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Childhood body size, adulthood adiposity, underlying mechanisms, and risk of incident hypertension: a prospective cohort study of 180,527 participants

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Abstract

Background Mechanisms underlying the association of life-course adiposity with incident hypertension in adulthood have not been comprehensively investigated. In this study, we aimed to investigate the potential biochemical and metabolomic mechanisms underlying the association between adiposity and incident hypertension.

Methods A total of 180,527 participants from the UK Biobank aged 37 to 73 years were included. Associations of childhood body size or adulthood adiposity status as well as child–adult weight status change with incident adulthood hypertension were estimated by multivariate Cox proportional regression models.

Results Participants with childhood thinner body size and adulthood obesity had the highest risk of incident hypertension (hazard ratio, HR = 3.09, 95% CI = 2.88–3.32) compared with those with "average → normal" pattern, followed by those with "average → obese" pattern (HR = 2.45, 95% CI = 2.31–2.61) and "plumper → obese" pattern (HR = 2.82, 95% CI = 2.62–3.02). Of note, those with "plumper → normal" pattern (HR = 1.11, 95% CI = 1.00–1.23) and "thinner → normal" pattern (HR = 1.17, 95% CI = 1.10–1.24) had the second and third lowest risk of incident hypertension. Adulthood overweight (mediation proportion: 58.7%, 95% CI: 40.4–74.8%) or obesity (mediation proportion = 46.7%, 95% CI: 29.4–64.9%) largely mediated the association between childhood plumper body size and hypertension. The association between adiposity and hypertension was mediated by biochemical indices (e.g., liver function, immunometabolism) and metabolites (e.g., alanine aminotransferase, apolipoprotein A) (mediation proportions ranging from 3.2 to 23.4%).

Conclusions Thinner or plumper body size in childhood increases the risk of incident adulthood hypertension, and adulthood adiposity partly mediated this association, suggesting the importance of maintaining normal weight across the life course. Several biochemical indices and metabolites mediated these associations providing clues to underlying biological mechanisms.

Keywords Childhood, Adulthood, Body size change, Life-course adiposity, Hypertension, Mechanisms

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Background

Obesity is a serious public health problem affecting both children and adults worldwide. According to the World Health Organization (WHO), over 1.9 billion adults and more than 340 million children and adolescents aged 5–19 years were classified as having overweight or obesity in 2016 [1]. There is an established positive association between obesity in adults and increased risk of hypertension [2]. However, interindividual variations in body composition mean that two persons with similar body mass index (BMI) can have very different levels of body fat mass (BFM) and body fat distribution, and a comprehensive understanding of the association between body composition and hypertension remains limited [3].

The impact of weight status changes from childhood to adulthood on the incidence of hypertension in adulthood is controversial, with some suggesting that excessive BMI gain at any life stage is associated with increased adult hypertension [4, 5], while others indicting that those who reversed from overweight in childhood to normal weight in adulthood did not have increased risk [6, 7]. Understanding how weight status changes across the life course might influence hypertension development would inform prevention and control programs. Additionally, while it has been shown that adiposity can affect systemic metabolism [8, 9], research on the metabolic changes related to adiposity and their contribution to hypertension is limited, and the mechanisms underlying the relationship between obesity and hypertension are not well understood. Understanding the association between adiposity and blood biochemical indices and metabolites is one avenue that may identify mediators and pathways linking adiposity to hypertension.

This study aims to explore the association between weight status changes from childhood to adulthood with incident hypertension and related mortality (hereafter as "hypertension"). Moreover, we seek to understand the mediation role of adult adiposity in the development of hypertension. Further, we aim to investigate the potential biochemical and metabolomic mechanisms that might underlie the association between adiposity and incident adulthood hypertension.

Methods

Design and participants

Data were from the UK Biobank which is a large-scale cohort with over 500,000 UK participants aged 37 to 73 years who lived within 25 miles of one of the 22 assessment centers located throughout England, Wales, and Scotland at baseline (2006–2010). The data included detailed socioeconomic status, lifestyle, biological and medical information, as well as the health-related records at baseline and during ongoing longitudinal follow-up [10]. Informed consent was provided through electronic signature at baseline. In this study, participants were followed up until the date of earliest incident hypertension, or the date of the last data collected by the general practitioner, date of death related to hypertension, or loss of follow-up, whichever came first. A total of 502,366 participants attended the baseline assessment, with 180,527 participants included in the final analysis for this study following exclusion of participants who had hypertension at baseline ($n=264{,}067$), who had missing values on childhood body size ($n=4986$) or adulthood BMI ($n=1186$ at baseline), who had adult BMI ≤ 18.5 kg/m^2 ($n=1799$ this subpopulation was excluded because of low statistical power for data analysis especially for analysis in combination with childhood weight status) at baseline, and who had missing data on covariates at baseline ($n=49{,}801$) (Fig. 1). The study was conducted under UK Biobank application number 96511.

Adiposity measurements in childhood and adulthood

The information on childhood body size was obtained by asking the participants "When you were 10 years old, compared to average would you describe yourself as thinner, plumper, or about average?" at baseline (2006–2010). Adult body size was measured at baseline. Weight was measured by the body composition analyzer (Tanita BC-418 MA), and height was measured by height measure (Seca 202). BMI (kg/m^2) was calculated as weight (kg)/height (m)^2, with overweight and obesity in adulthood defined as BMI ≥ 25.0 kg/m^2 and ≥ 30.0 kg/m^2, respectively, according to the WHO [11]. Waist circumference (WC) and hip circumference (HP) were measured using a Wessex non-stretchable sprung tape. Waist-to-height ratio (WHtR) was calculated as waist circumference/height, and waist-to-hip ratio (WHR) was calculated as waist circumference/hip. Abdominal obesity was defined as WC ≥ 94 cm for males and ≥ 80 cm for females [12]. Body composition was measured using the body composition analyzer (Tanita BC-418MA) by bioimpedance with the following indices considered: arm fat mass ratio = arm fat mass/whole body fat mass; arm fat-free mass ratio = arm fat-free mass/whole body fat-free mass (leg/trunk fat mass ratio and leg/trunk fat-free mass ratio in the same way); arm fat mass index = arm fat mass/height; arm fat-free mass index = arm fat-free mass/height (leg/trunk fat mass index and leg/trunk fat-free mass index in the same way). Detailed information on the UK Biobank is provided on the website [13].

Hypertension status in adulthood

Blood pressure at baseline was measured using the digital blood pressure monitor (Omron HEM-7015IT). Participants at baseline with self-reported hypertension history,

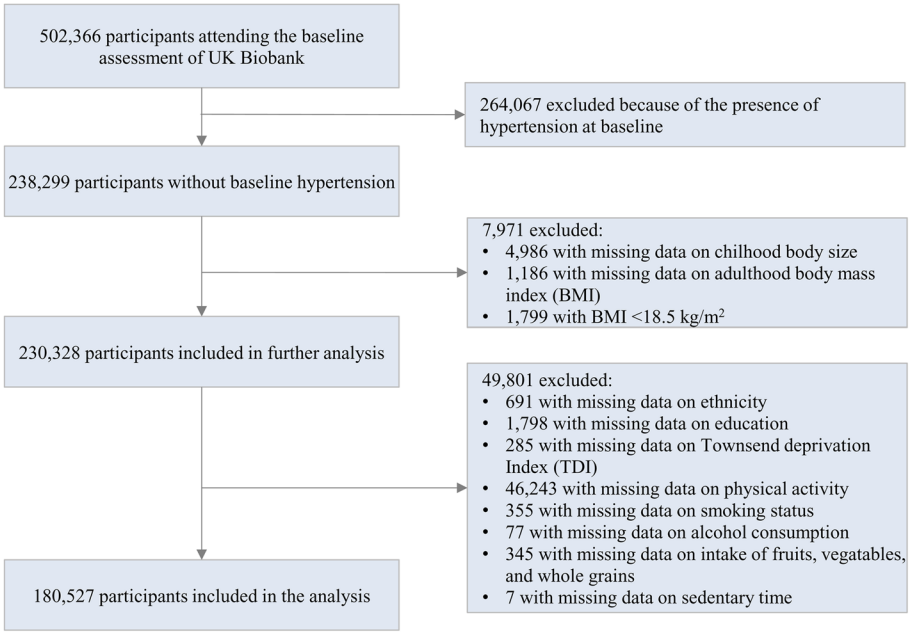

Fig. 1 Flowchart for the selection of the analyzed study sample from the UK Biobank

diagnosed with hypertension by a physician, systolic/diastolic blood pressure (SBP/DBP) ≥ 140/90 mmHg, or taking antihypertensive medicine were excluded from the data analysis. Hypertension and related mortality at follow-up were diagnosed according to the International Classification of Diseases ICD-10 codes (I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9).

Blood biochemical indices and metabolites in adulthood

Data on blood biochemical indices and metabolic biomarkers were obtained from a blood test of participants taken at the baseline assessment. Blood biochemical indices included 5 parts: liver function, bone and joint, immunometabolism, renal function, and endocrine. Metabolic biomarkers (including cholesterol, triglycerides, phospholipids, cholesteryl esters, free cholesterol, total lipids, lipoprotein particle concentrations, other lipids, apolipoproteins, fatty acids, amino acids, glycolysis-related metabolites, ketone bodies, fluid balance, and inflammation) were measured by nuclear magnetic resonance (NMR) at the central laboratory [14]. More detailed information can be found on the website [15].

Covariates

Socioeconomic status was assessed with the Townsend deprivation index (TDI), which was derived from the postcode of residence using aggregated data on unemployment, car and home ownership, and household overcrowding [16]. Using tertiles as the cut-offs, TDI was grouped into low, moderate, and high deprivation. Leisure-time physical activity (PA) was self-reported using the validated International Physical Activity Questionnaire [17]. Total leisure-time PA was calculated by multiplying the metabolic equivalent (MET) value of activity by the number of physical activity hours per week and was divided into low, moderate, high, and too low or too high. Other covariates (including ethnicity, education, smoking status, alcohol consumption, intake of fruits, intake of vegetables, intake of whole grains, sleep duration, and sedentary time) were obtained through a self-completed questionnaire. The variables used in the main analysis are shown in Additional file 1: Table S1, and the definition of cancer history at baseline is shown in Additional file 1: Table S2.

Statistical analysis

Basic characteristics for participants were presented as median (P25, P75) for continuous variables and percentage for categorical variables. The differences of variables across groups by status of incident hypertension at follow-up were compared using the *Kruskal–Wallis rank sum* test *or chi-square* test. The cumulative hazard curves were used to compare the cumulative hazard of hypertension according to categories of childhood body size, adulthood BMI, and body size change groups. The proportional hazard assumption was assessed using Schoenfeld's residual methods, and no violation was found (Additional file 1: Fig. S1). Associations of childhood and adulthood body size at baseline as well as

child–adult body size change with incident hypertension were estimated by multivariate Cox regression models after adjusting for potential covariates. The restricted cubic spline (RCS) model was used to estimate the dose–response association of adulthood BMI at baseline with incident hypertension, and the reference point was set at HR = 1. Mediation analyses were conducted to investigate the role of adulthood body size in the association between childhood body size and incident hypertension, and the difference method was used to calculate the mediation proportion by the mediator (adulthood body size) [18]. Then, a series of subgroup analyses were conducted: (a) the association of childhood body size, adulthood body size, and child–adult body size change with incident hypertension according to the age at baseline, age of hypertension onset, sex, TDI, education; (b) dose–response relationship of adulthood adiposity at baseline with incident hypertension; (c) mediation analyses of adulthood adiposity in the association between childhood body size and incident hypertension. Five sensitivity analyses were performed: (a) exclusion of participants with events that occurred in the first two years of follow-up; (b) exclusion of participants with cancer at baseline; (c) examination of associations with prevalent hypertension at baseline; (d) examination of associations by further adjusting for fish, processed meats, unprocessed red meats, refined grains; (e) based on data after multiple imputation of the missing values of covariates. Third, we performed metabolic mechanism analyses: (a) linear associations of childhood body size, adulthood adiposity, and child–adult body size changes with blood biochemical indices and metabolites; (b) non-linear associations ($y = \beta x^2 + \alpha x + c$) of adulthood body size with biochemical indices and metabolites; (c) Cox proportional hazard regression models and RCS models used to investigate the associations of blood biochemical indices and metabolites with incident hypertension; and (d) mediation analyses of blood biochemical indices and metabolites in the association between adulthood body size and incident hypertension, aiming to investigate to what degree these biochemical indices and metabolites contributed to the adiposity-hypertension association. Analyses were performed using R Statistical Software (v4.4.1; R Core Team 2024) and SAS 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of the study population by status of incident hypertension at follow-up

Among the 180,527 participants included in the analysis, a total of 16,491 participants developed incident hypertension at follow-up. The median (P25, P75) baseline age of the overall participants was 54 (47, 60) years, and 107,299 (59.4%) were females. There were 59,543 (33.0%) participants reported to have thinner body size in childhood, 93,296 (51.7%) reported about average, and 27,688 (15.3%) reported plumper. The proportion of participants across each BMI group in adulthood at baseline was 79,525 (44.1%) classified as normal weight, 73,894 (40.9%) as overweight, and 27,108 (15.0%) as obese. There were significant differences in the distributions of age, sex, ethnicity, education, Townsend deprivation index, physical activity, smoking status, alcohol consumption, intake of fruits, sleep duration, sedentary time, childhood body size, and BMI at baseline of study population by status of incident hypertension at follow-up, and no significant differences in the distributions of intake of whole grains and intake of vegetables (Table 1).

Childhood or adulthood body size and incident hypertension

Participants who were identified as being thinner or plumper in childhood (*vs.* those who were identified as average body size in childhood), or those with overweight/obesity in adulthood (*vs.* those with normal weight in adulthood), or those with "thinner → obese" pattern (*vs.* those with "average → normal" pattern) had a higher cumulative hazard of hypertension (Fig. 2). After adjusting for age, sex, ethnicity, Townsend deprivation index, education, smoking, drinking, physical activity, and intakes of fruits, vegetables, whole grains, sleep duration and sedentary time, thinner body size in childhood (hazards ratio (HR) = 1.14, 95% CI: 1.10–1.17), plumper body size in childhood (HR = 1.27, 95% CI: 1.21–1.32), adult overweight (HR = 1.46, 95% CI: 1.40–1.51), and adult obesity (HR = 2.50, 95% CI: 2.39–2.60) were all associated with higher risk of incident hypertension (Table 2). Central obesity and some body composition indices (e.g., leg fat-free mass ratio, trunk fat-free mass ratio) were also associated with incident hypertension (Additional file 1: Table S3).

Child–adult weight status change and incident hypertension

Compared with participants who had average weight in childhood and normal weight in adulthood, those whose weight status changed from average to overweight or obese status had a higher risk of incident hypertension (average → overweight: HR = 1.46, 95% CI = 1.39–1.54; average → obese: HR = 2.45, 95% CI = 2.31–2.61), with the thinner → obese group having the highest risk (HR = 3.09, 95% CI = 2.88–3.32). However, participants whose weight status changed from plumper status to normal weight status had the second lowest risk compared to those who kept normal weight in both periods (HR = 1.11, 95% CI = 1.10–1.23) (Table 2). Similarly, compared with participants who

Table 1 Baseline characteristics of the study population by status of incident hypertension at follow-up

Characteristic	Overall	No hypertension	Hypertension	*P value*
N	180,527	164,036	16,491	
Age at baseline (years), median (P25, P75)	54 (47, 60)	53 (46, 60)	60 (53, 64)	< 0.001
Sex, *n* (%)				< 0.001
Female	107,299 (59.4)	99,242 (60.5)	8057 (48.9)	
Male	73,228 (40.6)	64,794 (39.5)	8434 (51.1)	
Race, *n* (%)				< 0.001
White	172,036 (95.3)	156,451 (95.4)	15,585 (94.5)	
Non-white	8491 (4.7)	7585 (4.6)	906 (5.5)	
Education[a], *n* (%)				< 0.001
College or above	82,380 (45.6)	76,443 (46.6)	5937 (36.0)	
High school or below	98,147(54.4)	87,593(53.4)	10,554 (64.0)	
Townsend deprivation index[a]				
Median (P25, P75)	− 2.24 (− 3.71, 0.27)	− 2.27 (− 3.72, 0.23)	− 2.00 (− 3.60, 0.80)	< 0.001
Categories, *n* (%)				< 0.001
Low deprivation	60,037 (33.3)	54,998 (33.5)	5039 (30.6)	
Moderate deprivation	60,286 (33.4)	54,874 (33.5)	5412 (32.8)	
High deprivation	60,204 (33.3)	54,164 (33.0)	6040 (36.6)	
Physical activity[c] (MET-min/week)				
Median (P25, P75)	960 (240, 2160)	960 (260, 2160)	860 (240, 2160)	< 0.001
Categories, *n* (%)				< 0.001
No MVPA[d]	21,361 (11.8)	18,903 (11.5)	2458 (14.9)	
Low (120–732)	51,144 (28.3)	46,484 (28.3)	4660 (28.3)	
Moderate (733–3333)	74,017 (41.0)	67,814 (41.3)	6203 (37.6)	
High (3334–7119)	22,300 (12.4)	20,214 (12.3)	2086 (12.6)	
Too low or too high (< 120 or > 7119)	11,705 (6.5)	10,621 (6.5)	1084 (6.6)	
Smoking status, *n* (%)				< 0.001
Never	103,838 (57.5)	96,042 (58.5)	7796 (47.3)	
Former	57,396 (31.8)	51,019 (31.1)	6377 (38.7)	
Current	19,293 (10.7)	16,975 (10.3)	2318 (14.1)	
Alcohol consumption, *n* (%)				< 0.001
Never	6507 (3.6)	5731 (3.5)	776 (4.7)	
Former	5802 (3.2)	5058 (3.1)	744 (4.5)	
Current	168,218 (93.2)	153,247 (93.4)	14,971 (90.8)	
Intake of fruits (servings/day), *n* (%)				0.034
< 3	104,465 (57.9)	95,051 (57.9)	9414 (57.1)	
≥ 3	76,062 (42.1)	68,985 (42.1)	7077 (42.9)	
Intake of vegetables (servings/day), *n* (%)				0.093
< 3	31,521 (17.5)	28,563 (17.4)	2958 (17.9)	
≥ 3	149,006 (82.5)	135,473 (82.6)	13,533 (82.1)	
Intake of whole grains (servings/day), *n* (%)				0.182
< 3	155,602 (86.2)	141,331 (86.2)	14,271 (86.5)	
≥ 3	24,925 (13.8)	22,705 (13.8)	2220 (13.5)	
Sleep duration (h), *n* (%)				< 0.001
< 7	41,221 (22.8)	36,723 (22.4)	4498 (27.3)	
7–8	127,733 (70.8)	117,161 (71.4)	10,572(64.1)	
> 8	11,573 (6.4)	10,152 (6.2)	1421(8.6)	
Sedentary time (h), *n* (%)				< 0.001
< 4	71,562 (39.6)	66,496 (40.5)	5066 (30.7)	
≥ 4	108,965 (60.4)	97,540 (59.5)	11,425 (69.3)	

Table 1 (continued)

Characteristic	Overall	No hypertension	Hypertension	*P value*
Childhood body size, *n* (%)				< 0.001
Thinner	59,543 (33.0)	53,778 (32.8)	5765 (35.0)	
About average	93,296 (51.7)	85,306 (52.0)	7990 (48.5)	
Plumper	27,688 (15.3)	24,952 (15.2)	2736 (16.6)	
Body mass index, (kg/m^2)				
Median (P25, P75)	25.54 (23.26, 28.27)	25.39 (23.16, 28.05)	27.15 (24.59, 30.25)	< 0.001
Categories, *n* (%)				< 0.001
Normal weight (18.5–24.9)	79,525 (44.1)	74,789 (45.6)	4736 (28.7)	
Overweight (25.0–29.9)	73,894 (40.9)	66,510 (40.5)	7384 (44.8)	
Obesity (> 30.0)	27,108 (15.0)	22,737 (13.9)	4371 (26.5)	

MET Metabolic equivalent task, *MVPA* Moderate-to-vigorous physical activity

P-values were calculated using the Kruskal–Wallis rank sum test or chi-square test

[a] Socioeconomic status was assessed with the Townsend deprivation index, which combines information on social class, employment, car availability, and housing, according to TDI tertiles low, moderate, and high deprivation

[c] Physical activity was presented using weekly total MET, calculated by multiplying the MET value of activity by the number of physical activity hours per week

[d] No MVPA refers to those reported 0 MET-mins/week of MVPA

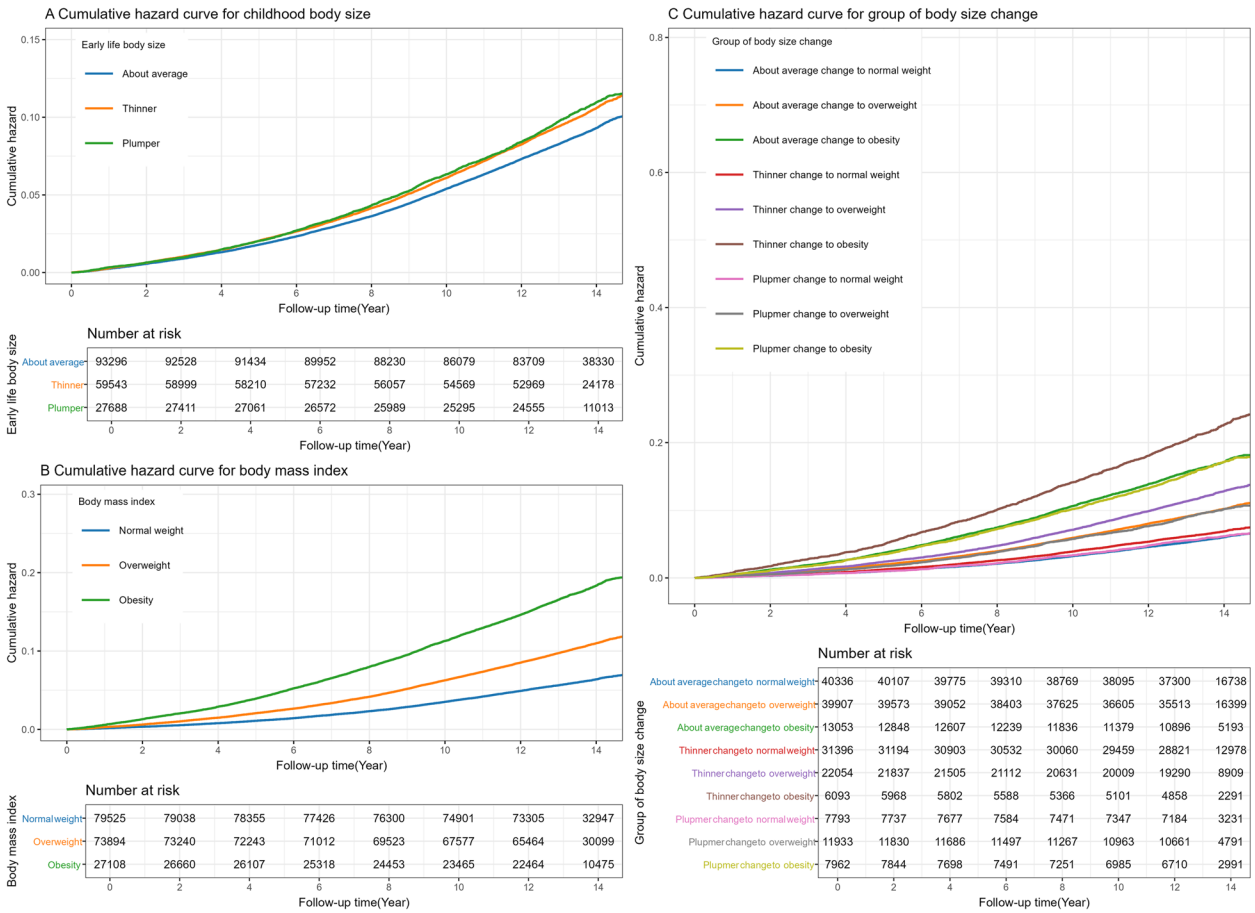

Fig. 2 Cumulative hazard of hypertension according to childhood body size and adulthood BMI at baseline

Table 2 Association of childhood body size, adulthood body size, and child–adult change in body size with incident hypertension

	No. events/No. total population	Person years	Model 1		Model 2	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Childhood body size						
Thinner	5765/59,543	779,436	1.15 (1.11–1.19)	< 0.001	1.14(1.10–1.17)	< 0.001
About average	7990/93,296	1,227,219	1.00		1.00	
Plumper	2736/27,688	361,551	1.29 (1.24–1.35)	< 0.001	1.27(1.21–1.32)	< 0.001
Adulthood body size						
Normal weight	4736/79,525	1,058,639	1.00		1.00	
Overweight	7384/73,894	966,615	1.54 (1.48–1.60)	< 0.001	1.46 (1.40–1.51)	< 0.001
Obesity	4371/27,108	342,952	2.84 (2.73–2.96)	< 0.001	2.50 (2.39–2.60)	< 0.001
Body size change pattern (childhood → adulthood)						
About average → normal weight	2263/40,336	537,899	1.00		1.00	
About average → overweight	3737/39,907	523,301	1.53 (1.45–1.61)	< 0.001	1.46 (1.39–1.54)	< 0.001
About average → obesity	1990/13,053	166,019	2.76 (2.60–2.94)	< 0.001	2.45 (2.31–2.61)	< 0.001
Thinner → normal weight	2026/31,396	417,007	1.18 (1.11–1.25)	< 0.001	1.17 (1.10–1.24)	< 0.001
Thinner → overweight	2550/22,054	286,887	1.90 (1.80–2.01)	< 0.001	1.77 (1.67–1.87)	< 0.001
Thinner → obesity	1189/6093	75,542	3.67 (3.42–3.93)	< 0.001	3.09 (2.88–3.32)	< 0.001
Plumper → normal weight	447/7793	103,733	1.11 (1.01–1.23)	0.039	1.11 (1.00–1.23)	0.042
Plumper → overweight	1097/11,933	156,427	1.66 (1.54–1.78)	< 0.001	1.58 (1.47–1.70)	< 0.001
Plumper → obesity	1192/7962	101,390	3.14 (2.93–3.37)	< 0.001	2.82 (2.62–3.02)	< 0.001

Model 1: adjusted for age and sex

Model 2: model 1 covariates plus ethnicity; Townsend deprivation index; education; smoking; drinking; physical activity; intakes of fruits, vegetables, and whole grains; sleep duration; and sedentary time

HR Hazard ratio, *CI* Confidence interval

had average weight in childhood and normal waist in adulthood, a change in status to having central obesity in adulthood increased the risk of incident hypertension Additional file 1: Table S3). Adulthood BMI at baseline had a significant nonlinearly positive association with incident hypertension, with the magnitude of the association becoming stronger when BMI was > 25.54 kg/m^2 (Fig. 3A). Mediation analyses showed that adulthood overweight (mediation proportion: 58.7%, 95% CI: 40.4–74.8%) and obesity (mediation proportion = 46.7%, 95% CI: 29.4–64.9%) significantly mediated the association between childhood plumper body size and hypertension (Fig. 3B). Adulthood WC, WHR, WHtR, body fat mass (BFM), whole body fat-free mass (BFFM), and whole body fat percentage (BFP) also had significantly nonlinear correlation with incident hypertension (Additional file 1: Fig. S2.1–S2.4) and mediated the association between childhood plumper body size and incident hypertension, with the proportion of mediation ranging from 24.5 to 62.9% (Additional file 1: Table S4.1). Regarding the association between childhood thinner body size and incident hypertension, only adult waist-to-hip ratio partly mediated the association (mediation proportion: 7.0%, 95% CI: 3.7–12.9%) (Additional file 1: Table S4.2).

Association of blood biochemical indices and metabolites with adiposity and hypertension

After adjustment for age; sex; ethnicity; Townsend deprivation index, education levels; smoking; drinking, physical activity; intake of fruits, vegetables, and whole grains; sleep duration; and sedentary time, most blood biochemical indices and metabolites in adulthood showed significant associations with childhood body size, adulthood body size, adulthood adiposity, child–adult weight status change (Additional file 1: Tables S5–S9), and incident hypertension (Additional file 1: Table S10). Higher levels of apolipoprotein A, HDL, SHBG, and testosterone showed inverse associations with incident hypertension, while alanine aminotransferase, triglycerides, cystatin C, and urate showed positive associations (Additional file 1: Table S10). Mediation analyses showed that mediation proportions ranged from 3.2 to 21.1% (Additional file 1: Table S11).

Subgroup analysis

Subgroup analyses were performed to estimate the association of childhood body size, adulthood body size, and child–adult weight status change with incident hypertension in different subgroups according to adult age at baseline (< 60, ≥ 60 years), age at onset

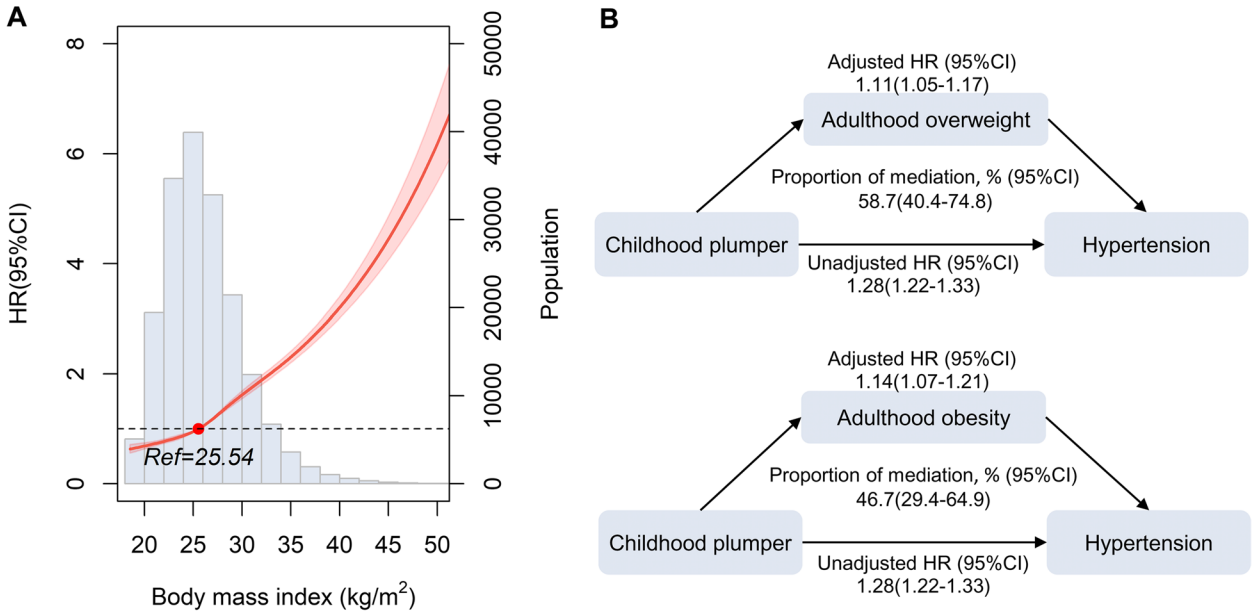

Fig. 3 Dose-response relationship of adulthood BMI with incident hypertension, and the mediation of adulthood overweight and obesity

of hypertension (< 65, ≥ 65 years), sex, Townsend deprivation index categories, and education categories. The results were consistent with the main analysis. However, the hazard ratios of incident hypertension associated with adulthood body size at baseline and childhood-adulthood body size change were higher among the younger group than those among the older group (*P* for interaction < 0.001). Additionally, the incidence density of hypertension was higher in the older group (Additional file 1: Figs. S3–S5, Table S12).

Sensitivity analysis

After excluding participants who were followed up for less than 2 years, those with cancer at baseline, or further adjusting for fish, processed meats, unprocessed red meats, and refined grains, the association of childhood body size, adulthood adiposity, and child–adult weight status change with incident hypertension was consistent with the results of the main analysis (Additional file 1: Tables S13–S15). The associations using prevalent hypertension at baseline as an outcome were also consistent with the main analysis using incident hypertension during follow-up as outcome (Additional file 1: Table S16). After multiple imputation of the missing values of covariates, the results were largely consistent with the main analysis (Additional file 1: Table S17).

Discussion

We found that participants who were thinner or plumper in childhood had an increased risk of incident hypertension in adulthood. Adult adiposity status was also associated with incident hypertension, and partly mediated the association between childhood body size and incident hypertension. The risk was highest when thinner status in childhood changed to obese status in adulthood, while the association was substantially attenuated when plumper children were normal weight by adulthood. In mediation analyses, we identified several biochemical indices and metabolites linked to adiposity and hypertension in adulthood, providing indications of underlying biological mechanisms.

Many previous studies exploring the association between childhood adiposity and adulthood hypertension have had inconsistent results. A population-based birth cohort study including 2840 participants in the United Kingdom showed that higher total fat mass index and BMI at age 10 years were significantly associated with hypertension at age 18 years [19]. However, the Institute of Nutrition of Central America and Panama Nutrition Trial Cohort study showed that early anthropometrics were not generally found to be associated with blood pressure in adulthood [20]. Regarding weight status change from childhood to adulthood, we found that compared to participants with normal weight in both childhood and adulthood, those who had overweight

in adulthood only or who had persistent overweight in both periods had an increased risk of incident hypertension. In contrast, those who changed from overweight in childhood to normal weight in adulthood did not have increased risk, which was consistent with several previous studies [6, 7]. Besides, our results further demonstrated that participants who changed from thinner body size in childhood to normal BMI in adulthood had a low risk of incident hypertension in adulthood. Similar findings were found when using WC in adulthood as an index of central obesity to assess the impact of changes of childhood body size to adulthood central obesity status on incident hypertension. Subgroup analyses showed that the hazard ratios of incident hypertension associated with adulthood adiposity were higher among the younger group than those among the older group. Several previous studies also found similar results with ours [21, 22]. This may be due to that the older adults with prevalent hypertension at baseline had been excluded, and the remaining older adults might be less susceptible to hypertension due to genetic or other protective factors (survivorship bias). On the other hand, some younger adults who were potentially at high risk but did not develop hypertension were not excluded. In addition, this phenomenon might be due to the large difference in the incidence density of hypertension between the older control group and the younger control group (e.g., the incidence density among the adults with normal weight aged < 60 years at baseline was 2.77/1000 person-years, while the incidence density among the adults with normal weight aged ≥ 60 years was 9.23/1000 person-years).

The association between childhood body size and adulthood hypertension is partially explained by the mediation effect of adulthood adiposity, with the proportion of mediation ranging from 27.4 to 62.9%. The use of adult WC and other markers of adiposity, in addition to BMI status, yielded similar results, further reinforcing the role of adult adiposity in this association. Unfortunately, most children who are plumper are more likely to maintain a higher weight status into adulthood. For example, of those in our study who were identified as being plumper in childhood, 71.8% were overweight or obese in adulthood. Other studies have also shown the persistence of obesity in the life course and the difficulty in interrupting overweight and obesity once established [6, 23]. Moreover, being underweight in childhood should also not be ignored as our results showed that thinner body size in childhood was positively associated with adult hypertension, and the risk of adult hypertension was the highest in participants changing from thinner status in childhood to obesity in adulthood. These findings suggest that the adverse effects of childhood body size on adult hypertension are largely, though not completely, driven by subsequent adult adiposity. This reinforces the importance of primordial prevention of adverse body size and that interrupting the continuation of childhood obesity to adulthood obesity may be protective for incident hypertension in adulthood. Effective strategies and measures must be taken to attain and maintain normal body weight in children.

In this study, we performed mediation analyses to explore the underlying mechanisms of adiposity-hypertension association. We found that higher HDL concentration was inversely related to obesity, was a protective factor for incident hypertension, and played an important mediating role in the obesity-hypertension association. The possible mechanisms may be due to that obesity increased the production of triglyceride-rich lipoproteins, leptin, cholesteryl-ester transfer protein, adipokine adiponectin, hepatic lipase activity, and the overexpression of endothelial lipase, and then caused the reduction of HDL which had the capacity of antioxidative, anti-inflammatory, antiapoptotic, anti-thrombotic, and anti-infectious, leading to the increased risk of hypertension [24–26]. Additionally, we found that the component of large/very large HDL played an important role in the mediation, and one previous study showed that the HDL particle size may be superior to HDL level as a predictor of cardiovascular disease, suggesting the assessment of HDL particle profile may be clinically useful [27].

Alanine aminotransferase, apolipoprotein A, triglycerides, cystatin C, urate, SHBG, and testosterone also mediated the association of adiposity with hypertension. Alanine aminotransferase and triglyceride, with higher levels in participants with obesity, have been found to be positively correlated with incident hypertension in adults [28, 29]. One possible explanation may be that alanine aminotransferase and triglyceride may be involved in insulin resistance, eventually contributing to the development of hypertension through elevating reabsorption of sodium in the renal tubules, activating the sympathetic nervous system, and altering vascular resistance with elevated calcium concentration in smooth muscle cells [30, 31]. Cystatin C and urate have also been found to be related to hypertension in previous studies [32–35]. The underlying mechanism for blood pressure increase implicates both oxidative stress and intracellular urate activity with primary involvement of xanthine-oxidoreductase activity [36]. Elevated levels of SHBG and testosterone are associated with a reduced risk of hypertension, which is consistent with previous findings [37, 38]. The potential mechanisms underlying the association of SHBG and testosterone with hypertension remain largely unknown, and the vasodilating effects of testosterone on vascular and non-vascular smooth muscle may be one possible reason [39, 40].

Despite the strength of our study, including a large sample size with a long-term follow-up, and comprehensive mediation analyses of blood biochemical indices and metabolites, several limitations should be noted. First, the reliance on retrospective self-reported information of body size in childhood by participants may introduce recall bias. However, previous studies have shown that the use of self-reported recall anthropometry in life-course epidemiology studies exhibits both high validity and reproducibility [41, 42]. Second, considering that the majority of participants were white and the potential healthy volunteer effect, the participants were not representative of the general population, especially those of other races/ethnicities. Third, we excluded participants with prevalent hypertension at baseline in the main analysis, who were more likely to have abnormal weight status, and thus the current estimates on the association might be underestimated. Finally, we could not evaluate the duration of childhood obesity and the trajectory of life-course adiposity due to the data not being available.

Conclusions

This study showed that thinner and plumper body sizes in childhood are associated with an increased risk of incident hypertension in adulthood, partly mediated by adult adiposity. These findings highlight the importance of maintaining a healthy weight throughout life and the potential benefit of resolving a child abnormal body weight before adulthood. Moreover, our findings also suggest potential biochemical and metabolomic pathways that may underlie the observed associations, and pre-assessment of biochemical indices and metabolites before incident hypertension may facilitate improvement in early prevention of hypertension, enhance identification of patients at high risk, and development of further strategies to improve cardiovascular health.

Abbreviations

BFM	Body fat mass
BMI	Body mass index
DBP	Diastolic blood pressure
HDL-C	HDL-cholesterol
MET	Metabolic equivalent
NMR	Nuclear magnetic resonance
PA	Physical activity
RCS	Restricted cubic spline
SBP	Systolic blood pressure
SD	Standard deviation
SHBG	Sex hormone-binding globulin
TDI	Townsend deprivation index
WC	Waist circumference
WHO	World Health Organization
HP	Hip circumference
WHtR	Waist-to-height ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03884-8.

Additional file 1. Table S1. UK biobank showcase variables used in main analysis. Table S2. The definition for cancer at baseline. Table S3. Associations of adulthood adiposity at baseline and child-adult body size change with incident hypertension. Table S4.1 Mediation analyses of adulthood adiposity in the association between childhood body size and incident hypertension. Table S4.2. Mediation analyses of adulthood adiposity in the association between childhood thinner body size and incident hypertension. Table S5.1. Linear associations of childhood body size with blood biochemical indices. Table S5.2. Linear associations of childhood size with metabolites. Table S6.1. Linear associations of adulthood body size with blood biochemical indices. Table S6.2. Linear associations of adulthood body size with metabolites. Table S7.1. Linear associations of adulthood adiposity with blood biochemical indices. Table S7.2. Linear associations of adulthood adiposity with metabolites. Table S8.1. Linear associations of child-adult body size change with blood biochemical indices. Table S8.2. Linear associations of child-adult body size change with metabolites. Table S9.1. Non-linear associations of adulthood body size with blood biochemical indices. Table S9.2. Non-linear associations of adulthood body size with metabolites. Table S10.1. Associations of blood biochemical indices with incident hypertension. Table S10.2. Associations of metabolites with incident hypertension. Table S11.1. Mediation analyses of blood biochemical indices in the association between adulthood body size and incident hypertension. Table S11.2. Mediation analyses of metabolites in the association between adulthood body size and incident hypertension. Table S12. Incidence density of hypertension in different body size groups. Table S13. Sensitivity analyses of the associations of childhood and adulthood body size at baseline as well as child-adult body size change with incident hypertension. Table S14. Sensitivity analyses of the associations of childhood and adulthood body size at baseline as well as child-adult body size change with incident hypertension by excluding participants with cancer at baseline. Table S15. Sensitivity analyses of associations of childhood body size, adulthood body size at baseline, and childhood-adulthood body size change with incident hypertension by further adjusting for more dietary variables. Table S16. Sensitivity analyses of associations of childhood body size, adulthood body size at baseline, and childhood-adulthood body size change with prevalent hypertension at baseline. Table S17.1. Sensitivity analyses of associations of childhood and adulthood body size at baseline as well as childhood-adulthood body size change with incident hypertension based on data using multiple imputation. Table S17.2. The Mediation analyses of adulthood adiposity in the association between childhood plumper and incident hypertension based on data using multiple imputation. Table S17.3. The Mediation analyses of adulthood adiposity in the association between childhood thinner and incident hypertension based on data using multiple imputation. Figure S1. The graph of scaled Schoenfeld residuals for childhood body size and adulthood BMI at baseline. Figure S2.1. Dose-response relationships of adulthood central adiposity at baseline with incident hypertension. Figure S2.2. Dose-response relationships of adulthood fatmass distribution at baseline with incident hypertension. Figure S2.3. Dose-response relationships of adulthood fatmass index at baseline with incident hypertension. Figure S2.4. Dose-response relationships of adulthood fat composition and basal metabolic rate at baseline with incident hypertension. Figure S3. Subgroup analyses for the association of childhood body size with incident hypertension. Figure S4. Subgroup analyses for the association of adulthood body size at baseline with incident hypertension. Figure S 5. Subgroup analyses for the association of childhood-adulthood body size change with incident hypertension

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Authors' contributions

B.X. conceived and designed this research, S.M. drafted the manuscript, X.L. and R.-L. L. performed the data analysis and had full access to all the data

used in present study. S.M., Y.Y., M.Z., Y.-F. Y., C.G. M. and B.X. contributed to the interpretations of the results of statistical analysis and critically revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The UK Biobank cohort was reviewed and approved by the UK National Health Service and the National Research Ethics Service. Informed consent was obtained from each participant. This study was conducted under UK Biobank application number 96511.

Consent for publication
All authors approve the publication of the final manuscript.

Competing interests
BX is a member of the BMC Medicine editorial board. None of the authors, including BX, were involved in the peer review or handling of this manuscript. The remaining authors declare that they have no competing interests.

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