimorbidity leading to a weight change). This left 382 678 participants for data analysis. With this sample size, we considered obesity-multimorbidity associations that yielded a hazard ratio (HR) ≥1.5,[9] and were significant at $\alpha = 0.05$; the power (1-β) was 1. In the separate analyses for various adiposity indicators, participants without missing data on the indicators were included (Figure S1).

Ethical approval of the UK Biobank study was given by the North West Multicentre Research Ethics Committee, the National Information Governance Board for Health & Social Care, and the Community Health Index Advisory Group.[30] This study was conducted with the approval of the Material Transfer Agreement (reference no. 79244). At recruitment, all participants gave informed consent to participate and be followed up through data linkage.

2.2 | Outcome indicators

The primary outcomes were the incidence of developing two or more multimorbidity diseases and the occurrence of a comorbidity pair with a morbidity rate >1%. A comorbidity pair refers to having two co-occurring chronic diseases. The date of developing two or more multimorbidity diseases was the date of occurrence for the second incident chronic disease. To test the robustness and potential variations in different subgroups, we repeated all analyses for the incidence of developing three or more multimorbidity diseases and four or more multimorbidity diseases. The dates of developing three or more multimorbidity diseases and four or more multimorbidity diseases were the dates of occurrence for the third and fourth incident chronic diseases, respectively.

2.3 | Adiposity indicators

Anthropometric parameters were assessed at baseline following a standardized protocol. Height (cm) was measured with a precision of 0.1 cm using a Seca 240 cm height measure. Waist circumference (cm) and hip circumference (cm) were measured using a Seca 200 cm tape measure.[12] Waist circumference was measured at the narrowest part of the trunk or at the level of the umbilicus after a normal expiration. Hip circumference was measured at the widest part of the buttocks. Body weight (kg) and fat percentages of the total body, trunk, and both arms and legs were measured using a body composition analyser (Tanita BC 418MA; Tanita Corporation). Based on these collected anthropometric parameters, various measures of the indices of general obesity, abdominal obesity and body fat percentage were calculated. The details were as follows: (a) general obesity indices: BMI was calculated as weight (kg) divided by height squared (m^2), and general obesity was defined using the WHO standards for overweight (25 kg/m^2 ≤ BMI<30 and obesity ≥30 kg/m^2); (b) to assess the dose-response relationship, obesity was further stratified into three levels: obesity 1 (BMI 30-34.99 kg/m^2), obesity 2 (BMI 35-39.99 kg/m^2), and obesity 3 (BMI > 40 kg/m^2); (c) abdominal obesity indices: waist-to-height ratio was calculated as dividing waist circumference (cm) by height (cm), waist-to-hip ratio was calculated as dividing waist circumference (cm) by hip circumference (cm), and hip-to-height ratio was calculated as dividing hip circumference (cm) by height (cm) and central obesity was defined according to WHO criteria, with waist circumference ≥102 cm for males and ≥88 cm for females[31]; and (d) the average of left and right leg fat percentages was used as the leg fat percentage, and the average of left and right arm fat percentages was used as the arm fat percentage.[32]

2.4 | Covariates

Covariates included age (years), sex (male, female), ethnicity (White and other ethnic groups), qualification levels [college or university degree, A levels/AS levels or equivalent, O levels/General Certificate of Secondary Educations (GCSEs) or equivalent, Certificate of Secondary Educations (CSEs) or equivalent, National Vocational Qualification (NVQ) or Higher National Diploma (HND) or Higher National Certificate (HNC) or equivalent], other qualifications, current employment status (in paid employment or self-employed, retired, unemployed), neighbourhood deprivation index, smoking (ever smoker, never smoker) and alcohol intake (never, previous, current). These variables were self-reported on a touchscreen questionnaire at baseline.

2.5 | Statistical analysis

First, the sociodemographic characteristics of the participants were described. To assess the differences between participants with or without the incidence of multimorbidity, the chi-squared test was employed for categorical variables, while the Student's t-test was utilized for continuous variables. Second, Kaplan-Meier survival curves were constructed to depict the cumulative incidence of multimorbidity based on sex, general obesity and central obesity. Third, Cox proportional hazard regressions were employed to assess the fully adjusted associations between adiposity indicators and the incidence of developing two or more multimorbidity diseases. The follow-up period began at baseline and extended until the occurrence of the specific diseases of interest, loss to follow-up, death, or the end of the follow-up period, whichever came first. The date of the last follow-up was 1 October 2023. Linear trends across obesity levels were tested by modelling this variable as a categorical variable in the Cox proportional hazard regressions. We also conducted sensitivity analysis for the associations between adiposity indicators and the incidence of multimorbidity with three or more and four or more chronic diseases. The effect size was expressed as a HR with a corresponding

TABLE 1 Baseline demographic characteristics of the study participants with and without incident of multimorbidity during the study period.

	All participants (n = 382 678)	No incident multimorbidity (n = 324 078)	Incident multimorbidity (n = 58 600)	*p*-Value[b]
Year of study entry				<.001
2006-2007	42 100 (11.00)	35 242 (10.80)	6858 (11.70)	
2008-2009	273 373 (71.44)	230 514 (71.10)	42 859 (73.20)	
2010	67 204 (17.56)	58 321 (18.00)	8883 (15.20)	
Age, years; mean ± SD	55.56 ± 8.07	54.91 ± 8.03	59.20 ± 7.28	<.001
Sex				<.001
Male	168 681 (44.08)	188 358 (58.10)	25 638 (43.80)	
Female	213 996 (55.92)	135 719 (41.90)	32 962 (56.20)	
Ethnicity				<.001
White	360 535 (94.36)	305 593 (94.43)	54 942 (93.96)	
Other ethnic groups	20 205 (5.29)	16 930 (5.23)	3275 (5.60)	
Don't know/prefer not to answer	1340 (0.35)	1085 (0.34)	255 (0.44)	
Qualification levels				<.001
College or university degree	134 531 (35.46)	117 998 (36.70)	16 533 (28.60)	
A levels/AS levels or equivalent	44 684 (11.78)	38 736 (12.00)	5948 (10.30)	
O levels/GCSEs or equivalent	81 217 (21.41)	69 149 (21.50)	12 068 (20.90)	
CSEs or equivalent	20 895 (5.51)	18 223 (5.70)	2672 (4.60)	
NVQ or HND or HNC or equivalent	23 277 (6.14)	18 744 (5.80)	4533 (7.80)	
Other professional qualifications	18 704 (4.93)	15 520 (4.80)	3184 (5.50)	
None of the above/prefer not to answer	56 079 (14.78)	43 196 (13.40)	12 883 (22.30)	
Current employment status				<.001
In paid employment or self-employed	240 776 (63.01)	211 725 (65.48)	29 051 (49.68)	
Retired	111 126 (29.08)	86 356 (26.71)	24 770 (42.36)	
Unemployed	26 588 (6.96)	22 275 (6.89)	4043 (6.91)	
None of the above/prefer not to answer	3607 (0.94)	2996 (0.93)	611 (1.04)	
Neighbourhood deprivation index, median (IQR)				
England	12.42 (15.04)	12.27 (14.73)	13.34 (16.77)	<.001
Wales	9.40 (13.40)	9.40 (13.40)	10.10 (14.63)	<.001
Scotland	7.98 (13.53)	7.81 (13.05)	9.52 (18.03)	<.001
BMI, kg/m^2; mean ± SD	26.96 ± 4.50	26.73 ± 4.37	28.23 ± 4.97	<.001
<18.5 (underweight)	2016 (0.53)	1761 (0.50)	255 (0.40)	<.001
18.5-24.9 (healthy weight)	135 818 (35.66)	120 827 (37.40)	14 991 (25.70)	
25.0-29.9 (overweight)	163 419 (42.91)	137 848 (42.70)	25 571 (43.90)	
≥30.0 (obesity)	79 619 (20.90)	62 207 (19.30)	17 412 (29.90)	
30.0-34.9 (obesity 1)	59 554 (74.80)	47 368 (76.15)	12 186 (69.99)	<.001
35.0-39.9 (obesity 2)	14 972 (18.80)	11 310 (18.18)	3662 (21.03)	
≥40.0 (obesity 3)	5093 (6.40)	3529 (5.67)	1564 (8.98)	
Waist circumference, cm; median (IQR)	88.79 (12.90)	87.86 (12.56)	93.89 (13.55)	<.001
Waist-to-height ratio, median (IQR)	0.53 (0.07)	0.52 (0.07)	0.55 (0.08)	<.001
Waist-to-hip ratio, median (IQR)	0.86 (0.13)	0.86 (0.13)	0.90 (0.13)	<.001
Central obesity[a]	112 398 (29.48)	88 658 (27.45)	23 740 (40.69)	<.001
Hip circumference, cm; median (IQR)	102.00 (10.00)	102.00 (10.00)	103.00 (11.00)	<.001
Hip-to-height ratio, median (IQR)	0.60 (0.07)	0.60 (0.07)	0.61 (0.07)	<.001

(Continues)

TABLE 1 (Continued)

	All participants (n = 382 678)	No incident multimorbidity (n = 324 078)	Incident multimorbidity (n = 58 600)	*p*-Value[b]
Body fat percentage indicators, median (IQR)				
Total body fat percentage	30.60 (12.40)	30.70 (12.50)	30.50 (12.30)	<.001
Left and right arms average fat percentage	27.95 (15.10)	28.10 (15.10)	27.15 (15.10)	.043
Trunk fat percentage	30.62 (7.91)	30.45 (7.90)	31.55 (7.86)	<.001
Left and right legs average fat percentage	33.35 (18.65)	33.90 (18.55)	28.70 (19.10)	<.001
Smoking status				<.001
Ever smoker	220 535 (57.91)	139 759 (43.30)	20 516 (35.20)	
Never smoker	160 275 (42.09)	182 841 (56.70)	37 694 (64.80)	
Alcohol intake				<.001
Never	15 397 (4.03)	12 691 (3.90)	2706 (4.60)	
Previous	10 639 (2.78)	8535 (2.60)	2104 (3.60)	
Current	355 614 (93.07)	302 044 (93.30)	53 570 (91.60)	
Prefer not to answer	431 (0.11)	338 (0.10)	93 (0.20)	

Note: Data are n (%) unless otherwise stated.
Abbreviations: BMI, body mass index; CSEs, Certificate of Secondary Educations; GCSEs, General Certificate of Secondary Educations; HND, Higher National Diploma; HNC, Higher National Certificate; IQR, interquartile range; NVQ, National Vocational Qualification.
[a]Central obesity was defined as a waist circumference ≥102 cm in males, and ≥88 cm in females according to WHO standards.
[b]The *p*-value was calculated using the chi-squared test for categorical variables and Student's t-test or Wilcoxon test for continuous variables among participants with versus without multimorbidity.

95% confidence interval. Fourth, to explore the potential curvilinear associations between adiposity indicators and the incidence of developing two or more multimorbidity diseases, restricted cubic splines were employed. Fifth, multinomial logistic regressions were fitted to explore the adjusted associations between adiposity indicators and the morbidity rate of comorbidity pairs. In all regression analyses and cubic spline fitting, BMI was additionally adjusted for the influences of abdominal obesity indices and total body fat percentage. Total body fat percentage and BMI were additionally adjusted for the effects of trunk, legs and arm fat percentages. Cox proportional hazard regressions, restricted cubic splines and multinomial logistic regressions were also used to examine the associations of adiposity indicators with incident multimorbidity and the morbidity rate of comorbidity pairs in males and females. The same covariates were adjusted in sex-stratified analyses.

Analyses were performed using R 4.2.1 (R Foundation for Statistical Computing). Two-sided $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

Of the 382 678 adults in the eligible population from the UK Biobank (Figure S1), approximately 56% (213 996 of 382 678) of them were females, and the mean age was 55.6 years. Approximately 63.8% (243 038 of 382 678) of participants had overweight or obesity, and 29.43% (112 220 of 382 678) had central obesity. Individuals who developed multimorbidity would probably be older, be female and present with general obesity or central obesity (all $p < .001$). They also have significantly lower educational qualifications and a higher neighbourhood deprivation index (all $p < .001$) (Table 1).

3.2 | Incidence of population multimorbidity in 10 years

The cumulative incidence of developing two or more multimorbidity diseases varied by their sex and adiposity indicators. During a 10-year follow-up period (mean follow-up of 8.0 years), the incidence in males and females was 54.49% and 45.37%, respectively; the incidence in adults with underweight, normal weight, overweight and obesity was 43.46%, 40.02%, 50.36% and 62.56%, respectively; and the incidence in adults without and with central obesity was 44.27% and 61.40%, respectively (Figure 1 and Table S2).

3.3 | Overall and sex-stratified associations between adiposity indicators and the incidence of developing two or more multimorbidity diseases

Our analysis of general obesity indices indicated that for every one-unit increase in BMI, the risk of incident multimorbidity increased by 5.2% (95% confidence interval 5.0%-5.4%). Individuals who were

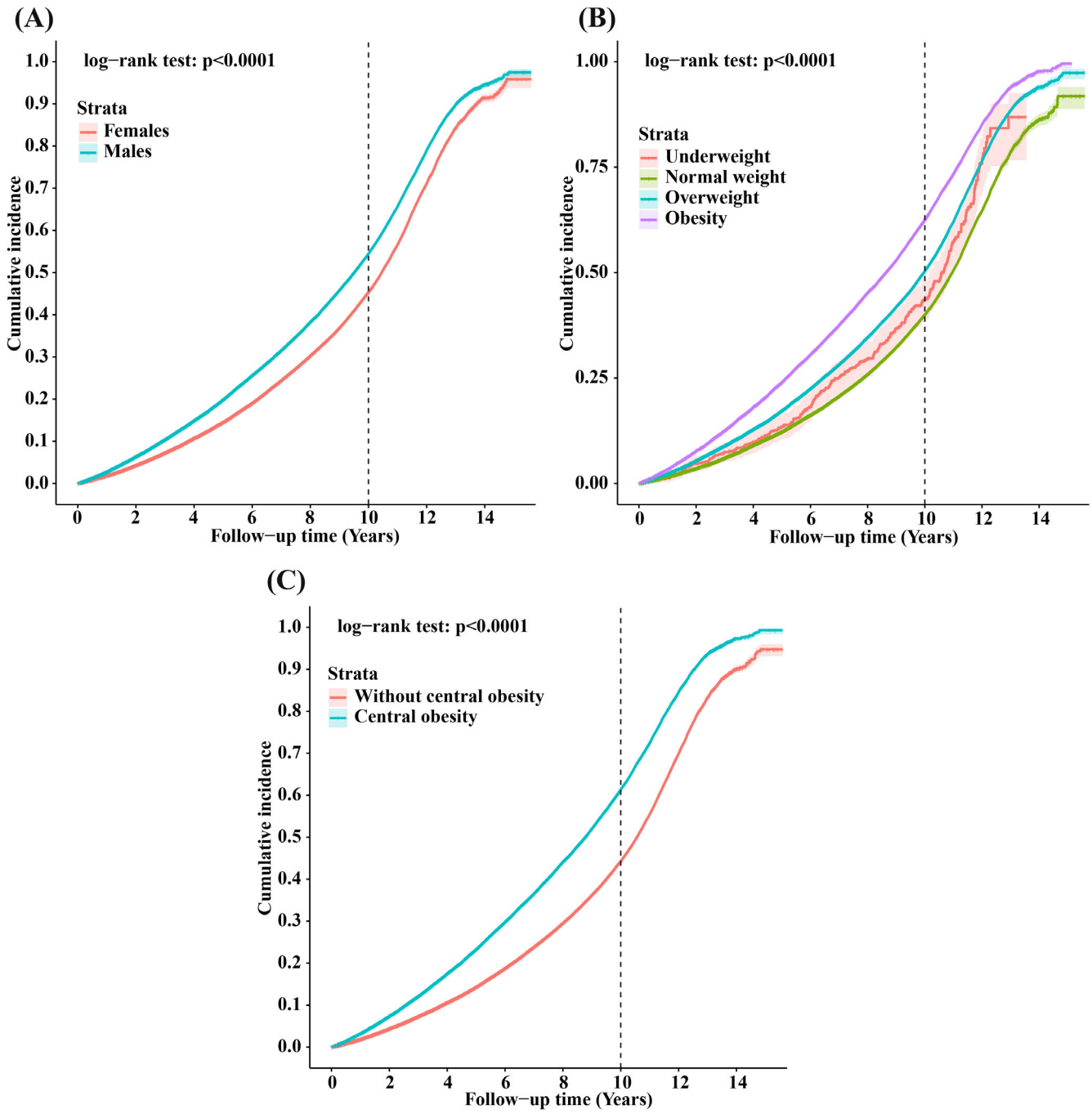

FIGURE 1 The cumulative incidence of multimorbidity among (A) males and females, (B) adults with and without general obesity, and (C) adults with and without central obesity at baseline. The Y-axis represents cumulative incidence. Log-rank test was used to compare the difference in cumulative incidence across sex and adiposity indicators at baseline.

overweight at baseline had a 25.9% (23.0%-28.9%) higher risk of developing multimorbidity than individuals with normal weight, whereas obese individuals had an elevated risk of 77.7% (73.2%-82.3%). Furthermore, a dose-response relationship was observed between the degree of obesity and the incidence of multimorbidity, with HRs ranging between 1.651 and 2.531. These associations held true for both males and females. Among both males and females, BMI, overweight and obesity also contribute to the increased risk of developing multimorbidity (Figure 2).

After adjustment for BMI and other covariates, our analysis on abdominal obesity indices revealed that for each unit increase in waist circumference, the risk of incident multimorbidity increased by 1.9% (1.7%-2.0%). For each 0.1 increment in the waist-to-height ratio and waist-to-hip ratio, the risk of incident multimorbidity increased by

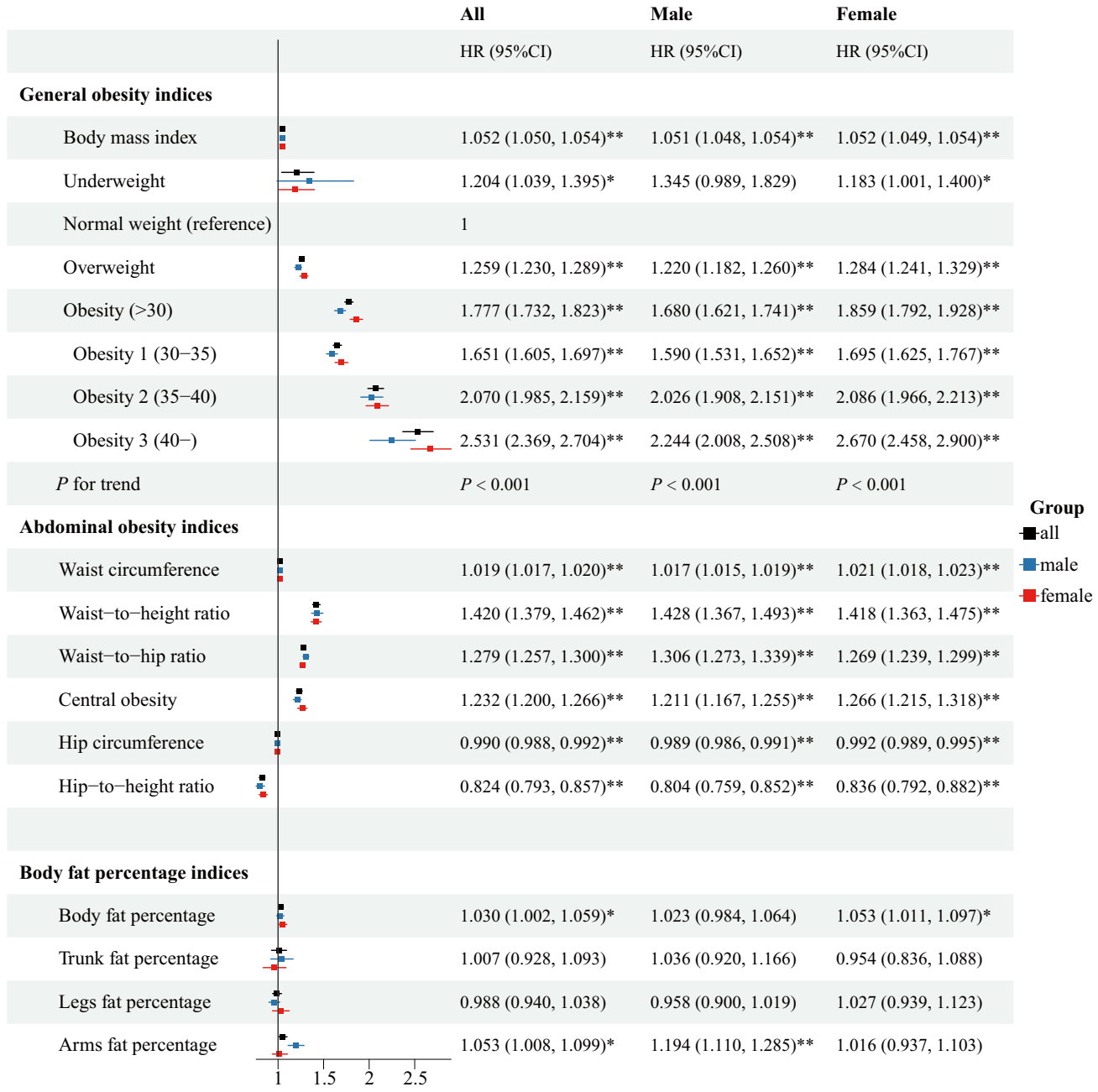

FIGURE 2 Associations between indices of general obesity, abdominal obesity and body fat percentage with the incident of multimorbidity among all adults, males, and females. Cox proportional hazard models were used to analyse the data. For the general obesity indices, covariates including age, sex, ethnicity, qualification levels, employment status, smoking, and alcohol drinking were adjusted in the models. For the indices of abdominal obesity and body fat percentage, the aforementioned covariates and body mass index were adjusted. The aforementioned covariates, body mass index, and total body fat percentage were adjusted for regional body fat percentages. In the models, body mass index, waist circumference, waist-to-height ratio, waist-to-hip ratio, hip circumference, hip-to-height ratio, body fat percentage, trunk fat percentage, fat percentage of legs and fat percentage of arms were used as continuous variables. In contrast, general obesity status and central obesity were used as categorical variables. Waist-to-height ratio, waist-to-hip ratio, and hip-to-height ratio increased by every 0.1 unit in the models, and total and regional body fat percentages increased by every 10% unit in the models. Linear trends across general obesity levels were tested by modelling this variable as a categorical variable in the Cox proportional hazard models. CI, confidence interval; HR, hazard ratio.

42.0% (37.9%-46.2%) and 27.9% (25.7%-30.0%), respectively. Individuals who had central obesity at baseline had a 23.2% (20.0%-26.6%) higher risk of developing multimorbidity than individuals without central obesity. Conversely, for each one-unit increase in hip circumference and each 0.1 increment in hip-to-height ratio, the risk of incident multimorbidity decreased by 1.0% (0.8%-1.2%) and 17.6% (14.3%-20.7%), respectively. These associations remained consistent across both males and females. Among both males and females, waist

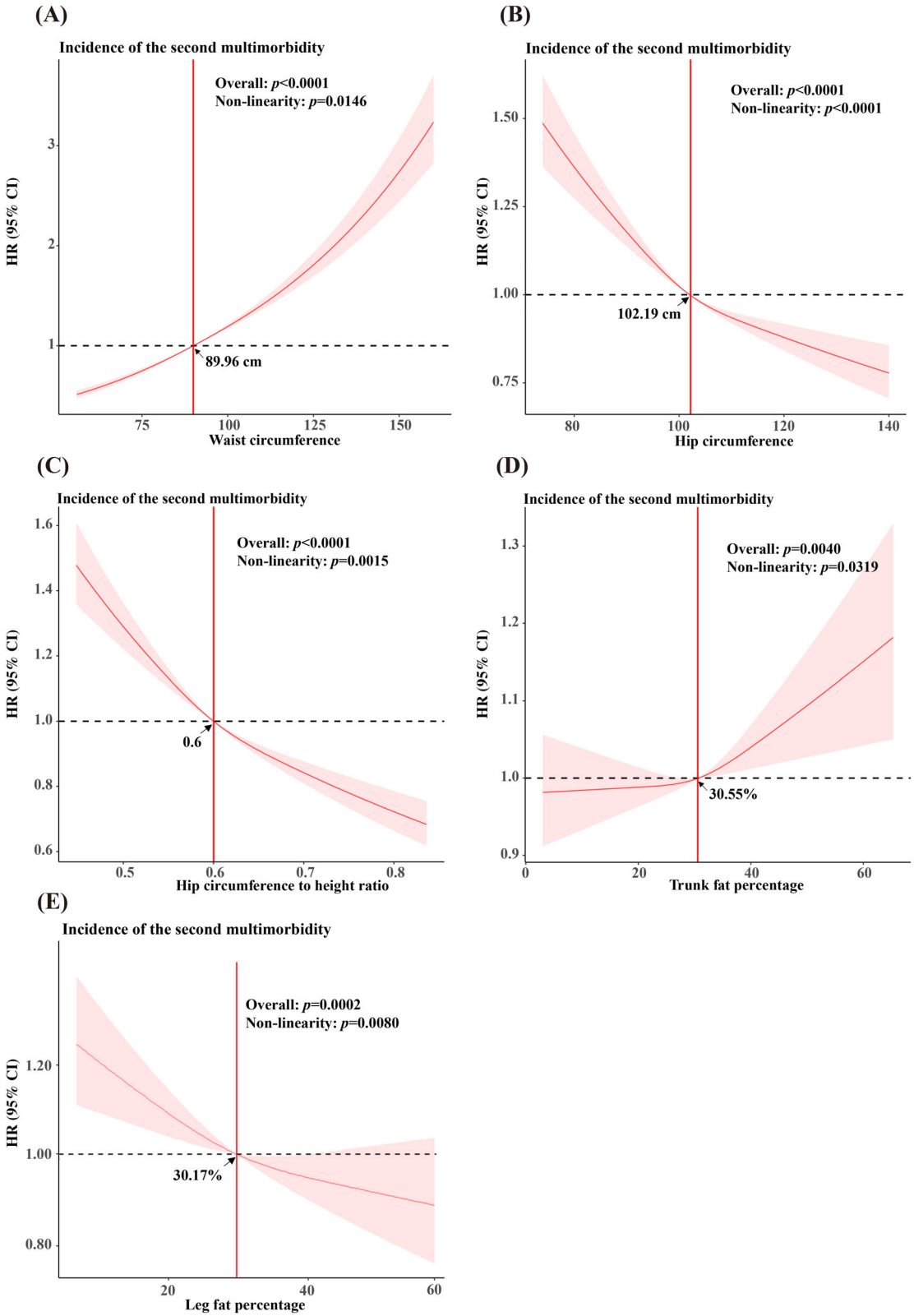

FIGURE 3 Significant curvilinear associations between adiposity indicators at baseline and the incidence of developing two or more multimorbidity diseases at follow-up analyzed by restricted cubic spline among all adults: (A) Waist circumference; (B) Hip circumference; (C) Hip circumference to height ratio; (D) Trunk fat percentage; (E) Leg fat percentage. The covariates including age, sex, ethnicity, qualification levels, employment status, smoking, and alcohol drinking were adjusted in the model for body mass index and waist circumference. The aforementioned covariates and body mass index were adjusted for total body fat percentage, waist circumference, hip circumference, waist-to-height ratio, hip-to-height ratio, and waist-to-hip circumference ratio. The aforementioned covariates, body mass index, and total body fat percentage were adjusted for regional body fat percentages. HR=Hazard ratio.

circumference, waist-to-height ratio, waist-to-hip ratio and central obesity were associated with an increased risk of multimorbidity onset, whereas hip circumference and hip-to-height ratio were associated with a decreased risk of incident multimorbidity (Figure 2).

Upon adjustment for BMI and other covariates, our analysis revealed that for every 10% increment in body fat percentage, the risk of developing multimorbidity increased by 3.0% (0.2%-5.9%) in all adults. In females, this increase was even more significant, with a 5.3% (1.1%-9.7%) rise. Furthermore, after adjusting for total body fat percentage, BMI and other covariates, we found that for every 10% increment in arm fat percentage, the risk of developing multimorbidity increased by 5.3% (0.8%-9.9%) in all adults, and this increase was 19.4% (11.0%-28.5%) in males (Figure 2).

Sensitivity analyses showed similar association patterns; the risk and protective effects of adiposity indicators were also observed for incident multimorbidity with three or more and four or more chronic diseases (Table S3).

3.4 | Overall and sex-stratified curvilinear associations between adiposity indicators and the incidence of developing two or more multimorbidity diseases

The curvilinear associations between all adiposity indicators and the incidence of multimorbidity were examined by the restricted cubic splines analysis, and the significant associations were shown in Figures 3 and 4 (all results were shown in Figures S2-S4). Among all adults, curvilinear associations of waist circumference, hip circumference, hip-to-height ratio, trunk fat percentage and leg fat percentage with the incidence of multimorbidity were observed. Among males, curvilinear associations of hip circumference, trunk fat percentage and arm fat percentage with the incidence of multimorbidity were observed. Among females, curvilinear associations of hip circumference and waist-to-height ratio with the incidence of multimorbidity were observed.

3.5 | Overall and sex-stratified associations between adiposity indicators and the morbidity rate of specific comorbidity pairs

We investigated 154 comorbidity pairs and presented 23 pairs whose morbidity rate was >1% in Figure 4. Our analyses of general obesity indices revealed there are significant associations between BMI and the increased risks of developing all comorbidity pairs, and the highest odds ratio (OR) values were observed for diabetes mellitus-related comorbidity [with other forms of heart disease, OR = 1.234 (1.221-1.248); with hypertensive diseases, OR = 1.228 (1.218-1.237); with diseases of the respiratory system, OR = 1.218 (1.202-1.233); with mental and behavioural disorders, OR = 1.206 (1.191-1.222)]. Similar patterns were observed in individuals who had overweight or obesity. Being underweight contributed to the decreased risks of developing diabetes mellitus-related comorbidity [with other forms of heart disease, OR = 0.848 (0.838, 0.858); with mental and behavioural disorders, OR = 0.859 (0.850, 0.867)]. However, underweight increased risks of developing mental and behavioural disorder-related comorbidities [with other forms of heart disease, OR = 2.253 (1.297, 3.915); with diseases of the respiratory system, OR = 2.157 (1.302, 3.575)]. In males, similar patterns of BMI and general overweight and obesity with the onset of comorbidity pairs were observed. Being underweight contributed to the increased risk of unspecified disorders of the circulatory system-related comorbidities. In contrast, in females, stronger associations were observed between BMI and general overweight and obesity indices and hypertensive disease-related comorbidities. Being underweight contributed to the increased risk of mental and behavioural disorder-related comorbidities (Figure 5 and Table S4).

Regarding the abdominal obesity indices, significant associations were observed between waist circumference and higher risks of developing all comorbidity pairs, and the highest OR values were observed for diabetes mellitus-related comorbidity [with diseases of the respiratory system, OR = 1.077 (1.065, 1.089); with mental and behavioural disorders, OR = 1.075 (1.063, 1.087); with hypertensive diseases, OR = 1.068 (1.061, 1.075); with other forms of heart disease, OR = 1.064 (1.054, 1.074)]. Similar patterns were shared in the associations of the onset of comorbidity pairs with waist-to-height ratio, waist-to-hip ratio and central obesity. In contrast, hip circumference was associated with decreased risks of developing certain comorbidity pairs, and the highest OR values were observed for diabetes mellitus-related comorbidity [with mental and behavioural disorders, OR = 0.952 (0.943, 0.962); with hypertensive diseases, OR = 0.956 (0.948, 0.964); with other forms of heart disease, OR = 0.963 (0.954, 0.972); with diseases of the respiratory system, OR = 0.965 (0.956, 0.975)]. Similar patterns were shared for the hip-to-height ratio and these comorbidity pairs. Sex-stratified analyses observed similar patterns in males; in contrast, in females, stronger associations were observed between abdominal obesity indices and hypertensive disease-related comorbidities (Figure 5 and Table S4).

Our analyses of body fat percentage indices revealed that the fat percentage of legs was associated with increased risks of developing certain comorbidity pairs, and the highest OR values were observed for the diabetes mellitus-related comorbidity (ORs: 1.030-1.580). The arm fat percentage was associated with increased risks of hypertensive disease-related comorbidities [with diseases of veins, lymphatic vessels and lymph nodes, not classified elsewhere, OR = 1.032 (1.008, 1.057); with diseases of the respiratory system, OR = 1.023 (1.005, 1.040)]. Trunk fat percentage was associated with decreased risks of developing certain comorbidity pairs, and the highest OR values were observed for mental and behavioural disorder-related comorbidities [with diseases of the respiratory system, OR = 0.906 (0.871, 0.942); with hypertensive diseases, OR = 0.907 (0.880, 0.936)]. Sex-stratified analyses revealed different association patterns. In males, trunk fat percentage contributed to the decreased risk of mental and behavioural disorder-related comorbidities, and arm fat percentage contributed to the increased risk of other forms of heart

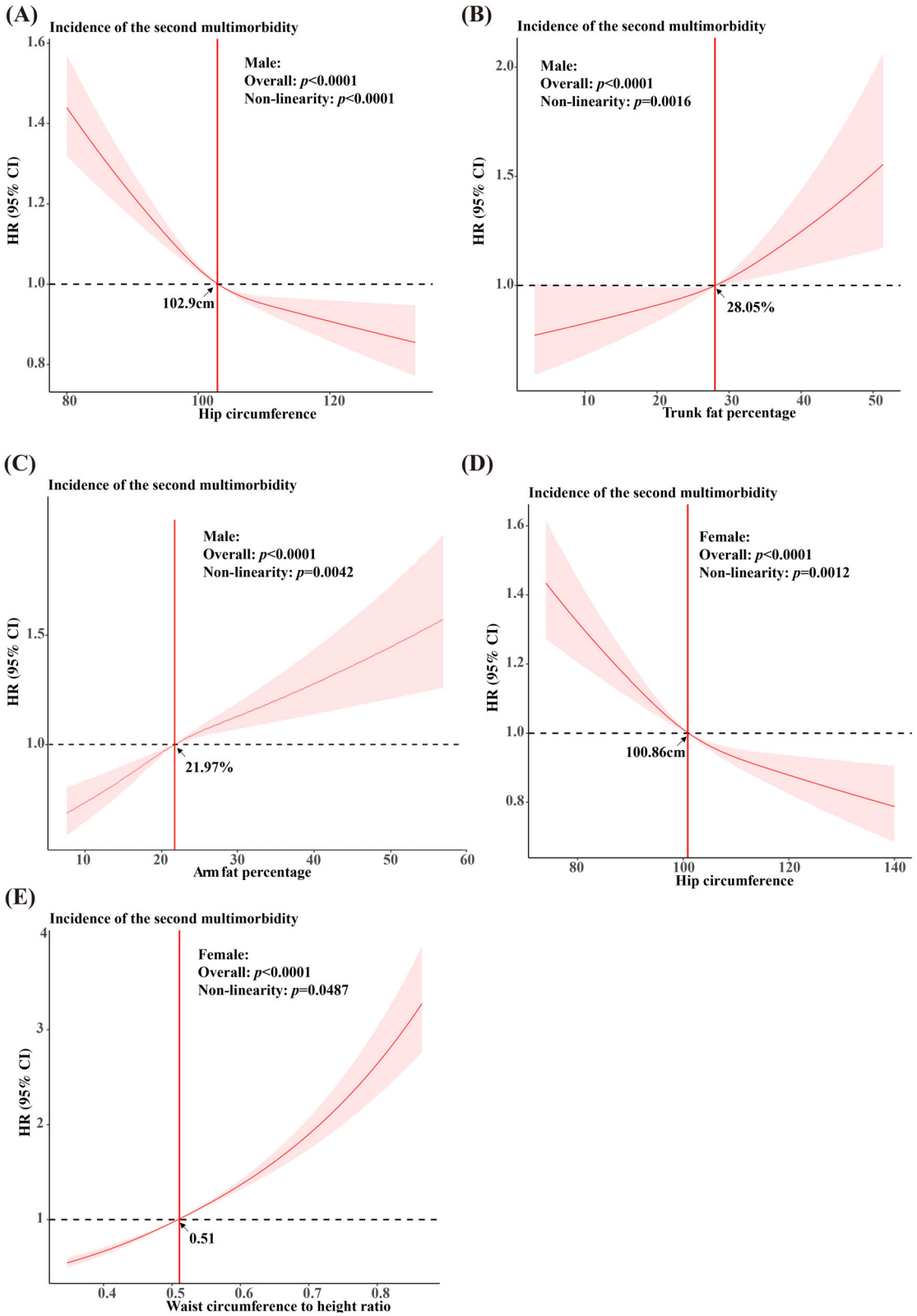

FIGURE 4 Significant curvilinear associations between adiposity indicators at baseline and the incidence of developing two or more multimorbidity diseases at follow-up by restricted cubic spline in males and females: (A): Hip circumference in males; (B): Trunk fat percentage in males; (C): Arm fat percentage in males; (D): Hip circumference in females; (E): Waist circumference to height ratio in females. The covariates including age, ethnicity, qualification levels, employment status, smoking, and alcohol drinking were adjusted in the model for body mass index and waist circumference. The aforementioned covariates and body mass index were adjusted for total body fat percentage, waist circumference, hip circumference, waist-to-height ratio, hip-to-height ratio, and waist-to-hip circumference ratio. The aforementioned covariates, body mass index, and total body fat percentage were adjusted for regional body fat percentages. HR=Hazard ratio.

(A) All adults

Diseases name and ICD-10 code	Percentage (%)	General obesity indices							Abdominal obesity indices						Body fat percentage indices			
		BMI	Underweight	Overweight	Obesity (BMI >30)	Obesity 1 (BMI: 30-35)	Obesity 2 (BMI: 35-40)	Obesity 3 (BMI >40)	WC	WtHR	WtHIR	Central obesity	HC	HtHR	BFP	TFP	LFP	AFP
Hypertensive diseases (I10-I15) and other forms of heart disease (I30-I52)	4.65	1.126		1.556	3.564	2.850	5.962	9.489	1.038	1.703	1.370	1.436	1.008		0.990			
Hypertensive diseases (I10-I15) and diseases of the respiratory system (J31-J96)	4.11	1.128		1.590	3.680	2.942	5.669	10.673	1.046	2.622	1.746	1.506	0.982	0.858		0.932	1.030	1.023
Hypertensive diseases (I10-I15) and mental and behavioral disorders (F00-F99)	4.05	1.102	1.738	1.479	2.914	2.431	4.433	6.197	1.048	2.597	1.737	1.465	0.983	0.813		0.907	1.061	
Hypertensive diseases (I10-I15) and ischaemic heart diseases (I20-I25)	3.78	1.111		1.786	3.347	2.876	4.969	6.502	1.033	2.171	1.599	1.419	0.979			0.938	1.044	
Hypertensive diseases (I10-I15) and diabetes mellitus (E10-E14)	3.39	1.228		2.858	11.919	8.388	23.563	41.549	1.068	3.816	2.534	2.314	0.956	0.500		0.956	1.041	
Other forms of heart disease (I30-I52) and ischaemic heart disease (I20-I25)	2.84	1.101		1.577	2.885	2.422	4.539	6.029	1.030	1.822	1.463	1.396	0.987	0.827		0.952	1.036	
Hypertensive diseases (I10-I15) and diseases of the musculoskeletal system (M00-M46)	2.67	1.161		2.333	5.947	4.771	9.275	17.013	1.031	1.808	1.489	1.442	0.983	0.753			1.032	
Diseases of the respiratory system (J31-J96) and other forms of heart disease (I30-I52)	2.52	1.099		1.238	2.595	2.085	3.897	8.223	1.040	2.090	1.548	1.499						
Diseases of the respiratory system (J31-J96) and mental and behavioral disorders (F00-F99)	2.37	1.060	2.157		1.903	1.635	2.598	4.128	1.044	2.549	1.639	1.410				0.906	1.045	
Other forms of heart disease (I30-I52) and mental and behavioral disorders (F00-F99)	2.32	1.091	2.253	1.223	2.457	2.041	3.853	5.200	1.048	2.201	1.636	1.550		0.800		0.941	1.040	
Hypertensive diseases (I10-I15) and diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	1.87	1.122		1.733	3.575	2.995	4.850	10.243	1.043	1.866	1.457	1.635					0.960	1.032
Other forms of heart disease (I30-I52) and diabetes mellitus (E10-E14)	1.51	1.234	0.848	2.846	12.850	8.932	26.220	47.072	1.064	3.214	2.379	2.144	0.963	0.490		0.944	1.062	0.973
Diseases of the respiratory system (J31-J96) and ischaemic heart diseases (I20-I25)	1.49	1.088		1.475	2.605	2.278	3.377	6.237	1.035	2.449	1.659	1.539	0.978			0.912	1.051	
Hypertensive diseases (I10-I15) and cerebrovascular diseases (I60-I69)	1.46	1.084		1.532	2.479	2.127	3.780	4.368	1.035	2.344	1.524	1.522	0.984					
Other forms of heart disease (I30-I52) and diseases of the musculoskeletal system (M00-M46)	1.41	1.145		1.829	4.745	3.902	7.166	12.763	1.032	1.534	1.361	1.445		0.727	0.982			
Mental and behavioral disorders (F00-F99) and ischaemic heart diseases (I20-I25)	1.37	1.083		1.363	2.438	2.094	3.495	4.958	1.049	2.862	1.876	1.491	0.976			0.924	1.051	
Diseases of the respiratory system (J31-J96) and diseases of the musculoskeletal system (M00-M46)	1.26	1.112		1.405	3.205	2.692	4.361	8.619	1.038	2.249	1.516	1.350						
Mental and behavioral disorders (F00-F99) and diseases of the musculoskeletal system (M00-M46)	1.23	1.106		1.504	3.053	2.591	4.187	7.318	1.038	2.011	1.639	1.365	0.983	0.722			1.039	
Mental and behavioral disorders (F00-F99) and diabetes mellitus (E10-E14)	1.18	1.206	0.859	2.593	10.078	7.200	18.960	32.288	1.075	4.095	2.840	2.317	0.952	0.436	1.029	0.939	1.055	
Diseases of the respiratory system (J31-J96) and diabetes mellitus (E10-E14)	1.15	1.218		2.540	10.194	7.011	18.480	44.047	1.077	4.399	2.624	2.288	0.965	0.545			1.038	
Hypertensive diseases (I10-I15) and diseases of arteries, arterioles and capillaries (I70-I79)	1.04	1.078		1.272	2.323	1.930	3.685	4.668	1.045	2.365	1.614	1.562						
Hypertensive diseases (I10-I15) and other and unspecified disorders of the circulatory system (I95-I99)	1.02	1.115		1.473	3.112	2.430	4.680	10.757	1.047	2.567	1.637	1.405						
Diseases of the respiratory system (J31-J96) and diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	1.00	1.086	2.278	1.245	2.485	2.074	2.710	8.438	1.048	2.161	1.561	1.700				1.071	0.945	

(B) Males

Diseases name and ICD-10 code	Percentage (%)	General obesity indices							Abdominal obesity indices						Body fat percentage indices			
		BMI	Underweight	Overweight	Obesity (BMI >30)	Obesity 1 (BMI: 30-35)	Obesity 2 (BMI: 35-40)	Obesity 3 (BMI >40)	WC	WtHR	WtHIR	Central obesity	HC	HtHR	BFP	TFP	LFP	AFP
Hypertensive diseases (I10-I15) and other forms of heart disease (I30-I52)	5.76	1.141		1.633	3.702	3.040	7.238	9.668	1.036	1.736	1.400	1.449						1.040
Hypertensive diseases (I10-I15) and ischaemic heart diseases (I20-I25)	5.05	1.116		1.822	3.292	2.924	5.387	5.214	1.025	2.064	1.542	1.372	0.976		1.021	0.949	1.031	
Hypertensive diseases (I10-I15) and diseases of the respiratory system (J31-J96)	4.42	1.120		1.428	3.071	2.618	5.043	8.686	1.052	3.304	2.032	1.657	0.977		1.024			1.042
Hypertensive diseases (I10-I15) and mental and behavioral disorders (F00-F99)	4.40	1.110		1.498	2.887	2.526	5.018	4.178	1.052	2.983	1.839	1.569			1.025	0.915	1.046	
Hypertensive diseases (I10-I15) and diabetes mellitus (E10-E14)	4.33	1.235		2.667	10.190	7.701	23.486	30.106	1.050	3.282	2.287	1.979	0.956	0.587	1.026		1.027	
Other forms of heart disease (I30-I52) and ischaemic heart diseases (I20-I25)	3.66	1.101		1.575	2.732	2.445	4.362	4.241	1.024	1.733	1.408	1.414				0.940	1.030	
Hypertensive diseases (I10-I15) and diseases of the musculoskeletal system (M00-M46)	2.90	1.172		2.615	6.369	5.374	11.690	14.156	1.028	1.889	1.487	1.512				0.948	1.035	
Diseases of the respiratory system (J31-J96) and other forms of heart disease (I30-I52)	2.79	1.090		1.169	2.186	1.823	3.973	5.831	1.035	2.124	1.536	1.529						1.073
Diseases of the respiratory system (J31-J96) and mental and behavioral disorders (F00-F99)	2.36	1.048			1.604	1.448	2.447	2.455	1.056	3.653	1.962	1.659			1.024	0.914	1.039	
Other forms of heart disease (I30-I52) and mental and behavioral disorders (F00-F99)	2.34	1.102			2.321	1.954	4.329	4.656	1.049	2.476	1.702	1.669				0.931		1.071
Hypertensive diseases (I10-I15) and diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	2.07	1.133		1.711	3.511	3.027	5.826	8.425	1.038	2.082	1.452	1.752					0.962	1.094
Diseases of the respiratory system (J31-J96) and ischaemic heart diseases (I20-I25)	1.91	1.075		1.307	2.166	2.028	2.738	3.864	1.036	2.914	1.741	1.738	0.974		1.041	0.933	1.040	
Hypertensive diseases (I10-I15) and cerebrovascular diseases (I60-I69)	1.75	1.088		1.546	2.312	1.981	4.377	3.208	1.028	2.507	1.496	1.417	0.985					1.068
Ischaemic heart diseases (I20-I25) and mental and behavioral disorders (F00-F99)	1.72	1.081		1.252	2.176	1.961	3.215	4.025	1.044	3.124	1.899	1.547	0.973		1.031			
Other forms of heart disease (I30-I52) and diabetes mellitus (E10-E14)	1.57	1.256		3.199	14.275	10.477	34.865	48.323	1.043	2.558	1.995	1.882	0.966	0.584		0.924	1.054	
Mental and behavioral disorders (F00-F99) and diabetes mellitus (E10-E14)	1.44	1.215		2.987	10.544	8.125	23.512	25.361	1.067	4.376	2.684	2.156	0.957	0.559	1.056		1.045	
Other forms of heart disease (I30-I52) and diseases of the musculoskeletal system (M00-M46)	1.43	1.165		2.013	5.280	4.430	9.676	13.291	1.034	1.550	1.421	1.686		0.689		0.912	1.047	
Diseases of the respiratory system (J31-J96) and diabetes mellitus (E10-E14)	1.39	1.223		2.557	9.440	7.055	21.747	29.641	1.061	4.395	2.620	2.188	0.953	0.645				
Hypertensive diseases (I10-I15) and diseases of arteries, arterioles and capillaries (I70-I79)	1.36	1.105		1.307	2.598	2.190	5.035	4.595	1.039	2.502	1.685	1.587	0.985			0.924		
Ischaemic heart diseases (I20-I25) and diabetes mellitus (E10-E14)	1.35	1.217		2.826	9.851	7.780	21.405	23.084	1.046	3.598	2.227	1.936	0.950	0.691	1.040	0.934	1.048	
Hypertensive diseases (I10-I15) and other and unspecified disorders of the circulatory system (I95-I99)	1.24	1.142	4.534	1.806	3.740	3.043	7.246	11.470	1.047	2.507	1.601	1.416						1.060
Mental and behavioral disorders (F00-F99) and diseases of the musculoskeletal system (M00-M46)	1.22	1.131		1.861	3.701	3.165	6.032	9.500	1.046	2.524	1.801	1.694	0.985			0.921		
Diseases of the respiratory system (J31-J96) and diseases of the musculoskeletal system (M00-M46)	1.19	1.113		1.476	3.245	2.944	4.301	8.137	1.032	2.695	1.562	1.486						1.054
Other forms of heart disease (I30-I52) and cerebrovascular diseases (I60-I69)	1.11	1.079			2.042	1.770	3.872		1.031	1.842	1.352	1.541						1.078
Other forms of heart disease (I30-I52) and other and unspecified disorders of the circulatory system (I95-I99)	1.07	1.096	4.974		2.269	1.903	3.767	7.895	1.043	2.201	1.433	1.400						1.077
Ischaemic heart diseases (I20-I25) and diseases of the musculoskeletal system (M00-M46)	1.02	1.150		2.090	4.607	4.100	7.648	6.630	1.034	2.220	1.584	1.566			1.033		1.053	
Diseases of the respiratory system (J31-J96) and diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	1.00	1.083			2.427	2.224	3.265	4.887	1.047	2.754	1.765	2.026					0.952	1.076

(C) Females

Diseases name and ICD-10 code	Percentage (%)	General obesity indices							Abdominal obesity indices						Body fat percentage indices			
		BMI	Underweight	Overweight	Obesity (BMI >30)	Obesity 1 (BMI: 30-35)	Obesity 2 (BMI: 35-40)	Obesity 3 (BMI >40)	WC	WtHR	WtHIR	Central obesity	HC	HtHR	BFP	TFP	LFP	AFP
Hypertensive diseases (I10-I15) and other forms of heart disease (I30-I52)	4.71	1.110		1.439	3.372	2.527	4.589	10.670	1.038	1.705	1.300	1.387	1.019					
Hypertensive diseases (I10-I15) and diseases of the respiratory system (J31-J96)	3.78	1.134		1.731	4.505	3.247	6.294	14.641	1.043	2.240	1.597	1.358	0.985			0.936	1.036	
Hypertensive diseases (I10-I15) and mental and behavioral disorders (F00-F99)	3.68	1.098	1.828	1.449	3.009	2.278	3.945	8.706	1.046	2.358	1.690	1.333	0.977	0.756	0.979	0.917	1.073	
Hypertensive diseases (I10-I15) and ischaemic heart diseases (I20-I25)	2.45	1.109		1.686	3.427	2.706	4.529	8.917	1.049	2.407	1.658	1.509				0.907	1.065	
Hypertensive diseases (I10-I15) and diabetes mellitus (E10-E14)	2.43	1.221		3.008	14.931	9.337	23.795	57.875	1.092	4.500	2.970	3.041	0.954	0.406	0.965	0.906	1.076	
Hypertensive diseases (I10-I15) and diseases of the musculoskeletal system (M00-M46)	2.42	1.155		2.062	5.806	4.185	7.535	21.933	1.032	1.725	1.465	1.282	0.981	0.671				
Mental and behavioral disorders (F00-F99) and diseases of the respiratory system (J31-J96)	2.39	1.072	2.990		2.356	1.814	2.717	7.380	1.041	2.164	1.497	1.379						
Other forms of heart disease (I30-I52) and diseases of the respiratory system (J31-J96)	2.02	1.102		1.253	3.097	2.299	3.644	11.652	1.043	1.893	1.445	1.439						
Other forms of heart disease (I30-I52) and mental and behavioral disorders (F00-F99)	1.92	1.085	2.894	1.291	2.627	2.038	3.406	7.282	1.049	1.937	1.567	1.453		0.682				0.944
Other forms of heart disease (I30-I52) and ischaemic heart diseases (I20-I25)	1.73	1.101		1.436	2.951	2.221	4.082	8.779	1.043	1.965	1.481	1.290						
Hypertensive diseases (I10-I15) and diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (I80-I89)	1.66	1.114		1.743	3.673	2.900	4.012	12.468	1.049	1.750	1.460	1.525		0.707		1.119	0.922	
Diseases of the respiratory system (J31-J96) and diseases of the musculoskeletal system (M00-M46)	1.32	1.116		1.340	3.310	2.241	4.384	10.872	1.041	2.040	1.467							
Mental and behavioral disorders (F00-F99) and diseases of the musculoskeletal system (M00-M46)	1.25	1.096		1.284	2.825	2.257	3.242	8.244	1.030	1.706	1.401		0.984					
Other forms of heart disease (I30-I52) and diseases of the musculoskeletal system (M00-M46)	1.18	1.125		1.512	4.027	3.085	4.372	15.776	1.026	1.373	1.234				0.965	1.132	0.924	
Hypertensive diseases (I10-I15) and cerebrovascular diseases (I60-I69)	1.15	1.085		1.463	2.743	2.380	3.159	5.731	1.044	2.187	1.590	1.652						
Diseases of the respiratory system (J31-J96) and ischaemic heart diseases (I20-I25)	1.06	1.109		1.749	3.478	2.602	4.585	11.255	1.040	2.149	1.543							
Mental and behavioral disorders (F00-F99) and ischaemic heart diseases (I20-I25)	1.01	1.087		1.522	2.826	2.203	3.991	6.484	1.060	2.765	1.898	1.440	0.978	0.645				

FIGURE 5 Associations between indices of general obesity, abdominal obesity, and body fat percentage and the occurrence of comorbidity pairs with morbidity rate >1% among (A) all adults, (B) males, and (C) females. Multinomial logistic regressions were fitted to explore the adjusted associations between adiposity indicators and the onset of comorbidity pairs. For the general obesity indices, covariates included age, sex, ethnicity, qualification levels, employment status, smoking, and alcohol drinking. For the indices of abdominal obesity and body fat percentage, the aforementioned covariates and body mass index were adjusted. The above covariates, body mass index, and total body fat percentage were adjusted for regional body fat percentages. The same covariates were adjusted in sex-stratified analyses.

disease-related comorbidities. In females, the stronger negative associations occurred between the trunk fat percentage and hypertensive disease-related comorbidities, whereas the strongest positive associations occurred between the fat percentage of legs and hypertensive disease-related comorbidities (Figure 5 and Table S4).

4 | DISCUSSION

In the present study, the cumulative incidences of multimorbidity in males and females were 54.49% and 45.37%, respectively, in 10 years. Our findings indicate that BMI-related general obesity indices are positive predictors of multimorbidity onset. High waist circumference-related abdominal obesity indices contribute to an elevated risk of developing multimorbidity, while high hip circumference and hip-to-height ratios imply a reduced risk of onset. For body fat percentage indices, fat percentages in the body and arms are associated with an increased risk of multimorbidity onset. Moreover, the associations between adiposity indicators and the onset of comorbidity pairs displayed sex-specific differences. Males exhibit a higher risk of developing diabetes mellitus-related comorbidity with increasing general obesity indices, waist circumference-related indices and the fat percentage of legs, and decreasing hip circumference-related indices, while females display an increased risk of hypertensive disease-related comorbidity with changes in the same indices.

Our study presents compelling evidence that supports the detrimental effects of BMI-related general obesity on the onset of multimorbidity in both males and females. These findings have significant implications for public health interventions aiming to prevent multimorbidity. Furthermore, the stronger associations observed between these adiposity indicators and the occurrence of the third and fourth multimorbidity diseases emphasize the cumulative burden of general obesity on multiple chronic conditions. These findings are consistent with previous research that has indicated a link between general obesity and the development of multimorbidity.[8–10,33] Data from previous studies have suggested that general obesity could increase the risks of coronary heart disease, stroke, diabetes, dyslipidaemia[8] and systemic inflammation, which could be common components of multimorbidity. Thus, our findings underscore the pressing need for comprehensive interventions to prevent and manage general obesity.

Notably, we observed that elevated waist circumference-related abdominal obesity indices contribute to an increased risk of multimorbidity onset, while hip circumference and hip-to-height ratio are associated with a reduced risk. These inverse associations suggest the heterogeneity of obesity, wherein abdominal fat has a detrimental effect while hip fat appears to be protective. Abdominal obesity was found to elevate plasma triglycerides and low-density lipoprotein concentrations, thereby increasing the risk of hyperlipidaemia, insulin resistance and cardiovascular disease.[24] Although no studies have examined the effects of hip circumference-related indices on multimorbidity onset, previous studies have reported inverse associations between hip circumference, height and the risk of diabetes,[34,30] cardiovascular diseases,[35] and mortality.[36] A larger hip circumference indicates greater muscle and fat mass in the gluteofemoral region. The metabolic effects of subcutaneous adipose tissue in the gluteofemoral and visceral regions differ.[37] Gluteofemoral fat is suggested to reduce cardiovascular and metabolic risk, irrespective of sex, by trapping excess fatty acids and preventing chronic exposure to elevated lipid levels.[37] Moreover, we observed that fat percentages in the body and arms contribute to an increased risk of multimorbidity onset. These findings indicate that in addition to measuring BMI, assessing the indices of abdominal obesity and body fat percentage may offer additional benefits for identifying multimorbidity in adults.

One of our significant contributions to this field is the discovery of sex-specific contributions of adiposity indicators to the occurrence of specific comorbidity pairs. In males, higher general obesity indices, waist circumference-related indices, the fat percentage of legs and lower hip circumference-related indices were found to increase the risks of diabetes mellitus-related comorbidity, whereas the same indices implied elevated risks of hypertensive disease-related comorbidities in females. Previous studies also found that more males were affected by obesity-related diabetes mellitus than females.[38] Various aspects of energy balance and glucose metabolism are regulated differently in males and females, which influences their susceptibility to diabetes mellitus and hypertensive diseases.[39,40] Diversities in biology, culture, lifestyle, environment and socioeconomic status contribute to this predisposition in males.[38] For example, males have lower sex hormone-binding globulin levels, which may be associated with a higher diabetes risk.[41] Given the higher global prevalence of diabetes,[42] the prevention of diabetes mellitus should focus on reducing obesity in males. In females, regardless of reproductive status and age, obesity has a strong association with hypertension and subsequent chronic diseases.[39] Obesity reportedly leads to hypertensive disease-related diseases through mechanisms specific to hormonal and reproductive status in females.[39,43] Effective control of obesity is crucial for the prevention of hypertension-related comorbidities in females. These findings highlight the necessity of sex-specific approaches in the prevention of multimorbidity.

Our study revealed that being underweight and having a lower trunk fat percentage contribute to the increased risks of mental and behavioural disorder-related comorbidities in females and males, respectively. Limited studies have reported that being underweight is associated with lifetime anorexia nervosa, obsessive-compulsive disorder and eating disorders among adults.[44,45] People who are underweight may have a negative body image, and their low self-esteem is correlated with mental and behavioural disorders.[46] Moreover, leptin levels are decreased in people with low BMI,[47] and a strong positive correlation between low leptin levels and depressive symptoms was observed.[48] However, no existing studies have examined the specific associations between trunk fat percentage and mental health disorders. Therefore, further investigation is necessary to explore the potential effects of underweight and trunk fat percentage on the onset of mental and behavioural disorders.

Our study has several limitations. First, the use of electronic health records to identify participants may exclude individuals with undiagnosed conditions or those who do not frequently seek health

care.[49,50] Moreover, the UK Biobank missed disease cases diagnosed and treated in primary care. These selection biases could potentially underestimate the true incidence of multimorbidity and may underestimate the association between adiposity indicators and incident multimorbidity. Second, participants in the UK Biobank are mostly white British and comparatively more affluent than the UK average. Furthermore, the participants primarily consist of middle-aged and elderly individuals. Therefore, participants may not be completely representative of the UK population, which limits the generalizability of the current findings. Third, multimorbidity was defined as the presence of two or more chronic conditions in the current study. We have carried out sensitivity analyses using incidents of three or more and four or more chronic conditions as outcome variables to ensure our findings are valid. However, we did not explore the associations between adiposity indicators and the number of conditions as a continuous variable. Because the total number of chronic conditions is discrete, it cannot be treated as a continuous variable. Fourth, other potentially important confounding factors associated with incident multimorbidity, such as medication taken and genetic predisposition, were not included in the model.[51] These data were not available in our applied dataset. Fifth, physical activity as a potentially important confounder was not adjusted in the model because only about half of the participants had self-reported their physical activity level at baseline; therefore, the inclusion of this variable would decrease the statistical power because of the decrease in sample size. Future studies could comprehensively assess potential confounders to better understand the relationships between adiposity and incident multimorbidity.

5 | CONCLUSIONS

In conclusion, our study shows that elevated general obesity indices, waist circumference-related abdominal obesity indices and fat percentages in the body and arms, along with reduced hip circumference-related indices, are associated with an increased incidence of multimorbidity in adults. In males, higher indices of general obesity and waist circumference-related and the fat percentage of legs, and lower hip circumference-related indices indicate an increased risk of diabetes mellitus-related comorbidity, while in females, they contribute to the increased risk of hypertensive disease-related comorbidity. These findings underscore the significance of implementing effective strategies for obesity prevention to mitigate the risk of developing multimorbidity.

AUTHOR CONTRIBUTIONS

LZ: full access to all the data in the study, took responsibility for the integrity of the data and the data analysis accuracy. All authors: study concept and design; administrative, technical, or material support. LM, ZBL and JJS: acquisition of data. LM, YL, GXL and XLZ analysis and interpretation of data. LM and LZ drafting of the manuscript. LM, LZ and YL critical revision of the manuscript for important intellectual content. LZ: obtained funding, study supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

CONSENT FOR PUBLICATION

UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15610.

DATA AVAILABILITY STATEMENT

The data sets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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