tvst

Artificial Intelligence

Associations of Metabolically Healthy Obesity and Retinal Age Gap

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Received: June 20, 2024
Accepted: October 15, 2024
Published: November 21, 2024

Keywords: metabolically healthy obesity; retinal age gap; accelerated biological age; sex differences

Citation: Zeng X, Chen R, Bulloch G, Peng Q, Cheng CY, He M, Yu H, Zhu Z. Associations of metabolically healthy obesity and retinal age gap. Transl Vis Sci Technol. 2024;13(11):26, https://doi.org/10.1167/tvst.13.11.26

Purpose: We investigated the association between metabolically healthy obesity (MHO) and retinal age gap and explored potential sex differences in this association.

Methods: This study included 30,335 participants from the UK Biobank. Body mass index (BMI) was classified into normal weight, overweight, and obesity. Metabolic health (MH) was defined as meeting the following criteria: systolic blood pressure of $<$130 mm Hg, no antihypertensive drugs, waist-to-hip ratio of $<$0.95 for women or 1.03 for men, and the absence of diabetes. Participants were categorized as MH normal weight (MHN), MH overweight (MHOW), MHO, metabolically unhealthy normal weight, metabolically unhealthy (MU) overweight, and MU obesity. Retinal age gap was defined as the difference between retinal age and chronological age. Linear regression models were used to investigate the association of metabolic phenotypes of obesity with retinal age gap.

Results: Compared with MHN, individuals with MHOW (β, 0.17; 95% confidence interval [CI], 0.01–0.32; $P = 0.039$) and MHO (β, 0.23; 95% CI, 0.02–0.44; $P = 0.031$) were associated with increased retinal age gap. Furthermore, individuals classified as metabolic unhealthy were also associated with higher retinal age gap, irrespective of body mass index categories (β for MU normal weight, 0.23; 95% CI, 0.08–0.38; $P = 0.003$; β for MU overweight: 0.31; 95% CI, 0.18–0.45; $P < 0.001$; β for MU obesity, 0.50; 95% CI, 0.36–0.65; $P < 0.001$). No significant sex difference was observed in the association between metabolic phenotypes of obesity and retinal age gap (all P for interaction > 0.05).

Conclusions: MHOW and MHO were associated significantly with an increased retinal age gap compared with MHN individuals. Weight management should be recommended for individuals who are overweight or obese, even in the absence of metabolic unhealth.

Translational Relevance: Retinal age gap provides a simple tool for identifying early health risks for MHOW and MHO individuals.

Introduction

Obesity is a global health concern that has reached epidemic proportions in recent years.[1] It is characterized by the excessive accumulation of body fat, resulting in various adverse health effects.[2] One of the significant consequences of obesity is the development of metabolic syndrome,[3,4] a cluster of conditions that increase the risk of cardiovascular diseases (CVDs), type 2 diabetes, and other chronic illnesses, posing substantial health burdens for both individuals and society.[1,5,6]

Although the cardiometabolic complications of obesity are recognized widely at the population level, clinical observations have identified a subset of obese individuals with normal metabolic features despite their increased adiposity. This subset has been referred to as metabolically healthy obesity (MHO) and seems to be relatively protected against worsening metabolic health (MH).[6,7] However, there is an ongoing debate surrounding the perception of MHO as a benign and safe status,[8–10] as a growing body of literature has revealed that MHO patients have a significantly elevated risk of developing both type 2 diabetes and CVD over time compared with metabolically healthy normal weight individuals.[11,12] The crucial reason for these inconsistent findings is the lack of common standards for defining MH.[13] In 2021, a new definition of MHO has been proposed based on systolic blood pressure, use of antihypertensives, waist-to-hip ratio, and self-reported diabetes using data from the third National Health and Nutrition Examination Survey and validated with the UK Biobank. MHO by this new definition showed stratification of mortality risk of CVD or total mortality for individuals with and without obesity.[14,15] Although the new definition is simpler and can be better applied in the community and clinics, whether this definition can be extended to other indicators representing cardiovascular health still needs to be verified by more research.

Retinal age has emerged recently as a simple measurement to provide a thoughtful and individual-specific reflection of overall health.[16,17] Retinal age gap, the deviation of retinal age from normal aging, has been verified as a reliable and promising indicator for mortality and morbidities, especially those related to metabolic and cardiovascular health.[17–19] To our knowledge, there is a lack of studies investigating the association between MHO and retinal age gap. Therefore, this study aimed to investigate the association of MHO defined by this new definition with retinal age gap in a large population-based UK Biobank cohort. Furthermore, considering that sex differences have been observed in obesity-related cardiometabolic diseases, we also investigated whether there are sex differences in the association of MHO with the retinal age gap.

Methods

Study Population

This study used data from the UK Biobank, a population-based prospective cohort consisting of approximately 500,000 participants aged 40 to 73 years registered with the National Health Service in the UK. Participants were assessed at baseline between 2006 and 2010 and attended 1 of the 22 assessment centers throughout the UK where they provided information on geographic factors, lifestyle, and other health-related aspects through comprehensive baseline questionnaires, interviews, and physical measurements. Details of the UK Biobank can be accessed elsewhere.[20]

The UK Biobank was reviewed and approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee (11/NW/0382). Data used in the present study were accessed through the Biobank consortium (Application No: 86091). This study was carried out in accordance with the Declaration of Helsinki, and informed consent was provided by all participants.

Metabolic Phenotypes of Obesity

Body measurements and MH information were assessed at baseline. Standing height was measured to the nearest centimeter using a Seca 202 stadiometer (Hamburg, Germany), and weight was recorded to the nearest 0.1 kg with a Tanita BC-418 body composition analyzer (Tokyo, Japan). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and was classified into three categories: normal weight (BMI $\geq$ 18.5 and $<$ 25 kg/m^2), overweight (BMI $\geq$ 25.0 and $<$ 30 kg/m^2), and obese (BMI $\geq$ 30 kg/m^2).[7]

MH was defined by the new definition as meeting the following three criteria: (1) systolic blood pressure of $<$130 mm Hg and no use of blood pressure-lowering medication; (2) waist-to-hip ratio of $<$0.95 (women) and $<$1.03 (men); and (3) no self-reported prevalent diabetes.[14] Systolic blood pressure was measured while the participant was seated, with two automatic measurements taken 1 minute apart. Waist

and hip circumferences were measured at the level of the umbilicus. Information on the use of blood pressure-lowering medication and the prevalence of diabetes was obtained through self-reported questionnaires.[14] Participants were categorized based on their BMI categories and metabolic status as metabolically healthy normal weight (MHN, reference group), metabolically healthy overweight (MHOW), MHO, metabolically unhealthy normal weight (MUN), MU overweight (MUOW), and MU obesity (MUO).

Fundus Photography

Between 2009 and 2010, ophthalmic examinations were introduced at six assessment centers across the UK.[21] In this study, we obtained 131,238 retinal fundus images from 66,500 participants at baseline. The 45° nonmydriatic retinal fundus and optical coherence tomography (OCT) imaging of the optic disc and macular were captured using a spectral domain OCT for each eye (Topcon 3D OCT 1000 Mk2, Topcon Corp, Tokyo, Japan). The image quality control process was described in detail elsewhere.[22] Briefly, image quality control was based on ground-truth manually labeled by two ophthalmologists using a three-level quality grading system (good, usable, and reject) and identifying indicators of poor quality (e.g., blur, uneven illumination, low contrast, and artifacts). Fundus images with the good and usable quality were considered to have reasonably good image quality. A total of 80,169 images from 46,969 participants passed the image quality check.[17] Fundus images of the right eye were used in the study. After excluding participants whose fundus images were used for training and validation of the age prediction model (n = 11,052), those with missing fundus images of the right eye (n = 4,359), those with age-related macular degeneration, glaucoma, or diabetic retinopathy at baseline (n = 1,075), those without data on obesity, metabolic phenotypes, or covariates (n = 148), 30,335 participants were included in the final analysis (Fig.).

Deep Learning (DL) for Retinal Age Prediction and Definition of Retinal Age Gap

The methods of retinal age prediction using DL models were described in detail in a previous study.[17] A total of 19,200 retinal fundus images from 11,052 healthy participants who trained and validated the DL model for age prediction. Mean absolute error and correlation coefficients between retina-predicted age and chronological age were used to assess DL model performance in the testing dataset. The retinal age predicted by the DL model achieved good performance, with an overall mean absolute error of 3.55 years and a correlation coefficient of 0.80 in healthy populations. Attention maps generated by the DL model for age prediction mainly highlighted areas around the retinal vessels in the fundus images. The retinal age gap was a continuous variable defined as the difference between the retinal age predicted by the DL model using fundus images and chronological age.

Covariates

The selection of covariates was based on previously published studies, because these covariates might have confounding effects on the exposure variables and outcome measures.[17,23] Covariates included baseline age, sex (female, male), Townsend deprivation index (an area-based proxy measure for socioeconomic status), ethnicity (White, non-White), educational attainment (college/university, others), smoking status (never, current/previous), drinking status (never, current/previous), physical activity evaluated using International Physical Activity Questionnaire (low, moderate, high, or unknown), fruit intake, vegetable intake, meat intake (0–7 a week, 8–14 a week, ≥15 a week), and history of CVD (no, yes). All covariates were collected at baseline.

Statistical Analyses

Descriptive statistics reported baseline characteristics of participants, where continuous variables were reported using means ± standard deviations, and categorical variables were summarized as numbers (%). Analysis of variance or t tests were used to identify differences in continuous variables, and χ^2 tests were used to compare distributions. Multiple linear regression models were applied to evaluate the associations between metabolic phenotypes of obesity and the retinal age gap. We examined two models: model 1 was adjusted for age, sex, and ethnicity; model 2 was additionally adjusted for Townsend deprivation index, educational attainment, smoking status, drinking status, physical activity, fruit intake, vegetable intake, meat intake, and history of CVD. We also conducted subgroup analyses and added interaction terms in the models to explore whether there were differences in association of BMI categories with retinal age gap across different metabolic phenotypes. Furthermore, a sex-stratified analysis was performed to test whether the association between metabolic phenotypes of obesity and retinal age gap was modified by

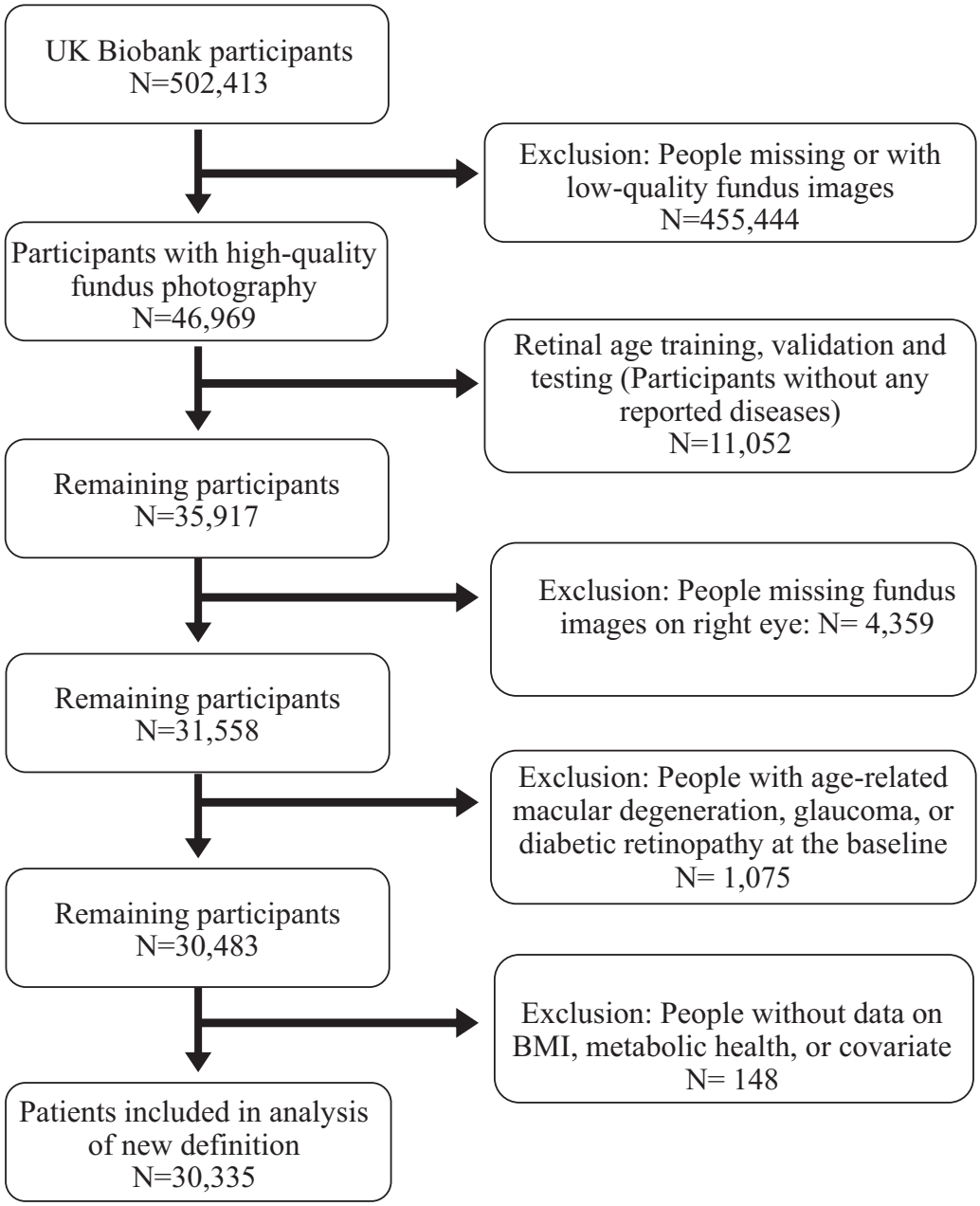

Figure. Flow chart distribution of study population.

sex. Statistical analyses were conducted using Stata, version 17.0 (Stata Corp, College Station, TX). All *P* values were two-sided with statistical significance set at <0.05.

Results

Baseline Characteristics of the Population

Table 1 summarizes the baseline characteristics of participants stratified by metabolic phenotypes of obesity using the new definition. This study included 30,335 participants with a mean age of 56.47 ± 8.06 years, of whom 56.07% were female. Of the participants, 15.41% were classified as MHN, 12.96% as MHOW, 5.39% as MHO, 16.79% as MUN, 29.62% as MUOW, and 19.84% as MUO. Compared with participants with MHN, those classified as MHO were more likely to be male, non-White, of a lower socioeconomic index, less educated, less physically active, consume higher amounts of meat and lower amounts of fruits and vegetables, had a higher prevalence of CVD, and were

Table 1. Baseline Characteristics of the Populations by Metabolic Phenotypes of Obesity

Baseline Characteristics	Overall	MHN	MHOW	MHO	MUN	MUOW	MUO	*P* Value
Participants	30,335 (100)	4674 (15.41)	3930 (12.96)	1635 (5.39)	5094 (16.79)	8985 (29.62)	6017 (19.84)	—
Age, years	56.47±8.06	53.09 (7.93)	53.84 (8.13)	53.10 (7.93)	58.24 (7.65)	58.36 (7.53)	57.43 (7.65)	**<0.001**
Sex								
Female	17,009 (56.07)	3426 (73.30)	2327 (59.21)	1096 (67.03)	3127 (61.39)	3935 (43.80)	3098 (51.49)	**<0.001**
Male	13,326 (43.93)	1248 (26.70)	1603 (40.79)	539 (32.97)	1967 (38.61)	5050 (56.20)	2919 (48.51)	
Townsend deprivation index, %	−1.11 ± 2.94	−1.06 ± 2.91	−0.97 ± 2.92	−0.52 ± 3.17	−1.44 ± 2.81	−1.32 ± 2.85	−0.79 ± 3.10	**<0.001**
Ethnicity								**<0.001**
White	28,478 (93.88)	4374 (93.58)	3681 (93.66)	1491 (91.19)	4828 (94.78)	8460 (94.16)	5644 (93.80)	
Non-White	1857 (6.12)	300 (6.42)	249 (6.34)	144 (8.81)	266 (5.22)	525 (5.84)	373 (6.20)	
Educational attainment								**<0.001**
College or university	10,644 (35.09)	2137 (45.72)	1501 (38.19)	495 (30.28)	2042 (40.09)	2866 (31.90)	1603 (26.64)	
Others	19,691 (64.91)	2537 (54.28)	2429 (61.81)	1140 (69.72)	3052 (59.91)	6119 (68.10)	4414 (73.36)	
Smoking status								**<0.001**
Never	13,401 (44.18)	1906 (40.78)	1752 (44.58)	742 (45.38)	2046 (40.16)	4089 (45.51)	2866 (47.63)	
Current/previous	16,934 (55.82)	2768 (59.22)	2178 (55.42)	893 (54.62)	3048 (59.84)	4896 (54.49)	3151 (52.37)	
Drinking status								**<0.001**
Never	1321 (4.35)	182 (3.89)	169 (4.30)	95 (5.81)	200 (3.93)	359 (4.00)	316 (5.25)	
Current/previous	29,014 (95.65)	4492 (96.11)	3761 (95.70)	1540 (94.19)	4894 (96.07)	8626 (96.00)	5701 (94.75)	
Physical activity								**<0.001**
Low	4490 (14.80)	549 (11.75)	597 (15.19)	359 (21.96)	561 (11.01)	1251 (13.92)	1173 (19.49)	
Moderate	10,417 (34.34)	1660 (35.52)	1400 (35.62)	556 (34.01)	1738 (34.12)	3072 (34.19)	1991 (33.09)	
High	10,073 (33.21)	1733 (37.08)	1320 (33.59)	405 (24.77)	1905 (37.40)	3140 (34.95)	1570 (26.09)	
Unknown	5355 (17.65)	732 (15.66)	613 (15.60)	315 (19.27)	890 (17.47)	1522 (16.94)	1283 (21.32)	
Meat intake								**<0.001**
0–7 a week	12,126 (39.97)	2345 (50.17)	1646 (41.88)	561 (34.31)	2354 (46.21)	3289 (36.61)	1931 (32.09)	
8–14 a week	17,743 (58.49)	2278 (48.74)	2234 (56.84)	1041 (63.67)	2676 (52.53)	5562 (61.90)	3952 (65.68)	
≥15 a week	466 (1.54)	51 (1.09)	50 (1.27)	33 (2.02)	64 (1.26)	134 (1.49)	134 (2.23)	
Fruit intake	1.81 ± 4.85	1.90 ± 4.92	1.67 ± 4.91	1.53 ± 4.92	2.18 ± 4.84	1.75 ± 4.81	1.67 ± 4.76	**<0.001**
Vegetable intake	4.27 ± 4.89	4.33 ± 4.84	4.25 ± 5.27	4.25 ± 4.96	4.38 ± 4.60	4.21 ± 4.85	4.24 ± 4.93	**0.426**
History of CVD								**<0.001**
No	27,766 (91.53)	4448 (95.16)	3602 (91.65)	1462 (89.42)	4754 (93.33)	8199 (91.25)	5301 (88.10)	
Yes	2569 (8.47)	226 (4.84)	328 (8.35)	173 (10.58)	340 (6.67)	786 (8.75)	716 (11.90)	

CVD, cardiovascular disease; MHN, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obesity; MUN, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obesity.

One-way analysis of variance was used to test the difference of continuous variables across subgroups and χ^2 for categorical variables. Significant associations are bolded.

Values are mean ± standard deviation or number (%).

Table 2. Association Between Metabolic Phenotypes of Obesity and Retinal Age Gap

Metabolic Phenotypes of Obesity	Model 1		Model 2	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
MHN	[Reference]	–	[Reference]	–
MHOW	0.18 (0.02–0.34)	**0.026**	0.17 (0.01–0.32)	**0.039**
MHO	0.28 (0.07–0.49)	**0.010**	0.23 (0.02–0.44)	**0.031**
MUN	0.21 (0.06–0.36)	**0.006**	0.23 (0.08–0.38)	**0.003**
MUOW	0.31 (0.17–0.45)	**<0.001**	0.31 (0.18–0.45)	**<0.001**
MUO	0.53 (0.39–0.68)	**<0.001**	0.50 (0.36–0.65)	**<0.001**

CI, confidence interval; MHN, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obesity; MUN, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obesity.

Linear regression models were used to estimate the association of metabolic phenotypes of obesity with retinal age gap. Model 1 was adjusted for age, sex, and ethnicity; model 2 was additionally adjusted for Townsend deprivation index, educational attainment, smoking status, drinking status, physical activity, meat intake, fruit intake, vegetable intake, and history of cardiovascular diseases. Significant associations are bolded.

Table 3. Association Between BMI Categories and Retinal Age Gap Across Different Metabolic Phenotypes

BMI Categories	Metabolic Healthy		Metabolic Unhealthy		*P* Value for Interaction
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	
Normal weight	[Reference]		[Reference]		
Overweight	0.18 (0.03 to 0.34)	**0.018**	0.06 (−0.07 to 0.20)	**0.344**	0.415
Obesity	0.28 (0.07 to 0.48)	**0.008**	0.23 (0.09 to 0.38)	**0.002**	0.765

BMI, body mass index; CI, confidence interval.

Linear regression models were used to estimate the association of BMI with retinal age gap across different metabolic phenotypes, adjusting for age, sex, ethnicity, Townsend deprivation index, educational attainment, smoking status, drinking status, physical activity, meat intake, fruit intake, vegetable intake, and history of cardiovascular diseases. Significant associations are bolded.

less likely to be a current or previous smoker and drinker.

Association Between Metabolic Phenotypes of Obesity and Retinal Age Gap

Table 2 shows the association between metabolic phenotypes of obesity and retinal age gap. Compared with individuals with metabolically healthy normal weight, individuals classified as metabolic healthy overweight (β, 0.17; 95% confidence interval [CI], 0.01–0.32; $P = 0.039$) and metabolic healthy obesity (β, 0.23; 95% CI, 0.02–0.44; $P = 0.031$) were associated with increased retinal age gap after adjusting for covariates in model 2. Furthermore, individuals classified as metabolic unhealthy by the new definition were also significantly associated with higher retinal age gap, regardless of BMI categories (β for MUN, 0.23; 95% CI, 0.08–0.38; $P = 0.003$; β for MUOW, 0.31; 95% CI, 0.18–0.45; $p < 0.001$; β for MUO, 0.50; 95% CI, 0.36–0.65; $P < 0.001$).

Association Between BMI Categories and Retinal Age Gap Across Different Metabolic Phenotypes

We further analyzed the association between BMI and retinal age gap across different metabolic phenotypes (Table 3). The results shows that obesity was associated with a higher retinal age gap compared with normal weight in both metabolically healthy phenotype (β, 0.28; 95% CI, 0.07–0.48; $P = 0.008$) and MU phenotype (β, 0.23; 95% CI, 0.09–0.38; $P = 0.002$), whereas overweight was significantly associated with a higher retinal age gap only in the metabolically healthy phenotype (β, 0.18; 95% CI, 0.03–0.34; $P = 0.018$). However, there was no significant interaction effect between the BMI categories and the metabolic phenotypes (all *P* for interaction > 0.05).

Table 4. Association Between Metabolic Phenotypes of Obesity and Retinal Age Gap Stratified by Sex

Metabolic Obesity Phenotypes	Female		Male		*P* Value for Interaction
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	
MHN	[Reference]		[Reference]		
MHOW	0.20 (0.001 to 0.39)	**0.047**	0.18 (−0.10 to 0.46)	0.215	0.915
MHO	0.27 (0.01 to 0.52)	**0.038**	0.22 (-0.16 to 0.61)	0.257	0.905
MUN	0.15 (-0.04 to 0.33)	0.118	0.40 (0.13 to 0.67)	**0.003**	0.147
MUOW	0.24 (0.06 to 0.41)	**0.007**	0.45 (0.21 to 0.69)	**<0.001**	0.196
MUO	0.44 (0.25 to 0.62)	**<0.001**	0.64 (0.39 to 0.90)	**<0.001**	0.192

CI, confidence interval; MHN, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obesity; MUN, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obesity.

Linear regression models were used to estimate the association between metabolic phenotypes of obesity and retinal age gap stratified by sex, adjusting for age, ethnicity, Townsend deprivation index, educational attainment, smoking status, drinking status, physical activity, meat intake, fruit intake, vegetable intake, and history of cardiovascular diseases. Significant associations are bolded.

Association Between Metabolic Phenotypes of Obesity and Retinal Age Gap Stratified by Sex

Table 4 presents the association between metabolic phenotypes of obesity and the retinal age gap, stratified by sex. Under the new definition, MHOW and MHO phenotypes are significantly associated with the retinal age gap in female participants (β for MHOW, 0.20; 95% CI, 0.001–0.39; $P = 0.047$; β for MHO, 0.27; 95% CI, 0.01–0.52; $P = 0.038$). However, these associations are not significant in males (β for MHOW, 0.18; 95% CI, −0.10 to 0.46; $P = 0.215$; β for MHO, 0.22; 95% CI, −0.16 to 0.61; $P = 0.257$). Conversely, MU phenotypes across all BMI categories showed a stronger association with increased retinal age gap in males (β for MUN, 0.40; 95% CI, 0.13–0.67; $P = 0.003$; (β for MUOW, 0.45; 95% CI, 0.21–0.69; $P < 0.001$; β for MUO, 0.64; 95% CI, 0.39–0.9; $P < 0.001$) than in females (β for MUN, 0.15; 95% CI, −0.04 to 0.33; $P = 0.118$; β for MUOW, 0.24; 95% CI, 0.06–0.41; $P = 0.007$; β for MUO, 0.44; 95% CI, 0.25–0.62; $P < 0.001$). However, the magnitude of the coefficient effects between the two sexes was not large enough to result in a significant interaction effect (all *P* for interaction > 0.05).

Discussion

To the best of our knowledge, this study is the first to reveal a significant association between MHO and accelerated biological age, as indexed by the retinal age gap. We found that the MHO phenotype, as defined by the new criteria, was associated significantly with accelerated retinal aging compared with metabolically healthy normal weight. Additionally, no significant sex differences were observed in the association between MHO and the retinal age gap.

The primary innovation of our study is the use of the retinal age gap as an outcome measure. The vasculature of the retina and the heart are known to have significant similarities and interactions. Our previous studies demonstrated that accelerated retinal age was associated significantly with an increased arterial stiffness index, which was used to estimate blood vessel stiffness and serves as an early indicator of atherosclerosis.[18] Additionally, the retinal age gap has been identified as a reliable and promising predictor of future risks of mortality,[17] incident CVD,[18] and stroke.[19] Therefore, the positive association between MHO and the increased retinal age gap suggests that the MHO phenotype might not represent a benign and safe status for cardiovascular health. This finding is aligned with substantial previous studies, which showed that the cardiovascular risk observed in MHO patients often exceeds that of metabolically healthy normal weight individuals.[10,12,24] However, our findings may differ from those reported by Zembic et al.,[14] who recently observed that MHO, based on the new definition, was not associated with CVD mortality or total mortality in the third National Health and Nutrition Examination Survey and when validated in the UK Biobank. A possible explanation for this discrepancy is that Zembic et al.[14] used CVD and total mortality as study end points, whereas the retinal age gap does not represent a specific disease status, but serves as a subclinical predictor for target organ damage, with accelerated retinal aging potentially reflecting earlier pathological changes leading to mortality and CVD. Another

prospective study from two population-based cohorts might help to elaborate on these differences. Wei et al.[15] recently reported that individuals with MHO, also using this new definition, may not present a higher short-term cardiovascular risk, but tend to have a metabolomic pattern associated with higher cardiovascular risk than those with a metabolically healthy normal weight, suggesting that MHO classified by the new definition was not completely healthy. Taking this evidence together, early and targeted intervention is needed for individuals with overweight or obesity, irrespective of MH status.

In the present study, we also observed that both MHOW and MHO phenotypes were associated significantly with the retinal age gap in females but not in males. However, the magnitude of the coefficient effects between the two sexes was not large enough to result in a significant interaction effect (all P for interaction $>$ 0.05), indicating that there is no significant sex difference in the association between metabolic phenotypes of obesity and the retinal age gap. Previous evidence regarding the cardiovascular risk associated with MHO between men and women has been inconsistent. A cohort study using data from 3.5 million individuals in The Health Improvement Network reported that females with MHO showed a stronger positive association with the risk of cerebrovascular disease and heart failure compared with males. However, this sex difference was not observed for coronary heart disease and peripheral vascular disease.[25] Conversely, a large study conducted in France found that MHO was associated with a higher risk of major adverse cardiovascular events in men (hazard ratio, 1.12–1.80), whereas it was associated with a lower risk for most events in women (hazard ratio, 0.49–0.99).[26] Therefore, future research is needed to assess differences in MH in the obese between men and women.

Our findings have important clinical implications. First, this study provides valuable insights into the associations between metabolic obesity phenotypes with accelerated biological age as indexed by the retinal age gap. Our findings demonstrated that both MHOW and MHO are not benign or safe conditions, even under the new definition. Thus, weight management interventions should be recommended for individuals with overweight or obesity, regardless of their metabolic status. In addition, our study demonstrated that retinal age gap assessment may serve as a valuable indicator of predisease health status before the onset of adverse health outcomes, highlighting the potential of retinal age gap as an easily accessible and feasible tool for general health.

Strengths of the present study include its relatively large sample size, standardized protocol for data collection, and comprehensive adjustment of confounding factors. Despite these factors, some limitations should be acknowledged. First, the cross-sectional design precludes any definitive causal inferences regarding the relationship between metabolic phenotypes of obesity and the retinal age gap. Second, owing to inadequate event numbers, we were unable to perform association analyses of the transition of metabolic status among the subgroup with the retinal age gap.[13,14] Third, subjective measurements of physical activity and diet through self-reported questionnaires may be subject to recall bias. Fourth, potential confounding effects of image quality must be considered when interpreting our results. As noted by Warwick et al.,[21] there is a correlation between image gradability and participant demographics, which may introduce a selection bias. Fifth, previous studies have suggested that the performance of DL models may be poorer in external test sets.[27] Currently, we do not have access to external cohorts with retinal images for validation. Further research is needed to validate these findings in external cohorts. Sixth, the UK Biobank provides single-field retinal images, which have limitations compared with multifield images, such as a restricted field of view and less ideal sensitivity values.[28] Therefore, future research could benefit from using multi-field retinal images for a more comprehensive assessment of retinal age and its association with MHO.

Conclusions

Our study revealed that individuals with MHOW and MHO were significantly associated with an increased retinal age gap compared with those with metabolically healthy normal weight. Weight management should be recommended for individuals who are overweight or obese, even in the absence of metabolic unhealthy.

Acknowledgments

The authors thank all participants and staff for their cooperation and assistance in the study. This research has been conducted using the UK Biobank Resource under Application Number 86091.

Supported by National Natural Science Foundation of China (82101173, 82171075), National Health and Medical Research Council Investigator Grant (2010072), China Scholarship Council (202308440506), High-level Talent Flexible Introduc-

tion Fund of Guangdong Provincial People's Hospital (KJ012019530), and the Global STEM Professorship Scheme (P0046113). The sponsor or funding organization had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contributions: XZ, ZZ, and HY conceived and designed the study. XZ conducted data analysis and performed data interpretation. XZ and RC drafted the initial manuscript. XZ, RC, GB, QP, CC, MH, HY, and ZZ made critical revisions of the manuscript for important intellectual content. All authors read the manuscript and approved the final draft. All authors had final responsibility for the decision to submit for publication.

Data Availability: Data are available in a public, open access repository (https://www.ukbiobank.ac.uk/).

Disclosure: **X. Zeng**, None; **R. Chen**, None; **G. Bulloch**, None; **Q. Peng**, None; **C.-Y. Cheng**, None; **M. He**, None; **H. Yu**, None; **Z. Zhu**, None

References

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15(5):288–298, doi:10.1038/s41574-019-0176-8.
2. WHO Consultation on Obesity (1999: Geneva, Switzerland) & World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i–xii, 1–253.
3. Tchkonia T, Thomou T, Zhu Y, et al. Mechanisms and metabolic implications of regional differences among fat depots. *Cell Metab*. 2013;17(5):644–656, doi:10.1016/j.cmet.2013.03.008.
4. Goossens GH. The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. *Obes Facts*. 2017;10(3):207–215, doi:10.1159/000471488.
5. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res*. 2020;126(11):1477–1500, doi:10.1161/CIRCRESAHA.120.316101.
6. Blüher M. Metabolically healthy obesity. *Endocr Rev*. 2020;41(3):bnaa004, doi:202112111103 4558000.
7. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol*. 2013;1(2):152–162, doi:10.1016/S2213-8587(13)70062-7.
8. Després JP. Taking a closer look at metabolically healthy obesity. *Nat Rev Endocrinol*. 2022;18(3):131–132, doi:10.1038/s41574-021-00619-6.
9. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758–769, doi:10.7326/0003-4819-159-11-201312030-00008.
10. Zhou Z, Macpherson J, Gray SR, et al. Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants. *Diabetologia*. 2021;64(9):1963–1972, doi:10.1007/s00125-021-05484-6.
11. Cuthbertson DJ, Wilding JPH. Metabolically healthy obesity: time for a change of heart? *Nat Rev Endocrinol*. 2021;17(9):519–520, doi:10.1038/s41574-021-00537-7.
12. Mongraw-Chaffin M, Foster MC, Anderson CAM, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol*. 2018;71(17):1857–1865, doi:10.1016/j.jacc.2018.02.055.
13. Stefan N, Schulze MB. Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment. *Lancet Diabetes Endocrinol*. 2023;11(6):426–440, doi:10.1016/S2213-8587(23)00086-4.
14. Zembic A, Eckel N, Stefan N, Baudry J, Schulze MB. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. *JAMA Netw Open*. 2021;4(5):e218505, doi:10.1001/jamanetworkopen.2021.8505.
15. Wei D, González-Marrachelli V, Melgarejo JD, et al. Cardiovascular risk of metabolically healthy obesity in two European populations: Prevention potential from a metabolomic study. *Cardiovasc Diabetol*. 2023;22(1):82, doi:10.1186/s12933-023-01815-6.
16. Nusinovici S, Rim TH, Li H, et al. Application of a deep-learning marker for morbidity and mortality prediction derived from retinal photographs: a cohort development and validation study. *Lancet Healthy Longev*. 2024;5(10):100593, doi:10.1016/S2666-7568(24)00089-8.
17. Zhu Z, Shi D, Guankai P, et al. Retinal age gap as a predictive biomarker for mortality risk. *Br J Ophthalmol*. 2023;107(4):547–554, doi:10.1136/bjophthalmol-2021-319807.
18. Zhu Z, Chen Y, Wang W, et al. Association of retinal age gap with arterial stiffness and incident

cardiovascular disease. *Stroke*. 2022;53(11):3320–3328, doi:10.1161/STROKEAHA.122.038809.
19. Zhu Z, Hu W, Chen R, et al. Retinal age gap as a predictive biomarker of stroke risk. *BMC Med*. 2022;20(1):466, doi:10.1186/s12916-022-02620-w.
20. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779, doi:10.1371/journal.pmed.1001779.
21. Warwick AN, Curran K, Hamill B, et al. UK Biobank retinal imaging grading: methodology, baseline characteristics and findings for common ocular diseases. *Eye (Lond)*. 2023;37(10):2109–2116, doi:10.1038/s41433-022-02298-7.
22. Fu H, Wang B, Shen J, et al. Evaluation of retinal image quality assessment networks in different color-spaces. In: Evaluation of Retinal Image Quality Assessment Networks in Different Color-Spaces, Vol. 11764. International Conference on Medical Image Computing and Computer-Assisted Intervention; 2019:48–56, doi:10.1007/978-3-030-32239-7_6.
23. Zhou Z, Macpherson J, Gray SR, et al. Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants. *Diabetologia*. 2021;64(9):1963–1972, doi:10.1007/s00125-021-05484-6.
24. Kramer CK, Zinman B, Retnakaran R. Are Metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758, doi:10.7326/0003-4819-159-11-201312030-00008.
25. Caleyachetty R, Thomas GN, Toulis KA, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *J Am Coll Cardiol*. 2017;70(12):1429–1437, doi:10.1016/j.jacc.2017.07.763.
26. Fauchier G, Bisson A, Bodin A, et al. Metabolically healthy obesity and cardiovascular events: A nationwide cohort study. *Diabetes Obes Metab*. 2021;23(11):2492–2501, doi:10.1111/dom.14492.
27. Rim TH, Lee G, Kim Y, et al. Prediction of systemic biomarkers from retinal photographs: development and validation of deep-learning algorithms. *Lancet Digit Health*. 2020;2(10):e526–e536, doi:10.1016/S2589-7500(20)30216-8.
28. Williams GA, Scott IU, Haller JA, Maguire AM, Marcus D, McDonald HR. Single-field fundus photography for diabetic retinopathy screening: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2004;111(5):1055–1062, doi:10.1016/j.ophtha.2004.02.004.