# Early life body mass index trajectories and albuminuria in midlife: A 30-year prospective cohort study

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## Summary

**Background** Albuminuria is a marker of vascular dysfunction and is associated with chronic renal and cardiovascular diseases. Data on the association between the longitudinal patterns of weight change early in life and albuminuria later in life are limited. We aimed to identify the body mass index (BMI) trajectory across a 30-year span and evaluate its association with middle-age albuminuria.

**Methods** Of the 4623 participants aged 6−18-year-old recruited by Hanzhong Adolescent Hypertension Study cohort in northern China from March 10, 1987 to June 3, 2017, a total of 1,825 participants followed up with 6 visits over 30 years were enrolled. Group-based trajectory modeling was used to identify distinct BMI trajectories in longitudinal analyses. Albuminuria was defined as a urinary albumin-to-creatinine ratio (uACR) ≥ 30 mg/g.

**Findings** Three distinct BMI trajectories were identified: low-increasing ($n$ = 671, 36.8%), moderate-increasing ($n$ = 940, 51.5%), and high-increasing ($n$ = 214, 11.7%); male participants exhibited a steeper increase in BMI than females. The uACR was increased linearly from the low- to high-increasing group. A total of 201 individuals developed albuminuria, with an incidence of 11.0%. Compared with the low-increasing group, the odds ratio (OR) of albuminuria in middle age was 2.13(95% confidence interval [CI]: 1.26 to 3.61) for the high-increasing group after full adjustment for age, sex, smoking, alcohol consumption, marital status, systolic blood pressure, diabetes, and hyperlipidemia. The unadjusted ORs of the high-increasing BMI group were 5.08 (2.76−9.37) for males and 3.45 (1.78 −6.69) for females, and the association remained significant in males in the fully adjusted models.

**Interpretation** Higher BMI trajectories are associated with higher uACR and an increased risk of albuminuria in middle age, especially in males. Identifying long-term BMI trajectories from an early age may assist in predicting the risk of renal diseases and cardiovascular disease later in life.

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Keywords: BMI trajectories; Childhood; Albuminuria; Middle age; Longitudinal cohort

## Research in context

### *Evidence before this study*

Albuminuria is an early sign of vascular dysfunction and is related with mortality, cardiovascular disease, and chronic renal disease. High body mass index (BMI) is identified with increased risk of albuminuria in the general adults. We searched PubMed using the Mesh terms "body mass index", ("albuminuria" or "albuminurias"), and ("middle age" or "middle aged") for articles without language restriction published up to April 3, 2022. Most available evidence on the association between BMI and albuminuria either had small sample sizes, were cross-sectional studies, or relied on single measurements of BMI, and only two studies revealed the associations between the longitudinal patterns of BMI change and subclinical kidney damage. The association and sex-differences of the trajectory of BMI from childhood onwards with albuminuria as well as urine albumin-to-creatinine ratio (uACR) 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 3 BMI measurements during follow-up and midlife albuminuria test. We identified three distinct BMI trajectories as low-increasing (36.8%), moderate-increasing (51.5%), and high-increasing (11.7%). We provide evidence that high BMI trajectory from childhood to adults is associated with higher uACR level and albuminuria risk, and such association remained in males in multivariable models.

### *Implications of all evidence available*

The findings signal a need for longitudinal and continuous screening for higher BMI and obesity through childhood to adults, early life BMI management may be helpful for delaying of developing CVD and CKD in midlife.

## Introduction

Cardiovascular disease (CVD) has become the leading cause of global mortality and is a major contributor to reduced quality of life. Effective primary prevention strategies for cardiovascular disease require early identification of high-risk groups and early intervention in these groups to achieve better results and reduce the burden of cardiovascular disease.[1,2] Albuminuria is a marker of vascular dysfunction and is correlated with the risk of all-cause mortality, CVD, and chronic kidney disease (CKD).[3–6] Albuminuria commonly occurs in 70% of young adults with normal blood pressure and glucose, suggesting an earlier onset of albuminuria than traditional cardiovascular risk factors.[7] Therefore, it is essential to identify risk factors for the development of albuminuria as early as possible.

Obesity is an established risk factor for hypertension, diabetes, CVD, and CKD.[8–12] Many studies have identified an increased risk of albuminuria with higher body mass index (BMI) in the general adult population.[13–15] Obesity begins in childhood, and childhood BMI predicts obesity and other long-term health outcomes in adulthood.[16,17] Thus, a better understanding of the associations of childhood BMI and BMI trajectories from childhood to middle age with albuminuria could provide strategies to prevent CVD, CKD, and all-cause mortality. Currently, only two studies have investigated the associations between BMI trajectories from childhood to adulthood and the risk of subclinical renal damage.[18,19] Detailed knowledge particularly sex differences of the relationship between the BMI trajectory from childhood onward and albuminuria as well as urinary albumin-to-creatinine ratio (uACR) levels in middle age needs further exploration.

Here, we used data from the ongoing Hanzhong Adolescent Hypertension Study cohort, which recruited children and adolescents in 1987 and followed up with them for 30 years, to identify population subgroups with similar BMI trajectories from childhood to middle age and reveal the relationship between early-life BMI trajectories and the incidence of albuminuria in middle age.

## Materials and methods

### Study cohort

This study was conducted with data from the Hanzhong Adolescent Hypertension Study, a population-based cohort study in northern China conducted from March 10, 1987 to June 3, 2017. The study began in 1987 when 4623 school children were enrolled from 26 rural sites in three towns (Qili, Laojun, and Shayan) in Hanzhong, Shanxi, China. During the baseline survey, the

inclusion criteria were as follows: participants aged 6–18 years old, free of chronic disease according to medical records, able to communicate frequently in Mandarin, and those who volunteered to participate in this study. Participants were excluded if they or their parents/guardians were unwilling to participate in the study or if they had a chronic disease according to the clinical data or self-report. Thereafter, we followed up the cohort in 1989, 1992, 1995, 2005, 2013, and 2017, resulting in a maximum follow-up time of 30 years (**Supplemental Figure 1**). During follow-up, we randomly selected every tenth participant ($K = 10$) from the large cohort using an isometric sampling method in 2005 and obtained BMI and other data from 436 individuals. Except for the visit in 2005, other follow-ups were large in scale and aimed to reach each individual who was enrolled in 1987. The response rate was 77·7% ($n = 3592$) in 1989, 84·8% ($n = 3918$) in 1992, 82·1% ($n = 3794$) in 1995, 65·3% ($n = 3018$) in 2013, and 60·1% ($n = 2780$) in 2017. The main reasons why participants were not reached to follow-up included their occupation (migrant workers or military service), emigration, or accidental death. The details of this study have previously been published.[20–23] No significant differences in baseline characteristics were observed between those who were lost at follow-up and those who remained in the study (**Supplemental Table 1**).

In the present study, to model BMI trajectories from childhood to middle age and further explore whether the early-life BMI trajectory could predict albuminuria in middle age, we included only participants with at least 3 BMI measurements during the follow-up period (1987–2017). In addition, we excluded data derived from only the four initial visits (1987, 1989, 1992, and 1995) or only the last three visits (2005, 2013, and 2017). Participants with incomplete age, sex, weight, height, estimated glomerular filtration rate (eGFR), and uACR data were also excluded (**Supplemental Figure 2**).

The 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 signed informed consent for each visit; for those <18 years of age at baseline, parent/guardian consent was obtained. This study adhered to the principles of the Declaration of Helsinki, and all study procedures were performed in accordance with institutional guidelines. This study was adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

### Data collection

Personal information, including demographic characteristics (age, sex, and marital status), personal and family medical history, physical activity, cigarette smoking, and alcohol consumption, was obtained from a questionnaire as previously described.[20–23] Body weight and height were measured by an automated instrument to the nearest 0·1 kg or 0·1 cm, respectively, while the participants wore light clothes and no shoes.[20] Replicate measurements were made twice, and the mean values were used for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height (kilograms per meter squared).

### Blood pressure measurement

Blood pressure (BP) was measured by three trained staff members using a standard mercury sphygmomanometer as described previously.[20,21,24,25] BP staff were blinded to the study design. The subjects were instructed to refrain from drinking alcohol, coffee or tea, smoking cigarettes, and exercising for at least 30 min prior to their BP measurement. Systolic BP (SBP) and diastolic BP (DBP) were determined as the first and fifth Korotkoff sounds, respectively.

### Blood biochemical analyses

Blood samples were obtained by peripheral venous puncture, immediately centrifuged at 3000 × *g* for 10 min, and then stored at −80 °C until analysis. Levels of total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum creatinine, and blood glucose were measured using an automatic biochemical analyzer (Model 7600; Hitachi, Ltd., Tokyo, Japan). Serum uric acid (SUA) levels were measured with a Hitachi clinical chemistry analyzer with the uricase HMMPS method. Five samples were used to evaluate the intra-assay and inter-assay coefficients of variation (CVs), which ranged from 2·3% to 4·5% and from 3·2% to 6·4%, respectively.

### Urinary biochemical analyses

A morning fasting midstream urine sample was collected from each participant and frozen at −20 °C to −40 °C. All urine samples were shipped in ambient packaging with the use of iceboxes to the clinical laboratory at the First Affiliated Hospital of Xi'an Jiaotong University in Xi'an, China. Urinary creatinine and albumin levels were measured by an automatic biochemical analyzer (Hitachi, Ltd., Japan) at a certified clinical lab. The intra- and inter-assay CVs were 1·25% and 2·17% for urinary creatinine and 0·64% and 2·13% for urinary albumin, respectively.

### Definitions

Participants who reported continuous or cumulative smoking for 6 months or more during their lifetime were categorized as cigarette smokers.[26] Participants were categorized as consuming alcohol if they reported that they consumed alcohol (liquor, beer, or wine) every day for at least 6 months.[24] Marital status was defined

as subjects who were married, divorced, or widowed.[25] Physical inactivity was defined as engaging in mild to moderate physical activity <3 h per week.[22] Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or the use of antihypertensive drugs according to the clinical data or self-reports.[27] Participants with diabetes were defined as having fasting blood glucose at least 7·0 mmol/L, currently taking antidiabetic medications or those with a previous history of diabetes mellitus.[28] Hyperlipidemia was defined as the occurrence of any one of the following four situations: hypertriglyceridemia (TG ≥ 2·26 mmol/L), hypercholesterolemia (TC ≥ 6·22 mmol/L), high levels of LDL (≥ 4·14 mmol/L), or low levels of HDL (≤ 1·04 mmol/L).[29] eGFR was calculated using the Modification of Diet in Renal Disease formula: $eGFR=175 \times \text{serum creatinine}^{-1.234} \times \text{age}^{-0.179}$ (× 0·79 for girls/women), where the serum creatinine concentration is in milligrams per deciliter, and age is in years.[30] The uACR was calculated as urine albumin in milligrams divided by the urine creatinine in millimoles (milligrams per millimole).[31] Albuminuria was defined as uACR ≥ 30 mg/g.[31]

### Statistical analyses

All statistical analyses were performed with Stata software version 16·0 (Stat Corp., College Station, Texas, USA). Group-based trajectory modeling (GBTM) was conducted to identify distinct BMI groups, in which individuals exhibited specific developmental changes over time.[32,33] We used the Stata "Traj" plugin to display age-scaled BMI trajectories from childhood to middle age.[34,35] The identification of the best-fitting model involved a 3-stage procedure. First, we selected a fit model according to the distribution of the variable. As BMI is considered a continuous variable, we chose a censored normal (cnorm) model to fit the trajectories. Second, we determined the numbers of the trajectory clusters and the shapes of the BMI trajectories. We assumed that BMI trajectories could be classified into 2 to 5 clusters. Next, we repeatedly fitted each trajectory with different shapes. The shape of each trajectory is presented as 0, 1, 2, or 3 (0=intercept, 1=linear, 2=quadratic, and 3=cubic). Model fit was generally initiated with a quadratic polynomial, and then the fit according to the Bayesian Information Criterion (BIC) was compared with different trajectory numbers. The lowest absolute BIC value indicates a good model fit as it balances the model complexity *versus* goodness of fit to the sample data. Based on the determination of the number of trajectory groups, the shape combination was adjusted, and the BIC was used to determine the most suitable trajectory. Third, we evaluated the best-fitted model. In addition to the BIC information, the optimal model should meet a higher average posterior probability >70%. To ensure that each trajectory group had a certain distribution, the group sample size should be >5%. Finally, we identified the three best fitting trajectories with cubic order terms.

Data are expressed as the geometric means (interquartile ranges) for non-normally distributed values, and as percentages. The differences between the groups were calculated using $\chi^2$-tests, Student's t tests, and Mann–Whitney tests as appropriate. An analysis of variance (ANOVA) was used to test the linearity across trajectories. The *P* trend test used the linear trend test for continuous variables and the Cuzick trend test for categorical variables. Univariate logistic regression analysis was conducted to screen for potential covariates. Multivariate logistic regression analyses were applied to examine the association between the BMI trajectory and albuminuria risk, presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The Cochran Armitage test was used to investigate whether there was a trend difference in albuminuria incidence among the BMI trajectories. To include potential covariates, variables traditionally or clinically thought to affect the risk of albuminuria, such as drug use or metabolic diseases, were added to the multivariate logistic regression analysis. We used several models in multivariate logistic analyses. Model 1 was unadjusted; Model 2 adjusted for sex and age in 2017; Model 3 further adjusted for smoking, alcohol consumption, marital status, SBP, diabetes, and hyperlipidemia in 2017.

To exclude the potential influence of antihypertensive, hypoglycemic, and lipid-lowering medications, we further conducted sensitivity analysis by excluding individuals with diabetes, hypertension, or dyslipidemia under treatment. To exclude the potential bias of middle-age BMI, we conducted a sensitivity analysis by further adjusting for middle-age BMI. In addition, the association of albuminuria with middle-age BMI has also been investigated. Two-sided *P* values <0·05 were considered significant in all analyses.

### Role of the funding source

The funders had no roles in study design, data collection, data analysis, interpretation of the data, as well as in the writing of the report and in the decision to submit the paper for publication. J.-J. M. and Y. L. had full access to the data in the study and had final responsibility for the decision to submit for publication.

## Results

### Study population

In total, data from 1825 participants were included in the trajectory analyses with a follow-up time of 30 years (from childhood to middle age). Males accounted for 58·0% of participants, and the median age in 2017 was 43·0 (40·0–45·0) years. Three distinct trajectories were named according to their morphological characteristics:

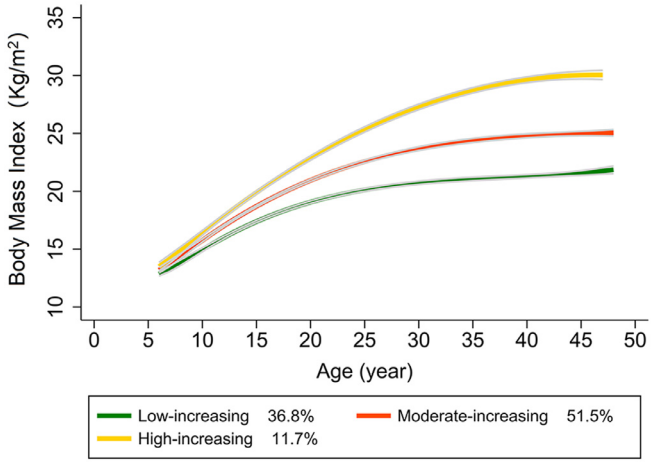


**Figure 1.** Long-term body mass index trajectories from childhood to middle age.

"low-increasing" ($n$ = 671, 36·8%), "moderate-increasing", ($n$ = 940, 51·5%), and "high-increasing" ($n$ = 214, 11·7%), respectively (Figure 1).

### Baseline characteristics of BMI trajectories from childhood to middle age

The age-scaled BMI levels of each trajectory are presented in Table 1. Higher BMI levels were positively correlated with elevated age and BMI trajectory. Individuals with higher BMIs tended to have higher SBP and DBP as well as levels of blood glucose, total cholesterol, triglycerides, LDL, SUA, and serum creatinine but lower HDL levels and eGFR. These individuals also tended to have a higher prevalence of hypertension, diabetes, hyperuricemia, smoking, and alcohol consumption (Table 2). The levels of uACR in the three BMI trajectory groups (low-increasing, moderate-increasing, and high-increasing) were 7·5 (5·0−12·6), 8·8 (5·7−15·4), and 13·8 (7·0−28·0), respectively ($P$ for trend=0·0031) (Figure 2).

### Association between BMI trajectory from childhood to middle age and albuminuria incidence

Over the 30-year follow-up, a total of 201 participants developed albuminuria, for an incidence rate of 11·0%. The incidences of albuminuria in the BMI trajectory groups from low- to high-increasing were 6·7%, 11·4%, and 22·9%, respectively ($P$ for trend <0·0001). Compared with the low-increasing group, the ORs (95% CIs) of albuminuria in moderate- and high-increasing groups were 1·86 (1·29−2·68) and 4·25 (2·73−6·62) ($P$ for trend < 0·0001), respectively, in the model adjusted for age and sex. In the multivariate model that further adjusted for smoking, alcohol consumption, marital status, SBP, diabetes, and hyperlipidemia in 2017, the ORs (95% CIs) of the latter two groups were 1·41 (0·93−2·14) and 2·13 (1·26−3·61), respectively ($P$ for trend=0·0053) (Table 3, **Supplemental Table 2**). Furthermore, we conducted post hoc comparisons. The results showed significant differences among the three groups ("low-increasing" *vs.* "moderate-increasing", $P$ = 0·014; "low-increasing" *vs.* "high-increasing",

| Groups | Low-increasing | Moderate-increasing | High-increasing |
|---|---|---|---|
| **N (%)** | 671 (36.8%) | 940 (51.5%) | 214 (11.7%) |
| **6−10, years** | 14.3 (13.8−15.1) | 15.0 (14.4−15.7) | 15.7 (15.0−16.1) |
| **11−15, years** | 16.2 (15.3−17.2) | 17.3 (16.4−18.5) | 18.1 (17.0−19.3) |
| **16−20, years** | 18.6 (17.6−19.7) | 20.4 (19.3−21.4) | 21.6 (20.3−22.3) |
| **21−25, years** | 19.4 (18.6−20.3) | 21.3 (20.2−22.5) | 23.4 (22.2−24.2) |
| **26−30, years** | 19.7 (18.4−21.0) | 22.7 (21.3−24.2) | 25.6 (23.8−27.4) |
| **31−35, years** | 20.8 (19.6−21.9) | 24.6 (23.3−25.6) | 28.4 (27.3−29.9) |
| **36−40, years** | 21.3 (20.1−22.1) | 24.9 (23.5−26.1) | 29.1 (28.1−30.6) |
| **41−45, years** | 21.4 (20.2−22.6) | 24.8 (23.6−26.3) | 29.2 (28.3−31.0) |
| **46−48, years** | 21.6 (20.4−22.7) | 24.9 (23.8−26.9) | 29.3 (28.6−30.7) |

***Table 1*: BMI (kg/m$^2$) levels by age periods in BMI trajectory groups from childhood to middle age.**
Non-normally distributed variables are expressed as the median (inter-quartile range). BMI, body mass index.

| Variables | Total | Low-increasing | Moderate-increasing | High-increasing | *P* for trend |
|---|---|---|---|---|---|
| **Baseline in 1987** | | | | | |
| **Boys (%)** | 1058 (58.0%) | 346 (51.6%) | 576 (61.3%) | 136 (63.6%) | <0.0001 |
| **Girls (%)** | 767 (42.0%) | 325 (42.4%) | 364 (47.5%) | 78 (10.2%) | <0.0001 |
| **Age, year** | 13 (10–15) | 13 (10–15) | 13 (10–15) | 12 (9–14) | 0.150 |
| **BMI, kg/m$^2$** | 16.3 (15.0–18.2) | 15.5 (14.4–17.2) | 16.7 (15.4–18.6) | 17.2 (15.5–19.3) | <0.0001 |
| **Follow-up in 2017** | | | | | |
| **Age, year** | 43 (40–45) | 43 (40–45) | 43 (40–45) | 42 (39–44) | 0.150 |
| **BMI, kg/m$^2$** | 23.9 (21.9–26.1) | 21.4 (20.2–22.5) | 24.8 (23.6–26.2) | 29.1 (28.3–30.8) | <0.0001 |
| **Smoking (%)** | 807 (44.4%) | 268 (40.2%) | 429 (45.8%) | 110 (51.6%) | 0.0020 |
| **Alcohol consumption (%)** | 541 (29.8%) | 167 (25.0%) | 308 (32.9%) | 66 (31.0%) | 0.0090 |
| **Marital status (%)** | 1704 (98.6%) | 621 (98.1%) | 879 (98.9%) | 204 (99.0%) | 0.199 |
| **Physical inactivity (%)** | 120 (10.9%) | 45 (11.0%) | 55 (9.7%) | 20 (15.6%) | 0.414 |
| **Hypertension (%)** | 392 (21.6%) | 74 (11.1%) | 231 (24.7%) | 87 (40.9%) | <0.0001 |
| **Diabetes (%)** | 83 (4.6%) | 21 (3.2%) | 38 (4.1%) | 24 (11.3%) | <0.0001 |
| **Hyperlipidemia (%)** | 799 (43.9%) | 192 (28.7%) | 466 (49.7%) | 141 (65.9%) | <0.0001 |
| **SBP, mmHg** | 121.7(112.7–131.7) | 116.7(109.0–126.7) | 123.3(114.7–133.0) | 129.3(119.7–143.7) | <0.0001 |
| **DBP, mmHg** | 76.3(69.3–84.3) | 73.0(66.3–80.3) | 77.7(70.3–85.3) | 82.7(75.0–90.7) | <0.0001 |
| **Heart rate, beats/min** | 74(67–80) | 74(66–81) | 73(66–79) | 75(70–82) | 0.486 |
| **Fasting glucose, mmol/l** | 4.58(4.29–4.91) | 4.50(4.22–4.82) | 4.59(4.29–4.92) | 4.79(4.41–5.16) | <0.0001 |
| **Total cholesterol, mmol/l** | 4.50(4.01–5.03) | 4.42(4.02–4.93) | 4.53(4.07–5.05) | 4.62(4.04–5.25) | 0.0001 |
| **Triglycerides, mmol/l** | 1.35(0.97–1.95) | 1.14(0.84–1.54) | 1.47(1.03–2.14) | 1.77(1.34–2.55) | <0.0001 |
| **LDL, mmol/l** | 2.50(2.14–2.91) | 2.44(2.06–2.77) | 2.53(2.17–2.97) | 2.54(2.17–3.08) | <0.0001 |
| **HDL, mmol/l** | 1.14(0.99–1.33) | 1.24(1.06–1.44) | 1.11(0.97–1.27) | 1.04(0.91–1.17) | <0.0001 |
| **SUA, mmol/l** | 282.6(227.6–337.5) | 263.7(214.1–310.6) | 291.3(238.5–342.6) | 319.6(263.4–372.7) | <0.0001 |
| **Serum creatinine, mmol/l** | 76.3(67.5–86.6) | 74.0(64.9–84.9) | 77.1(68.7–87.3) | 78.3(68.2–87.3) | <0.0001 |
| **eGFR, ml/min per 1.73 m$^2$** | 96.8 (86.7–110.3) | 98.4 (87.6–111.6) | 96.0 (86.0–109.3) | 95.3 (87.0–106.8) | 0.018 |

***Table 2*: Demographic characteristics and cardiovascular risk factors by the BMI trajectory groups from childhood to middle age.**
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SUA, serum uric acid; eGFR, estimated glomerular filtration rate. Non-normally distributed variables are expressed as the median (interquartile range) or as numbers (percentage).

$P$ = 0·014; "moderate-increasing" *vs.* "high-increasing", $P$ = 0·021, respectively; **Supplemental Table 3**).

### Association between sex-specific BMI trajectories from childhood to middle age and albuminuria incidence

As shown in **Supplemental Table 4**, males had higher BMI, SBP, DBP, heart rate, and uACR as well as levels of total cholesterol, triglycerides, LDL, SUA, and serum creatinine, and the prevalence of hypertension, diabetes, hyperlipidemia, alcohol consumption, and smoking was also higher in males. From childhood to middle age, male participants clearly exhibited a steeper increase in BMI than females (**Figure 3**). As shown in **Table 4**, the incidence of albuminuria was 106 (10·0%) in male participants and 95 (12·4%) in females. In the univariate analysis, the ORs of the high-increasing BMI group were 2·63 (1·27–5·45) for males and 1·62 (0·73–3·57) for females. After adjustment for multiple confounders, the ORs of albuminuria for males in the moderate- and high-increasing groups were 1·43 (0·77–2·62) and 2·63 (1·27–5·45) ($P$ for trend=0·0090) compared with the low-increasing group; females also tended to show an increased risk of albuminuria according to their BMI trajectory groups (**Table 4**, **Supplemental Table 5**). There was no significant interaction between sex and BMI trajectory on albuminuria risk (in the moderate-increasing, $P$ for interaction=0·977; in the high-increasing group, $P$ for interaction=0·4000).

### Sensitivity analysis

Several sensitivity analyses were performed. First, we excluded participants taking renin-angiotensin-aldosterone system (RAAS) inhibitors ($n$ = 25); the early-life BMI trajectory was still significantly associated with albuminuria incidence (**Supplemental Table 6**). We further excluded all individuals treated for diabetes, hypertension, or dyslipidemia under treatment. A significant association with albuminuria incidence was still observed in all three trajectory groups (**Table 3**). Similar results were observed after adjusting for middle-age BMI (**Supplemental Table 7**). In addition, we further divided the entire population into tertile groups according to middle-age BMI measured in 2017. A higher middle-age BMI tertile was associated with a higher risk of

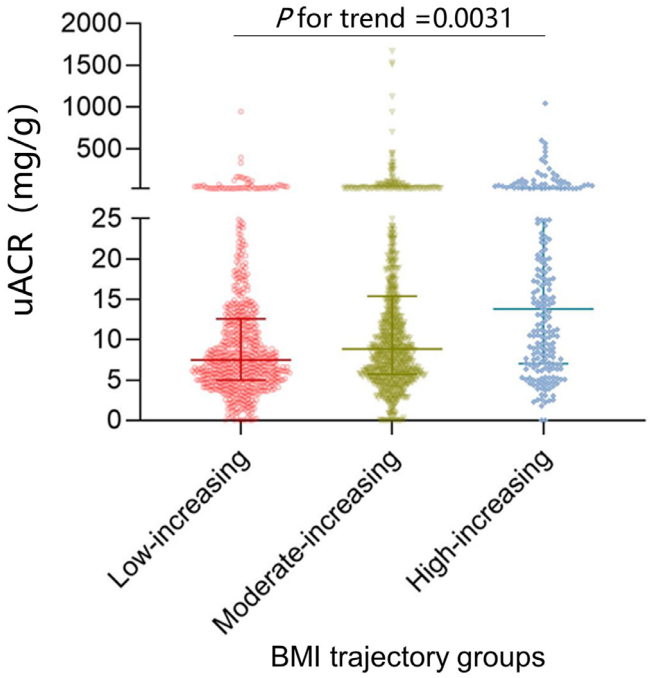


**Figure 2.** The urinary albumin-to-creatinine ratio levels among different body mass index trajectory groups. uACR, urinary albumin-to-creatinine ratio; BMI, body mass index.

| Variables | Low-increasing | Moderate-increasing | High-increasing | *P* for trend |
|---|---|---|---|---|
| **N (%)** | 671 (36.8%) | 940 (51.5%) | 214 (11.7%) | – |
| **Case, n (%)** | 45 (6.7%) | 107 (11.4%) | 49 (22.9%) | <0.0001 |
| **Model 1** | 1.00 | 1.79 (1.24–2.57) | 4.13 (2.66–6.41) | <0.0001 |
| **Model 2** | 1.00 | 1.86 (1.29–2.68) | 4.25 (2.73–6.62) | <0.0001 |
| **Model 3** | 1.00 | 1.41 (0.93–2.14) | 2.13 (1.26–3.61) | 0.0053 |
| **Sensitivity analysis** | 1.00 | 1.48 (0.96–2.27) | 2.08 (1.19–3.62) | 0.011 |

***Table 3*: Associations of BMI trajectories from childhood to middle age with albuminuria.**
Model 1: unadjusted; Model 2: adjusted for sex, age in 2017; Model 3: further adjusted for smoking, alcohol consumption, marital status, systolic blood pressure; diabetes, and hyperlipidemia in 2017. Sensitivity analysis was conducted with Model 3 after exclude participants with diabetes, hypertension or dyslipidemia under treatment ($n = 78$). BMI, body mass index.

albuminuria. Similar results were obtained when we used continuous BMI rather than categorical BMI (**Supplemental Table 8**).

## Discussion

In this study, three distinct BMI trajectories from childhood to middle age were identified by GBTM over a 30-year follow-up; in this period, China began to institute reforms and open up, and people's lifestyles have undergone tremendous changes. A significant association was observed between BMI trajectory and uACR as well as the incidence of albuminuria in middle age (that is, the higher the early-life BMI is, the higher the uACR and risk of albuminuria in middle age).

Elevated uACR and albuminuria are early markers of vascular dysfunction. The Steno hypothesis states that systemic vascular inflammation is accompanied by increased vascular permeability and could result in endothelial damage, albumin escape, and glomerular and tubular damage.[36,37] Additionally, this hypothesis proposes the causal pathophysiological link between CKD and CVD. Several studies have shown that albuminuria is associated with all-cause mortality and CVD in the general population.[38,39] Hillege et al. reported that a 2-fold increase in urinary albumin concentration is associated with a 29% increased risk of CVD

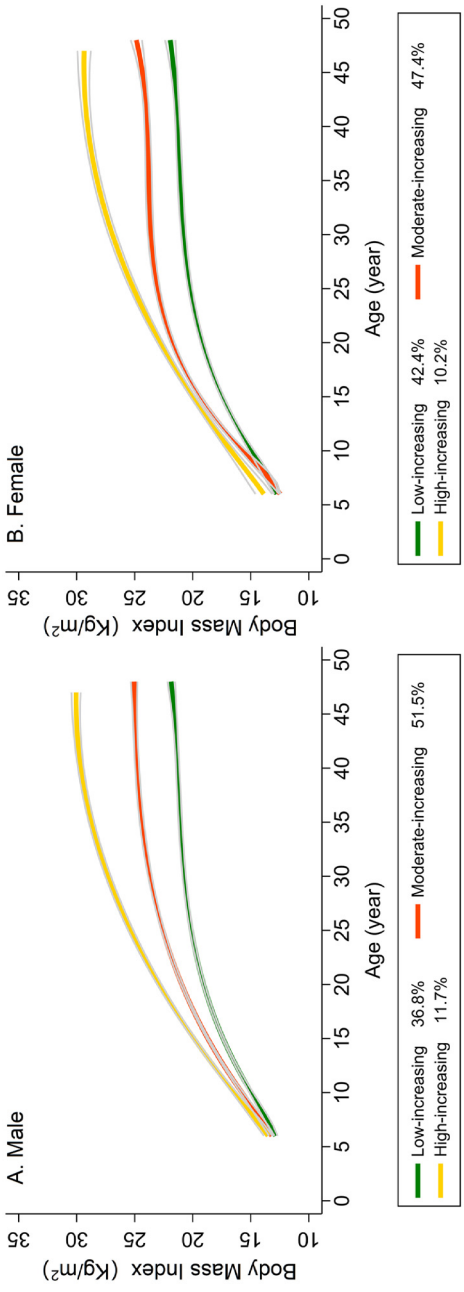


**Figure 3.** Long-term body mass index trajectories from childhood to middle age stratified by sex.

mortality.[38] A systematic review also reported a positive relationship between uACR and mortality.[39] Therefore, early detection of the risk factors for albuminuria or high uACR could benefit the primary prevention of vascular dysfunction, thus delaying the occurrence of CVD and CKD.

Obesity is an established risk factor for hypertension, diabetes, and CVD, and is also increasingly recognized to contribute to albuminuria. Many studies have reported that obesity leads to glomerular hyperfiltration, causing a higher GFR and increased renal blood flow,[40,41] thereby contributing to kidney damage. In addition, obesity increases the secretion of adipokines, which promotes kidney damage by inducing oxidative stress, inflammation, etc.[42] Many clinical studies have confirmed that obesity is a strong risk factor for albuminuria.[11,18,19] A systematic review and meta-analysis confirmed that obesity is also an important independent predictor of CKD in the general population.[11] These associations persist in cross-sectional studies based on patients with chronic diseases such as type 2 diabetes[9] and hypertension.[43] In addition, abdominal obesity was reported to be related to the development of elevated albuminuria in nondiabetic subjects over a 6-year follow-up.[44] However, these studies were conducted based on a single or short-term weight change, which did not adequately reflect the continuous effects of obesity on albuminuria and was susceptible to lifestyle, dietary conditions, and other factors, resulting in differences in the above research results.

Group-based trajectory modeling takes into account variations over time to distinguish changes in BMI over time and heterogeneity within multiple BMI measurements. It assigns individuals that share similar BMI trajectories to the same subgroup on the basis of multiple measurements over a long time period.[32,33] It is an effective approach for studying the life-course association between certain predictors and their potential effects on target organs. Available evidence has shown that continuous and high BMI trajectories over the course of years are closely correlated with diabetes, hypertension, metabolic syndrome and cardiometabolic risk.[34,45–47] Previously, Liu et al. and Yan et al. explored the association between BMI trajectory from childhood and onward and subclinical kidney injury in Australia and China, respectively. They both reported an adverse effect of increased BMI trajectory in childhood on subclinical kidney damage risk in later life.[18,19] In this study, we used GBTM to explore BMI trajectories over 30 years in this cohort, which represented the weight change of the population in the 30 years of reform and opening-up in China, and showed that the BMI trajectory in childhood, adolescence, adulthood, and middle age that exhibited a gradually rising trend was associated with higher uACR and albuminuria risk in later life.

Although the association between BMI trajectories and albuminuria incidence was more prominent in

| Variables | Low-increasing | Moderate-increasing | High-increasing | *P* for trend |
|---|---|---|---|---|
| **Male (*n* = 1058)** | | | | |
| **N (%)** | 346 (32.7%) | 576 (54.4%) | 136 (12.9%) | – |
| **Case, n (%)** | 19 (5.5%) | 56 (9.7%) | 31 (22.8%) | <0.0001 |
| **Model 1** | 1.00 | 1.85 (1.08–3.18) | 5.08 (2.76–9.37) | <0.0001 |
| **Model 2** | 1.00 | 1.85 (1.08–3.17) | 4.88 (2.64–9.03) | <0.0001 |
| **Model 3** | 1.00 | 1.42 (0.77–2.61) | 2.60 (1.25–5.40) | 0.0100 |
| **Sensitivity analysis** | 1.00 | 1.46 (0.77–2.78) | 2.44 (1.10–5.40) | 0.028 |
| **Female (*n* = 767)** | | | | |
| **N (%)** | 325 (42.4%) | 364 (47.4%) | 78 (10.2%) | – |
| **Case, n (%)** | 26 (8.0%) | 51 (14.0%) | 18 (23.1%) | 0.0010 |
| **Model 1** | 1.00 | 1.87 (1.14–3.08) | 3.45 (1.78–6.69) | <0.0001 |
| **Model 2** | 1.00 | 1.88 (1.14–3.10) | 3.46 (1.78–6.71) | <0.0001 |
| **Model 3** | 1.00 | 1.42 (0.80–2.51) | 1.60 (0.73–3.57) | 0.233 |
| **Sensitivity analysis** | 1.00 | 1.50 (0.84–2.68) | 1.71 (0.76–3.82) | 0.193 |

***Table 4*: Associations of BMI trajectories from childhood to middle age with albuminuria by sex.**
Model 1: unadjusted; Model 2: adjusted for sex, age in 2017; Model 3: further adjusted for smoking, alcohol consumption, marital status, systolic blood pressure, diabetes, and hyperlipidemia in 2017. Sensitivity analysis was conducted with Model 3 after exclude participants with diabetes, hypertension or dyslipidemia under treatment ($n$ = 54 for males; $n$ = 24 for females). BMI, body mass index.

males, no significant effect of the interaction between sex and BMI trajectory on albuminuria was observed in our study. Previous studies on the association between obesity and albuminuria in males and females have yielded inconsistent results. Studies from China and Korea have reported that abdominal obesity is related to albuminuria but only in females.[13,15] In contrast, a study from Japan showed that higher BMI was associated with albuminuria only in males.[48] The potential association between sex differences in obesity and albuminuria needs further investigation.

The current study has several strengths. A large prospective cohort was followed over 30 years, thus representing changes in weight after the reform and opening up of China. At baseline, our cohort included children and adolescents who then regularly underwent several follow-ups, providing us with a unique opportunity to investigate the effect of early-life obesity on albuminuria risk in middle age. These findings from a Chinese population with varied BMI have more statistical power than that of previous studies.[18,19] However, this study also had several limitations. All the recruited participants were Han Chinese from northern China. Therefore, our findings may not be applicable to other populations. In addition, we randomly selected only 436 subjects from the whole population to visit in an isometric manner in 2005. However, the analyzed population had three or more BMI measurements, including one or more measurements from visits in 1987, 1989, 1992, and 1995 and at least one measurement in 2005, 2013, and 2017. Indeed, the majority of the 2780 subjects ($n$ = 2350; 84·5%) had five or more BMI measurements. In addition, albuminuria was evaluated on a single spot morning urine sample. Compared with data from a spot morning urine sample, data from 24 h urine samples or multiple samples would provide more stable data for evaluating albumin excretion. However, in the collection of many epidemiological specimens, the use of spot samples is an acceptable alternative for assessing uACR.[49] Finally, there was no significant effect of the interaction between sex and BMI trajectories on albuminuria risk, which could be due to a lack of power given that cases of microalbuminuria increase significantly later in life.

In conclusion, our study revealed that early-life BMI trajectories are independently associated with higher uACR and albuminuria incidence in middle age. The findings signal a need for longitudinal and continuous screening for higher BMI and obesity, which may be helpful for achieving early identification of individuals at risk for developing CVD and CKD in middle age.

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## Contributors

Y.W., Y.L. and J.-J.M. conception and design of research; W.-H.L. and J.-J.M. subject recruitment; Y.W., C.C., X.Z., X.-Y.Z., Y.-Y.L., M.-F.D., T.Z., Q.M., C.C., D. W., K.-K.W., Y.Y., Y.S., G.-L.H., H.J., H.L., Z.-JX.N., R.-C.Y., Z.-Y.M., L.W., W.-J.L., J.Z. and C.-H.L. performed experiments; Y.W., Y.L. and J.-J.M. accessed and verified the underlying data; Y.W., F.L. and Y.L. analyzed data; Y.W., Y.L. and J.C. drafted manuscript; Y.L. R.S. and J.-J.M. edited and revised manuscript. All authors read, critically revised and approved the final version of manuscript.

## Data sharing statement

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

## Declaration of interests

All authors declare no competing interests.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2022.101420.

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