The association of long-term trajectories of BMI, its variability, and metabolic syndrome: a 30-year prospective cohort study

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Summary

Background Limited data exists on how early-life weight changes relate to metabolic syndrome (MetS) risk in midlife. This study examines the association between long-term trajectories of body mass index (BMI), its variability, and MetS risk in Chinese individuals.

Methods In the Hanzhong Adolescent Hypertension study (March 10, 1987–June 3, 2017), 1824 participants with at least five BMI measurements from 1987 to 2017 were included. Using group-based trajectory modeling, different BMI trajectories were identified. BMI variability was assessed through standard deviation (SD), variability independent of the mean (VIM), and average real variability (ARV). Logistic regression analyzed the relationship between BMI trajectory, BMI variability, and MetS occurrence in midlife (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02734472).

Findings BMI trajectories were categorized as low-increasing (34.4%), moderate-increasing (51.8%), and high-increasing (13.8%). Compared to the low-increasing group, the odds ratios (ORs) [95% CIs] for MetS were significantly higher in moderate (4.27 [2.63–6.91]) and high-increasing groups (13.11 [6.30–27.31]) in fully adjusted models. Additionally, higher BMI variabilities were associated with increased MetS odds (ORs for SD_{BMI}, VIM_{BMI}, and ARV_{BMI}: 2.30 [2.02–2.62], 1.22 [1.19–1.26], and 4.29 [3.38–5.45]). Furthermore, BMI trajectories from childhood to adolescence were predictive of midlife MetS, with ORs in moderate (1.49 [1.00–2.23]) and high-increasing groups (2.45 [1.22–4.91]). Lastly, elevated BMI variability in this period was also linked to higher MetS odds (ORs for SD_{BMI}, VIM_{BMI}, and ARV_{BMI}: 1.24 [1.08–1.42], 1.00 [1.00–1.01], and 1.21 [1.05–1.38]).

Interpretation Our study suggests that both early-life BMI trajectories and BMI variability could be predictive of incident MetS in midlife.

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Keywords: Body mass index; Body mass index trajectory; Body mass index variability; Central obesity; Metabolic syndrome

Introduction

Metabolic syndrome (MetS), characterized by a cluster of interrelated metabolic abnormalities, including central obesity, dyslipidemia, hypertension, and impaired glucose metabolism, has garnered significant attention in both clinical and epidemiological research

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Research in context

Evidence before this study

Metabolic syndrome (MetS) has increasingly become a focal point in both clinical and epidemiological research due to its complex link with cardiovascular diseases (CVD). A higher body mass index (BMI) is associated with a higher prevalence of MetS in general adults. We searched PubMed using the Mesh terms "body mass index," "metabolic syndrome," and ("middle age" or "middle-aged") for articles without language restriction published up to August 31, 2023. Limited studies have explored the relationship between BMI trajectories and MetS, which had small sample sizes or relied on single measurements of BMI, and only a few studies revealed the associations between the long-term BMI trajectory and the incidence of MetS. Moreover, no study examined the association between long-term BMI variability and the incidence of MetS. The association and sex-differences of the trajectory of BMI and variability of BMI from childhood onwards with the incidence of MetS in later life need further exploration.

Added value of this study

We used Hanzhong Adolescent Hypertension Cohort, which recruited children and adolescents in 1987 and has been followed up for over 30 years, with at least 5 BMI measurements. We identified three distinct BMI trajectories: low-increasing (34.4%), moderate-increasing (51.8%), and high-increasing (13.8%). Additionally, we calculated standard deviation, variability independent of the mean, and average real variability to assess BMI variability. According to multivariable models, our findings indicate that high BMI trajectory and greater BMI variability from childhood to adulthood are associated with a higher risk of MetS in both sexes.

Implications of all the available evidence

Our findings underscore the importance of longitudinal and continuous monitoring for elevated BMI and obesity from childhood to adulthood. Early-life BMI management may help delay the onset of MetS and CVD in midlife.

due to its intricate association with cardiovascular diseases (CVD) and other adverse outcomes.[1–5] Recent epidemiological studies indicate a steady rise in the prevalence of MetS among Chinese adults. The rate has significantly increased, rising from 9.5% in 2002 to more than 30% in 2017,[6–8] with certain northern Chinese communities surpassing 40%.[9]

Several studies have assessed the impact of childhood and adulthood weight and their variations on the development of cardiovascular outcomes.[10–13] However, the intricate interplay between BMI trajectories, BMI variability, and the development of MetS requires further elucidation.[14,15] A 16-year follow-up study involving 544 participants from the China Health and Nutrition Survey revealed an association between BMI trajectory and the onset of MetS in middle age.[16] However, the above study has a restricted follow-up period and a small sample size. Moreover, there still needs to be more relevant research data concerning the relationship between BMI variability persisting from childhood to middle age and the incidence of MetS in midlife.

This prospective cohort study aims to bridge these gaps in knowledge by using data from the Hanzhong Adolescent Hypertension Study, a well-established, ongoing population-based study with 30 years of follow-up.[17–19] By constructing longitudinal BMI trajectories from childhood to adulthood and assessing BMI variability, this study seeks to elucidate the intricate relationship between long-term BMI patterns, variability, and the risk of developing MetS in the Chinese population. The findings from this study will contribute to our understanding of MetS pathogenesis and aid the development of targeted prevention and intervention strategies tailored to this high-risk population.

Methods

Study cohort

The Hanzhong Adolescent Hypertension Study details have been previously published.[17,18] In summary, the study commenced in 1987 with the enrollment of 4623 school children from 26 rural sites in three towns (Qili, Laojun, and Shayan) in Hanzhong, Shaanxi, China. The inclusion criteria in selecting participants for the baseline survey were as follows: elementary and middle school students in 1987, absence of chronic diseases according to medical records, proficiency in Mandarin for effective communication, and voluntary participation. Exclusions were made for individuals whose parents/guardians were unwilling to participate or had a chronic disease based on clinical data or self-reporting. Follow-up examinations were conducted in 1989, 1992, 1995, 2005, 2013, and 2017, giving a total follow-up time of 30 years. Throughout the follow-up period, we employed a systematic sampling approach in 2005 to randomly select every tenth participant ($K = 10$) from the extensive cohort. This process yielded data from 436 individuals, including their BMI and other relevant information. Except for the visit in 2005, all other follow-ups were conducted on a large scale, aiming to visit everyone enrolled in 1987. The response rates were as follows: 77.7% (n = 3592) in 1989 (visit 2), 84.8% (n = 3918) in 1992 (visit 3), 82.1% (n = 3794) in 1995 (visit 4), 65.3% (n = 3018) in 2013 (visit 6), and 60.1% (n = 2780) in 2017 (visit 7) (Figure S1). Participants were

lost to follow-up due to occupation (migrant workers, military service), emigration, or death. Based on our study design, participants included in this research had at least three BMI measurements in the first four visits, and BMI values for both last two visits. This means that, across all seven follow-ups, all participants had at least five BMI measurements. No significant differences in age and BMI were observed between those included in the final analysis and those lost to follow-up (Table S1).

This study adheres to the principles of the Declaration of Helsinki, and all study procedures were conducted following institutional guidelines. The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Code: XJTU1AF2015LSL-047). All participants in this study gave their informed consent for each visit, and for those under the age of 18 at the baseline, permission was obtained from a parent or guardian. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02734472).

Definitions

In the present study, adult MetS was defined at the final visit in 2017, based on the guidelines provided by the International Diabetes Federation.[20,21] For Chinese people, MetS was defined as central obesity based on ethnic-specific waist circumference (WC) cutoffs, which were ≥90 cm for men and ≥80 cm for women in the Chinese population, along with the presence of two or more of the following high-risk indicators: 1) Raised blood pressure (BP) (SBP ≥130 mmHg or DBP ≥85 mmHg) or treatment of previously diagnosed hypertension (HT); 2). Raised fasting blood glucose (FBG) (≥5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus (DM); 3). Raised triglyceride (TG) (>1.7 mmol/L) or the use of medication for lipid disorders. 4). Reduced high-density lipoprotein cholesterol (HDL-C): HDL-C <1.03 mmol/L for men and <1.29 mmol/L for women or the use of medication for lipid abnormalities. HT was defined as having a prior diagnosis of HT with or without using anti-hypertensive medication or having a measured BP ≥140/90 mm Hg. DM was defined as having a previous diagnosis of DM or having a measured FBG ≥7.0 mmol/L or using diabetes medication.

Statistics

All statistical analyses are conducted using Stata (version 17.0) or R studio (version 4.3.0). Given our need to analyse longitudinal data, we employed Group-Based Trajectory Modeling (GBTM), primarily used to identify distinct groups or subpopulations within a larger population that share similar developmental trajectories over time.[22] We used the Stata "Traj" plugin to display age-scaled BMI trajectories from childhood to middle age.[23,24] The identification of the best-fitting model involved a 3-stage procedure. In stage 1, we hypothesize the expected numbers of latent classes of the BMI curve. Based on our knowledge, we assumed that BMI trajectories could be classified into 2–4 groups in our study. In stage 2, we conducted model specification and estimation. we chose a censored normal model to fit the trajectories as BMI is considered a continuous variable. Next, we repeatedly fitted each trajectory with different shapes. The shape of each trajectory is presented as 1, 2, or 3 (1 = linear, 2 = quadratic, and 3 = cubic). Model fit was generally initiated with a linear polynomial, and then the fit according to the Bayesian Information Criterion (BIC) was compared with different trajectory numbers. The lower BIC value indicates a better model fit as it balances the model complexity versus goodness of fit to the sample data. Then, combined with our knowledge and statistical considerations, we chose the most suitable model. In stage 3, we conducted the model selection. We chose the model considering these criteria: (1) The lower BIC value indicates the better model fit. (2) We make sure that the average of the posterior probabilities of group membership for individuals assigned to each group exceeds 0.7. (3) The odds of correct classification based on the posterior probabilities of group membership exceed a minimum threshold of 5. (4) We ensure that the group sample size should be >5% to ensure that each trajectory group has a specific distribution. The statistical information for different models is presented in Table S2. Finally, we identified the three best-fitting trajectories with quadratic order terms.

On the other hand, we used the BMI of the participants in the seven visits to assess the variability of BMI in childhood. We calculated the following indicators as BMI variability index: standard deviation (SD), coefficient of variation (CV), variability independent of the mean (VIM), maximum and minimum BMI difference (MMD), and average real variability (ARV). VIM is calculated as the SD divided by the mean to the power x. Power x was modeled as $SD = k \times mean^x$ and derived from fitting curves by nonlinear regression analysis implemented in the R studio.[25] ARV across multiple visits is determined by calculating the average absolute differences between successive BMI measurements in each visit. Unlike CV and SD, AVR takes the order of BMI measurement into account and is less affected by the trend. The formulas for calculating all BMI variability metrics are displayed in the appendix. Here, we report BMI variability using SD, VIM, and ARV because CV and MMD strongly correlate with SD or VIM ($r = 0.97–1.00$; both $P < 0.001$, Table S3).

Continuous variables were presented as median with interquartile ranges. Categorical variables were expressed as frequency and percentage. We used the Mann–Whitney U or Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables to assess statistically significant differences among the

groups. In the case of multiple comparisons, we applied the Bonferroni correction to the testing threshold. A logistic regression was performed to examine the association between BMI trajectory groups or BMI variability and MetS in midlife expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Additionally, the association between BMI trajectory or BMI variability and subfactors of the MetS was also examined. The regression model adjusted for cardiovascular risk factors, including age, sex, adult socioeconomic status (visit 7), and mean BMI.

To test the robustness of the results, sensitivity analyses were performed by excluding participants taking medication such as antihypertensive, hypoglycemic, or lipid-lowering drugs. Considering the impact of sex on cardiovascular variables, we conducted further evaluations stratified by sex. Finally, due to the small sample size of participants in 2005 (visit 5), we conducted a reanalysis after excluding the participants' data from visit 5 to validate the stability of the results. Statistical significance was set as a two-sided *P*-value <0.05.

Role of funding source

The funders had no roles in study design, data collection, data analysis, or interpretation of the data, as well as in the writing of the report and in the decision to submit the paper for publication. Tongshuai Guo, Sirui Zheng and Jianjun Mu have accessed and verified the data, and Jianjun Mu and Duolao Wang were responsible for the decision to submit the manuscript.

Results

Baseline characteristics of the study population

As of 2017, a total of 2780 participants were enrolled in the study. However, 956 participants were excluded from the final analysis for various reasons: either their BMI values for 2013 or 2017 were unavailable, or they lacked two or more BMI values in the initial four visits. Consequently, data from 1824 participants were included in the final analysis and followed up for 30 years (Figure S1). Among the included participants, 58.0% were male, and the median age in 2017 was 43 years, ranging from 40 to 45 years. As indicated in Table 1, the group of participants with MetS exhibited consistently higher BMI values even from the initial four visits between 1987 and 1995. In addition to having higher FBG, BP, TG, and TC levels, participants in the MetS group also had elevated uric acid levels (all $P < 0.001$).

Furthermore, the study identified three distinct trajectories based on morphological characteristics, namely "low-increasing" (n = 628, 34.4%), "moderate-increasing" (n = 944, 51.8%), and "high-increasing" (n = 252, 13.8%) trajectory (Fig. 1). The age-scaled BMI levels for each trajectory are provided in Table 2. We found a significantly higher proportion of participants in the MetS group were classified into the "high-increasing" trajectory compared to the non-MetS group (36.5% vs. 7.0%, $P < 0.001$) (Table 1). It was observed that participants in the MetS group had higher BMI variability compared to those in the non-MetS group (SD_{BMI}: 4.5 vs. 3.1 kg/m^2; VIM_{BMI}: 18.4 vs. 13.9; ARV_{BMI}: 2.1 vs 1.4 kg/m^2, all $P < 0.001$), as shown in Table 1. What's more, compared with the low-increasing group, participants in the moderate-increasing group and the high-increasing group also had higher BMI variability (Table S4).

Association between BMI trajectory from childhood to middle age and MetS incidence

Among the 1824 participants included in the study, the final visit revealed an overall incidence rate of MetS of 23.1% (n = 422). No significant differences were observed in sex, BMI, WC, TC, TG, HDL-C, and FBG in 2017 between the participants eventually included in the study and those excluded. We conducted a comparison of MetS outcomes based on BMI trajectory groups. As shown in Fig. 2, we found that the moderate-increasing and high-increasing groups exhibited higher WC, FBG, TG, SBP, and DBP levels (all $P < 0.001$) and lower HDL-C levels (all $P < 0.001$) when compared to the low-increasing group.

The incidences of MetS in the BMI trajectory groups from low-to high-increasing were 4.9%, 25.1%, and 61.1%, respectively ($P < 0.001$). Compared with the low-increasing group, the ORs (95% CIs) of MetS in moderate- and high-increasing groups were 4.33 [2.68–6.97] and 13.48 [6.54–27.79] ($P < 0.001$), respectively, in the model adjusted for age, sex and mean BMI. In the multivariate model that further adjusted for smoking, alcohol consumption, marital status, and physical activity in 2017, the ORs (95% CIs) of the latter two groups were 4.27 [2.63–6.91] and 13.11 [6.30–27.31], respectively (all $P < 0.001$) (Table 3).

As shown in Table 3, the fully adjusted ORs of central obesity in moderate- and high-increasing groups increased significantly compared to the low-increasing group (OR = 4.44 [3.04–6.49], OR = 54.83 [23.65–127.10], respectively). Compared with those in the low-increasing group, participants in the moderate- and high-increasing groups had significantly higher odds of raised TG after total adjustment (OR = 2.00 [1.41–2.83]; OR = 3.48 [1.90–6.40], respectively). For reduced HDL-C, those in the higher two groups had a 2.04 [1.49–2.80] and 3.20 [1.80–5.68] fold greater odds than those in the low-increasing group. Similar trends existed in the relationship between BMI trajectory groups and raised FBG or DM, as well as the relationship between BMI trajectory groups and raised BP or HT (all $P < 0.05$) (Table 3).

Association between BMI variability from childhood to middle age and MetS incidence

Table 4 displays the associations between SD_{BMI}, VIM_{BMI}, and ARV_{BMI} during childhood with the risk of

Variables	Total (n = 1824)	Non-MetS (n = 1402)	MetS (n = 422)	*P* value
Baseline in 1987				
Male (%)	1058 (58.0%)	814 (58.1%)	244 (57.8%)	0.94
Age, y	13 (10–15)	12 (10–15)	13 (10–15)	0.20
BMI, kg/m^2	16.1 (14.9–18.1)	16.0 (14.8–17.9)	16.4 (15.1–18.5)	<0.001
BMI 1989–2013				
BMI in 1989, kg/m^2	17.1 (15.6–19.0)	17.0 (15.5–18.8)	17.4 (16.2–19.7)	<0.001
BMI in 1992, kg/m^2	19.4 (17.6–21.0)	19.2 (17.4–20.8)	20.0 (18.4–21.6)	<0.001
BMI in 1995, kg/m^2	20.3 (19.0–21.6)	20.1 (18.9–21.5)	20.8 (19.5–22.4)	<0.001
BMI in 2005, kg/m^2	22.6 (20.2–22.4)	22.0 (19.9–23.7)	24.3 (22.5–25.8)	<0.001
BMI in 2013, kg/m^2	23.6 (21.7–26.0)	22.9 (21.3–25.0)	26.5 (24.5–28.6)	<0.001
Midlife (2017)				
BMI, kg/m^2	23.8 (21.9–26.0)	23.0 (21.4–24.8)	26.8 (25.1–28.6)	<0.001
WC, cm	84.6 (78.2–91.7)	82.3 (76.4–88.1)	94.1 (90.2–98.8)	<0.001
HC, cm	92.1 (88.7–95.6)	91.0 (88.0–94.1)	96.2 (93.4–99.3)	<0.001
SBP, mmHg	121.7 (113.0–131.7)	119.3 (111.7–128.2)	131.3 (120.7–143.0)	<0.001
DBP, mmHg	76.3 (69.3–84.3)	74.7 (68.0–82.0)	84.0 (75.3–91.3)	<0.001
HR, beats/min	74 (67–80)	73 (66–80)	75 (69–83)	<0.001
Hypertension (%)	218 (12.0%)	110 (7.8%)	108 (25.6%)	<0.001
Diabetes (%)	60 (3.3%)	25 (1.8%)	35 (8.3%)	<0.001
Hyperlipidemia (%)	174 (9.5%)	75 (5.4%)	99 (23.5%)	<0.001
Smoking (%)	834 (45.7%)	628 (44.8%)	206 (48.8%)	0.15
Alcohol (%)	563 (30.9%)	415 (29.6%)	148 (35.1%)	0.03
Marital status (%)				0.45
Unmarried	28 (1.5%)	24 (1.7%)	4 (1.0%)	
Married	1753 (96.6%)	1345 (96.3%)	408 (97.8%)	
Divorced	29 (1.6%)	25 (1.8%)	4 (1.0%)	
Widowed	4 (0.2)	3 (0.2%)	1 (0.2%)	
Physical activities (%)				0.34
Vigorous physical activity	38 (2.1%)	31 (2.2%)	7 (1.7%)	
Moderate physical activity	66 (3.6%)	47 (3.4%)	19 (4.5%)	
Mild physical activity	945 (52.0%)	716 (51.2%)	229 (54.4%)	
No activity	770 (42.3%)	604 (43.2%)	166 (39.4%)	
FBG, mmol/L	4.58 (4.28–4.91)	4.52 (4.24–4.83)	4.77 (4.42–5.21)	<0.001
TG, mmol/L	1.37 (0.97–1.98)	1.17 (0.88–1.58)	2.19 (1.74–2.94)	<0.001
TC, mmol/L	4.50 (4.04–5.00)	4.46 (4.01–4.96)	4.62 (4.18–5.16)	<0.001
LDL-C, mmol/L	2.50 (2.12–2.89)	2.49 (2.12–2.87)	2.52 (2.17–2.97)	0.11
HDL-C, mmol/L	1.14 (0.98–1.33)	1.20 (1.05–1.40)	0.98 (0.87–1.10)	<0.001
Serum uric acid, mmol/L	280.9 (226.1–335.6)	271.6 (219.0–325.1)	307.1 (254.7–362.3)	<0.001
Serum creatinine, μmol/L	76.0 (67.1–86.3)	75.7 (66.5–86.2)	76.8 (68.7–86.7)	0.08
BMI Trajectory				<0.001
Low-increasing (%)	628 (34.4)	597 (42.6)	31 (7.4)	
Moderate-increasing (%)	944 (51.8)	707 (50.4)	237 (56.2)	
High-increasing (%)	252 (13.8)	98 (7.0)	154 (36.5)	
BMI variability				
SD, kg/m^2	3.4 (2.4–4.3)	3.1 (2.2–3.8)	4.5 (3.5–5.3)	<0.001
VIM	14.9 (10.5–18.5)	13.9 (9.8–17.3)	18.4 (14.3–22.4)	<0.001
ARV, kg/m^2	1.6 (1.1–2.0)	1.4 (1.0–1.8)	2.1 (1.7–2.5)	<0.001

ARV, average real variability; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; VIM, variability independent of the mean; WC, waist circumference.

Table 1: **Characteristics and metabolic risk factors for the subjects.**

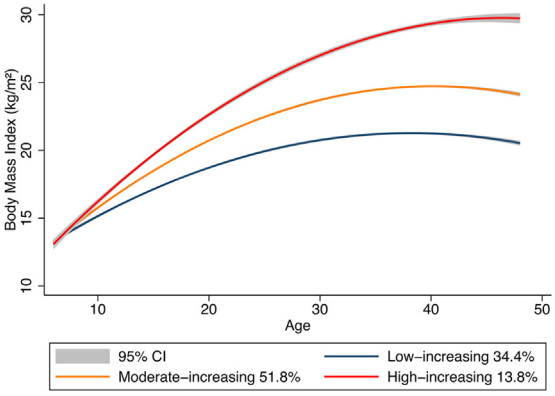

Fig. 1: Long-term body mass index (BMI) trajectories from childhood to middle age.

MetS in midlife. An increased BMI variability was related to a higher odds of MetS in the full adjustment model (model 2, ORs [95% CIs] were 2.30 [2.02–2.62] for SD_{BMI}, 1.22 [1.19–1.26] for VIM_{BMI}, and 4.29 [3.38–5.45] for ARV_{BMI}). In addition, a higher BMI variability was related to a higher odds of central obesity in the full adjustment model (model 2, ORs [95% CIs] were 4.44 [3.74–5.26] for SD_{BMI}, 1.43 [1.37–1.48] for VIM_{BMI}, and 16.31 [11.88–22.38] for ARV_{BMI}). Similarly, a higher BMI variability was related to a higher odds of raised TG (model 2, ORs [95% CIs] were 1.61 [1.45–1.78] for SD_{BMI}, 1.12 [1.10–1.15] for VIM_{BMI}, and 2.32 [1.92–2.81] for ARV_{BMI}), reduced HDL-C (model 2, ORs [95% CIs] were 1.46 [1.33–1.61] for SD_{BMI}, 1.10 [1.07–1.12] for VIM_{BMI}, and 2.11 [1.76–2.52] for ARV_{BMI}), raised FBG or DM (model 2, ORs [95% CIs] were 1.51 [1.30–1.75] for SD_{BMI}, 1.11 [1.07–1.15] for VIM_{BMI}, and 1.72 [1.30–2.28] for ARV_{BMI}), and raised BP or HT (model 2, ORs [95% CIs] were 1.53 [1.38–1.69] for SD_{BMI}, 1.11 [1.08–1.13] for VIM_{BMI}, and 2.18 [1.81–2.62] for ARV_{BMI}), as shown in Table 4.

Association of childhood to adolescence BMI trajectory and variability with midlife MetS incidence

To examine the effect of childhood to adolescence BMI changes on the incidence of MetS in midlife, we identified BMI trajectories from childhood to adolescence (1987–1995). We found that compared with the low-increasing group, the ORs (95% CIs) of MetS in moderate- and high-increasing groups were 1.49 [1.00–2.23] and 2.45 [1.22–4.91] in the full adjusted model. As for central obesity, we found that compared to the low-increasing group, only the high-increasing group showed an increased incidence odds, with OR (95% CIs) being 2.28 (1.24–4.20). However, no significant correlations were observed between BMI trajectories and the incidence of other MetS subfactors, as shown in Table S5.

Next, we calculated BMI variability from childhood to adolescence (1987–1995). We found an increased BMI variability from childhood to adolescence was related to a higher odds of middle-age MetS in the full adjustment model (model 2, ORs [95% CIs] were 1.24 [1.08–1.42] for SD_{BMI}, 1.00 [1.00–1.01] for VIM_{BMI}, and 1.21 [1.05–1.38] for ARV_{BMI}). In addition, in the full adjustment model, a higher BMI variability was related to a higher odds of the subfactors of MetS, including central obesity, raised TG, reduced HDL-C, raised FBG or DM, and raised BP or HT, as shown in Table S6.

Sensitivity analysis

Medications used may affect blood lipid levels, BP, and blood glucose levels. In our study, the lipid-lowering drugs mainly include statins such as atorvastatin, lovastatin, and simvastatin, as well as fenofibrate and Xuezhikang (a traditional Chinese medicine) capsules. The primary antihypertensive drugs were calcium channel blockers (amlodipine, nifedipine, lacidipine), ACE inhibitors (enalapril, captopril), ARBs (losartan, valsartan, telmisartan), beta-blockers (metoprolol), and

Age cohort	Low-increasing	Moderate-increasing	High-increasing
N (%)	628 (34.4)	944 (51.8)	252 (13.8)
6–10, years	14.5 (13.7–15.1)	15.0 (14.3–15.6)	15.5 (14.7–16.2)
11–15, years	15.9 (14.9–17.1)	17.2 (16.0–18.5)	17.9 (16.6–19.5)
16–20, years	18.7 (17.6–19.7)	20.3 (19.1–21.4)	21.5 (20.2–23.0)
21–25, years	19.3 (18.3–20.1)	21.1 (20.1–22.2)	23.1 (22.1–24.4)
26–30, years	19.4 (18.3–20.2)	22.1 (21.1–23.5)	25.7 (23.9–27.4)
31–35, years	20.7 (19.6–21.6)	24.3 (23.3–25.4)	28.4 (27.2–29.8)
36–40, years	21.2 (20.1–22.1)	24.5 (23.3–25.8)	28.9 (27.9–30.5)
41–45, years	21.2 (20.1–22.3)	24.6 (23.3–25.9)	29.0 (27.8–30.5)
46–48, years	21.4 (20.3–22.3)	24.7 (23.6–25.6)	29.1 (28.4–32.0)

Variables are expressed as the median (inter-quartile range). BMI, body mass index.

Table 2: **BMI (kg/m^2) levels by age cohort in BMI trajectory groups from childhood to middle age.**

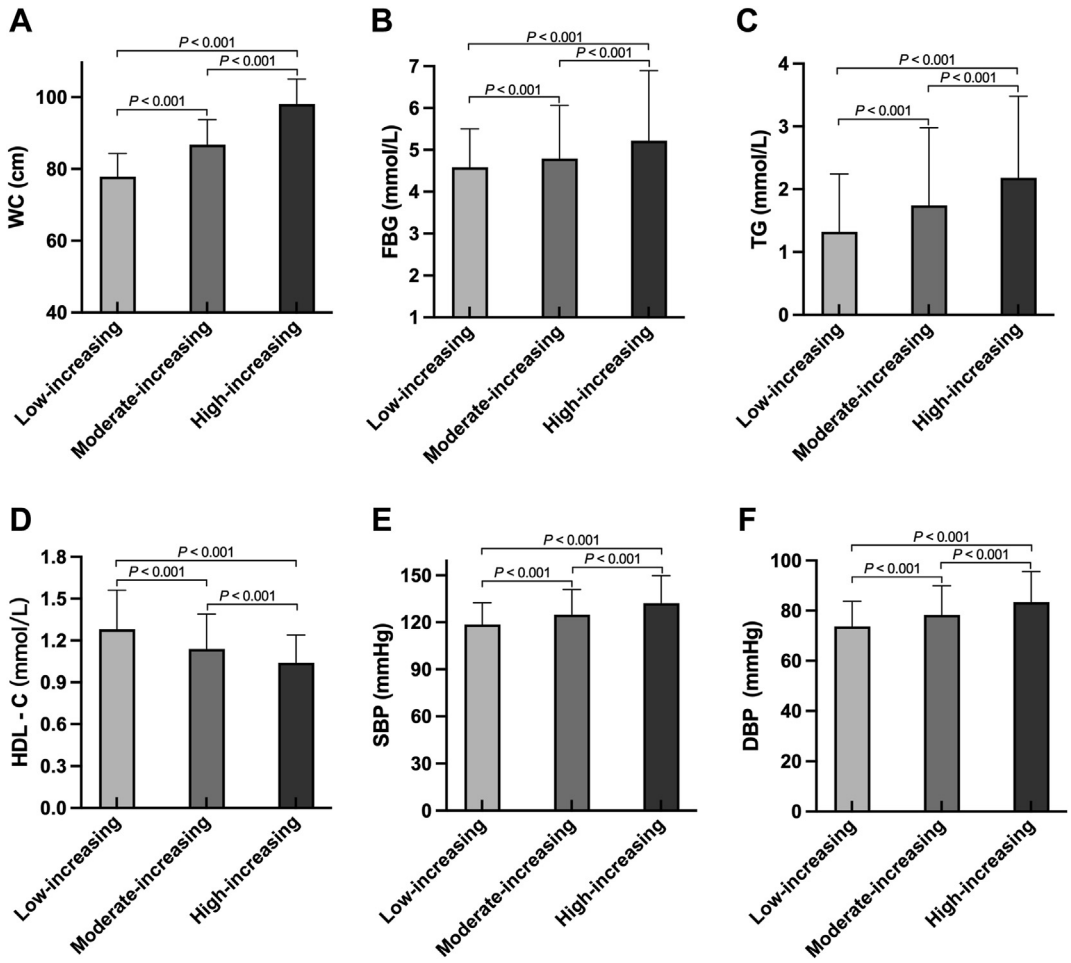

Fig. 2: Comparison of each MetS component among BMI trajectory groups. **A**. Waist circumference (WC); **B.** Fasting blood glucose (FBG); **C.** triglyceride (TG); **D.** high-density lipoprotein cholesterol (HDL-C); **E.** systolic blood pressure (SBP); **F.** diastolic blood pressure (DBP).

diuretics (hydrochlorothiazide, indapamide). For antidiabetic drugs, the list includes insulin, metformin, glimepiride, repaglinide, and acarbose. After excluding individuals treated with the above medications, the results remained unchanged (Tables S7 and S8).

Next, considering that males and females have different BMI developmental trends during their growth and development, we conducted subgroup analyses separately for men and women. The results were consistent with the overall male population, showing significant associations between BMI trajectory and variability with MetS and related subfactors. However, BMI trajectory was not associated with raised TG or BP in females. Nevertheless, BMI variability remained significantly associated with MetS and related indicators in females (Tables S9–S12).

Finally, since systematic sampling (K = 10) was employed at visit 5, resulting in a smaller sample size, this might have impacted the assessment of BMI trajectory and BMI variability. Therefore, after completely removing the BMI data from visit 5, we re-evaluated the situation. The results showed that BMI trajectory and BMI variability can still predict the onset of midlife MetS, as shown in Tables S13 and S14.

Discussion

In our prospective cohort from childhood to adulthood for 30 years, we found that both BMI trajectories and BMI variability were associated with the occurrence of MetS in midlife: (1) Compared with the low-increasing BMI trajectory group, participants in the moderate-increasing and high-increasing groups showed a noteworthy elevation in the prevalence of MetS and the related indicators. (2) Greater long-term visit-to-visit BMI variability was also associated with MetS incidence in midlife independent of the mean BMI levels. (3) The incidence of MetS in midlife can be influenced by the trajectories and variability of BMI during early life. Nevertheless, the efficacy of BMI trajectories from

Outcomes/BMI trajectory group	N (%)	Model 1			Model 2		
		ORs[a]	95% CI	*P* value	ORs[a]	95% CI	*P* value
MetS							
Low-increasing	31 (4.9)	1.00			1.00		
Moderate-increasing	237 (25.1)	4.33	2.68–6.97	**<0.001**	4.27	2.63–6.91	**<0.001**
High-increasing	154 (61.1)	13.48	6.54–27.79	**<0.001**	13.11	6.30–27.31	**<0.001**
Central obesity							
Low-increasing	97 (15.5)	1.00			1.00		
Moderate-increasing	503 (53.3)	4.34	2.99–6.31	**<0.001**	4.44	3.04–6.49	**<0.001**
High-increasing	240 (95.2)	49.60	21.65–113.66	**<0.001**	54.83	23.65–127.10	**<0.001**
Raised TG							
Low-increasing	109 (17.4)	1.00			1.00		
Moderate-increasing	328 (34.8)	2.06	1.46–2.91	**<0.001**	2.00	1.41–2.83	**<0.001**
High-increasing	138 (54.8)	3.74	2.05–6.83	**<0.001**	3.48	1.90–6.40	**<0.001**
Reduced HDL-C							
Low-increasing	200 (31.9)	1.00			1.00		
Moderate-increasing	454 (48.1)	1.99	1.46–2.73	**<0.001**	2.04	1.49–2.80	**<0.001**
High-increasing	152 (60.3)	3.18	1.80–5.60	**<0.001**	3.20	1.80–5.68	**<0.001**
Raised FBG or DM							
Low-increasing	18 (2.9)	1.00			1.00		
Moderate-increasing	76 (8.1)	2.31	1.21–4.41	**0.01**	2.24	1.17–4.29	**0.02**
High-increasing	49 (19.4)	5.11	1.90–13.76	**0.001**	4.89	1.81–13.20	**0.002**
Raised BP or HT							
Low-increasing	141 (22.5)	1.00			1.00		
Moderate-increasing	360 (38.1)	1.82	1.30–2.55	**<0.001**	1.85	1.31–2.60	**<0.001**
High-increasing	137 (54.4)	3.37	1.85–6.11	**<0.001**	3.39	1.85–6.19	**<0.001**

BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; MetS, metabolic syndrome; OR, Odds ratio; TG, triglyceride. Model 1: adjusted for sex, age in 1987, and mean BMI. Model 2: model 1 + smoking habits, alcohol consumption, marital status, and physical activity in 2017. Values in bold are statistically significant. [a]ORs were calculated by the logistic regression models and defined as the relative ratios for a given class versus the low-increasing group.

Table 3: **ORs and 95% CIs of incident MetS by BMI trajectories.**

childhood through adolescence to predict the incidence of MetS in midlife is mainly determined by its effectiveness in identifying central obesity. Conversely, the predictive value of BMI variability during the formative years is more sensitive, including relevant subfactors such as central obesity, elevated TG, reduced HDL-C levels, hyperglycemia, and hypertension.

The relationship between obesity and MetS has been widely discussed, and many studies have shown that people with obesity in adolescence are more likely to develop MetS as adults.[14,15] Nonetheless, we still need to find better ways to monitor weight change from childhood to adulthood to assess its predictive role more precisely. Pimenta et al. investigated weight gain from childhood to adolescence/young adulthood and found a higher weight gain was associated with a higher risk of adult MetS.[26] However, the weight change is calculated from the difference between the weight at 5 years and the weight at 20 years. Moreover, the study was conducted using a questionnaire, and selection bias was more likely to affect the conclusion. In another study, from the China Health and Nutrition Survey,[16] the researchers utilized BMI data from 544 participants and a 16-year follow-up period to formulate the BMI trajectory. The findings revealed that a BMI trajectory characterized by more rapid weight gain was correlated with a higher incidence of MetS, which was consistent with our results. However, compared with the previous study, our study has a larger sample, more follow-up times, and much longer follow-up years, so the BMI trajectory model of the participants can be constructed more accurately. Our study confirmed the association between BMI trajectory and the incidence of MetS, independent of the mean BMI values and demographic characteristics such as age, sex, and physical activity level. Furthermore, we found that BMI trajectories from childhood to adolescence were associated with MetS onset in midlife. Combined with our previous findings that childhood to adolescence BMI trajectories can predict the onset of proteinuria in midlife,[27] our study highlights the importance of weight control in childhood to prevent the occurrence of cardiovascular diseases in adulthood. This insight could inform public health policies focused on early intervention strategies. In clinical practice, our findings highlight the need for healthcare providers to emphasize long-term weight

Outcomes/BMI variability	Model 1			Model 2		
	ORs	95% CI	*P* value	ORs	95% CI	*P* value
MetS (vs Normal)						
SD_{BMI}	2.28	2.01–2.59	**<0.001**	2.30	2.02–2.62	**<0.001**
VIM_{BMI}	1.22	1.19–1.26	**<0.001**	1.22	1.19–1.26	**<0.001**
ARV_{BMI}	4.30	3.40–5.43	**<0.001**	4.29	3.38–5.45	**<0.001**
Central obesity (vs Normal)						
SD_{BMI}	4.25	3.60–5.02	**<0.001**	4.44	3.74–5.26	**<0.001**
VIM_{BMI}	1.41	1.36–1.47	**<0.001**	1.43	1.37–1.48	**<0.001**
ARV_{BMI}	15.12	11.14–20.52	**<0.001**	16.31	11.88–22.38	**<0.001**
Raised TG (vs Normal)						
SD_{BMI}	1.61	1.45–1.78	**<0.001**	1.61	1.45–1.78	**<0.001**
VIM_{BMI}	1.12	1.10–1.15	**<0.001**	1.12	1.10–1.15	**<0.001**
ARV_{BMI}	2.33	1.93–2.81	**<0.001**	2.32	1.92–2.81	**<0.001**
Reduced HDL-C (vs Normal)						
SD_{BMI}	1.45	1.31–1.59	**<0.001**	1.46	1.33–1.61	**<0.001**
VIM_{BMI}	1.09	1.07–1.12	**<0.001**	1.10	1.07–1.12	**<0.001**
ARV_{BMI}	2.07	1.74–2.47	**<0.001**	2.11	1.76–2.52	**<0.001**
Raised FBG or DM (vs Normal)						
SD_{BMI}	1.49	1.28–1.73	**<0.001**	1.51	1.30–1.75	**<0.001**
VIM_{BMI}	1.10	1.07–1.15	**<0.001**	1.11	1.07–1.15	**<0.001**
ARV_{BMI}	1.71	1.30–2.26	**<0.001**	1.72	1.30–2.28	**<0.001**
Raised BP or HT (vs Normal)						
SD_{BMI}	1.52	1.38–1.68	**<0.001**	1.53	1.38–1.69	**<0.001**
VIM_{BMI}	1.11	1.08–1.13	**<0.001**	1.11	1.08–1.13	**<0.001**
ARV_{BMI}	2.15	1.79–2.58	**<0.001**	2.18	1.81–2.62	**<0.001**

ARV, average real variability; BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; MetS, metabolic syndrome; OR, Odds ratio; SD, standard deviation; TG, triglyceride; VIM, variability independent of the mean. Model 1: adjusted for sex, age in 1987, and mean BMI. Model 2: model 1 + smoking habits, marital status, alcohol consumption, and physical activity in 2017. Values in bold are statistically significant.

Table 4: **ORs and 95% CIs of incident MetS by BMI variability.**

management plans for patients rather than relying solely on short-term solutions to reduce the risk of MetS.

The health significance of BMI variability in MetS in the general population has received little attention. Although there is much literature on body weight variability, we still need to realize that short-term variability may refer to the weight cycle more, which is affected by diet and exercise status.[28–30] Long-term variability, such as weight variability over decades, focuses more on the natural changes in an individual's weight over the life course.[12,14,31] Nevertheless, consistent with prior studies,[32,33] we observed positive associations of BMI variability with MetS and its related indicators. What's more, in the Framingham Heart Study,[12] researchers also observed that high variability in BMI was significantly associated with obesity or metabolic unhealthy status, but only in normal-weight participants. Childhood body weight should be equally considered as a metabolic risk in adulthood.[34,35] In our study, we calculated BMI variability based on the first four visits, when the participants grew from childhood to adolescence. We observed that higher variability of BMI in childhood was associated with an increased risk of MetS in middle age. This finding provides more direct evidence that maintaining a stable weight in childhood reduces metabolic risks in adulthood. Future longitudinal studies involving diverse populations are necessary to validate and expand upon our findings, Future research should also explore the biological mechanisms underlying the association between BMI variability and MetS.

The present study has several notable strengths. We meticulously tracked a substantial prospective cohort over 30 years, effectively capturing the shifts in weight patterns that occurred in tandem with China's reform and opening up. From the outset, our cohort encompassed children and adolescents who subsequently underwent a series of regular follow-ups. This affords us a distinctive opportunity to probe the impact of weight fluctuations in early life on the risk of MetS during middle age. However, this study also had several limitations. Due to the absence of blood samples collected during participant recruitment, we could not identify individuals diagnosed with MetS for exclusion purposes. Nevertheless, it is essential to note that given China's relatively nascent economic development

during the 1990s, the incidence of MetS remained notably low. Consequently, its potential influence was limited. Furthermore, we adopted a systematic sampling approach in 2005 by randomly selecting only 436 participants from the entire population for follow-up visits, potentially introducing some bias. Nevertheless, it is worth noting that all 1824 participants had a minimum of three BMI measurements in 1987, 1989, 1992, and 1995, along with two measurements each in 2013 and 2017. Notably, in our sensitivity analysis, the exclusion of data from the year 2005 yielded no discernible changes in the observed outcomes. Finally, all the recruited participants were Han Chinese from northern China. Therefore, our findings may not apply to other populations.

In conclusion, our study revealed that early-life BMI trajectories and BMI variability are independently associated with the incidence of MetS in midlife. The findings signal a need for longitudinal and continuous screening for higher BMI and obesity, which may help achieve early identification of individuals at risk for developing cardiovascular diseases in middle age.

Contributors

Conceptualization, Tongshuai Guo, Duolao Wang, and Jianjun Mu; methodology, Tongshuai Guo, Sirui Zheng, Tao Chen; formal analysis, Tongshuai Guo, Sirui Zheng, Duolao Wang; investigation, Tongshuai Guo, Chao Chu, Jie Ren, Yue Sun, Yang Wang, Mingjun He, Yu Yan, Mingfei Du, Hao Jia, Yueyuan Liao, Yumeng Cao, Dan Wang; writing original draft preparation, Tongshuai Guo; writing review and editing, Jianjun Mu, Duolao Wang; supervision, Zuyi Yuan. All authors have read, critically revised and agreed to the published version of the manuscript.

Data sharing statement

The dataset used in this study is available when the publication is online from the corresponding authors (email: mujjun@163.com.) on reasonable request without any additional restrictions.

Declaration of interests

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102486.

References

1 O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev*. 2015;16(1):1–12.
2 Lu Y, Li XM, Liu YT, et al. Trends in prevalence and treatment of metabolic syndrome and individual components by race/ethnicity, 1999-2020. *Circulation*. 2022;146:3.
3 Li XL, Li XL, Lin HL, et al. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. *J Clin Neurosci*. 2017;40:34–38.
4 Kurl S, Laaksonen DE, Jae SY, et al. Metabolic syndrome and the risk of sudden cardiac death in middle-aged men. *Int J Cardiol*. 2016;203:792–797.
5 Mente A, Yusuf S, Islam S, et al. Metabolic syndrome and risk of acute myocardial infarction A case-control study of 26,903 Subjects from 52 countries. *J Am Coll Cardiol*. 2010;55(21):2390–2398.
6 He Y, Li Y, Bai G, et al. Prevalence of metabolic syndrome and individual metabolic abnormalities in China, 2002-2012. *Asia Pac J Clin Nutr*. 2019;28(3):621–633.
7 Ma A, Fang K, Dong J, Dong Z. Prevalence and related factors of metabolic syndrome in Beijing, China (Year 2017). *Obes Facts*. 2020;13(6):538–547.
8 Liu B, Chen G, Zhao R, Huang D, Tao L. Temporal trends in the prevalence of metabolic syndrome among middle-aged and elderly adults from 2011 to 2015 in China: the China health and retirement longitudinal study (CHARLS). *BMC Public Health*. 2021;21(1):1045.
9 Du Z, Xing L, Liu S, et al. Prevalence and determinants of metabolic syndrome based on three definitions in rural northeast China. *Public Health Nutr*. 2020;23(18):3379–3386.
10 Calling S, Johansson SE, Nymberg VM, Sundquist J, Sundquist K. Trajectories of body mass index and risk for coronary heart disease: a 38-year follow-up study. *PLoS One*. 2021;16(10):14.
11 Lee SR, Choi EK, Han KD, Lee SH, Oh S. Effect of the variability of blood pressure, glucose level, total cholesterol level, and body mass index on the risk of atrial fibrillation in a healthy population. *Heart Rhythm*. 2020;17(1):12–19.
12 Sponholtz TR, van den Heuvel ER, Xanthakis V, Vasan RS. Association of variability in body mass index and metabolic health with cardiometabolic disease risk. *J Am Heart Assoc*. 2019;8(7):30.
13 Zheng Y, Song MY, Manson JE, Giovannucci EL, Hu FB. Group-based trajectory of body shape from ages 5 to 55 years and cardiometabolic disease risk in 2 US cohorts. *Am J Epidemiol*. 2017;186(11):1246–1255.
14 Sun JH, Xi B, Yang LL, Zhao M, Juonala M, Magnussen CG. Weight change from childhood to adulthood and cardiovascular risk factors and outcomes in adulthood: a systematic review of the literature. *Obes Rev*. 2021;22(3):15.
15 Giudici KV, Rolland-Cachera MF, Gusto G, et al. Body mass index growth trajectories associated with the different parameters of the metabolic syndrome at adulthood. *Int J Obes*. 2017;41(10):1518–1525.
16 Ying M, Hu XM, Li Q, Dong HJ, Zhou YL, Chen ZJ. Long-term trajectories of BMI and cumulative incident metabolic syndrome: a cohort study. *Front Endocrinol*. 2022;13:9.
17 Chu C, Dai Y, Mu JJ, et al. Associations of risk factors in childhood with arterial stiffness 26 years later: the Hanzhong adolescent hypertension cohort. *J Hypertens*. 2017;35:S10–S15.
18 Zheng WL, Mu JJ, Chu C, et al. Association of blood pressure trajectories in early life with subclinical renal damage in middle age. *J Am Soc Nephrol*. 2018;29(12):2835–2846.
19 Wang Y, Zhao P, Chu C, et al. Associations of long-term visit-to-visit blood pressure variability with subclinical kidney damage and albuminuria in adulthood: a 30-year prospective cohort study. *Hypertension*. 2022;79(6):1247–1256.
20 Alberti K, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. *Lancet*. 2005;366(9491):1059–1062.
21 Herrera-Enriquez K, Narvaez-Guerra O. Discordance of metabolic syndrome and abdominal obesity prevalence according to different criteria in Andean highlanders: a community-based study. *Diabetes Metab Syndr*. 2017;11(Suppl 1):S359–S364.
22 Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2018;27(7):2015–2023.
23 Dai H, Li F, Bragazzi NL, et al. Distinct developmental trajectories of body mass index and diabetes risk: a 5-year longitudinal study of Chinese adults. *J Diabetes Investig*. 2020;11(2):466–474.
24 Jones BL, Nagin DS. A note on a Stata plugin for estimating group-based trajectory models. *Sociol Methods Res*. 2013;42(4):608–613.
25 Yano Y. Visit-to-visit blood pressure variability—what is the current challenge? *Am J Hypertens*. 2017;30(2):112–114.
26 Pimenta AM, Beunza JJ, Sanchez-Villegas A, Bes-Rastrollo M, Martinez-Gonzalez MA. Childhood underweight, weight gain during childhood to adolescence/young adulthood and incidence of

adult metabolic syndrome in the SUN (Seguimiento Universidad de Navarra) project. *Public Health Nutr*. 2011;14(7):1237–1244.
27 Wang Y, Li F, Chu C, et al. Early life body mass index trajectories and albuminuria in midlife: a 30-year prospective cohort study. *eClinicalMedicine*. 2022;48:11.
28 Montani J-P, Viecelli A, Prévot A, Dulloo AG. Weight cycling during growth and beyond as a risk factor for later cardiovascular diseases: the 'repeated overshoot'theory. *Int J Obes*. 2006;30(4):S58–S66.
29 Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med*. 2017;376(14):1332–1340.
30 Kim MK, Han K, Park YM, et al. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation*. 2018;138(23):2627–2637.
31 Zhang Y, Yatsuya H, Li Y, et al. Long-term weight-change slope, weight fluctuation and risk of type 2 diabetes mellitus in middle-aged Japanese men and women: findings of Aichi Workers' Cohort Study. *Nutr Diabetes*. 2017;7:5.
32 Montani JP, Schutz Y, Dulloo AG. Dieting and weight cycling as risk factors for cardiometabolic diseases: who is really at risk? *Obes Rev*. 2015;16(Suppl 1):7–18.
33 Dulloo AG, Montani JP. Pathways from dieting to weight regain, to obesity and to the metabolic syndrome: an overview. *Obes Rev*. 2015;16:1–6.
34 Bornhorst C, Tilling K, Russo P, et al. Associations between early body mass index trajectories and later metabolic risk factors in European children: the IDEFICS study. *Eur J Epidemiol*. 2016;31(5):513–525.
35 Petkeviciene J, Klumbiene J, Kriaucioniene V, Raskiliene A, Sakyte E, Ceponiene I. Anthropometric measurements in childhood and prediction of cardiovascular risk factors in adulthood: kaunas cardiovascular risk cohort study. *BMC Public Health*. 2015;15:8.