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Body shape trajectories and the incidence of hypertension in a Mediterranean cohort: The sun study☆

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Abstract *Aims:* Our aim was to assess the association between trajectories of body-shape across the first 40 years of life and subsequent development of hypertension in a Mediterranean cohort.
Methods and Results: We used a group-based modeling approach to assess body shape trajectories from age 5 to 40 years, among 7514 participants included in the SUN study (1999–2016), and assessed the subsequent incidence of hypertension. To create the trajectories, we used a censored normal model as a polynomial function of age. Cox models were used to estimates hazard ratios (HR) for hypertension according to body shape trajectories. Identified trajectories were “childhood lean -mid-life increase", "childhood medium-mid-life stable", " childhood heavy -mid-life decrease", and "childhood heavy -mid-life increase" for women; and "childhood lean-mid-life increase", "childhood medium-mid-life stable", "childhood medium -mid-life increase" and "childhood heavy-mid-life stable" for men. After a follow-up of 63,068 person-years, 865 incident cases of hypertension were found. Among women, compared to those in the “childhood medium-mid-life stable” trajectory, those, in the "childhood heavy -mid-life increase” trajectory showed higher risk to develop hypertension [HR = 1.72 (1.17–2.53)]. In men, compared with those in the “childhood medium-mid-life stable” trajectory, those in the “childhood lean and childhood medium -mid-life increase” and the “childhood heavy- mid-life stable” trajectories showed higher subsequent incidence of hypertension [HR = 1.43 (1.11–1.85), HR = 1.52 (1.17–1.97) and HR = 1.56 (1.14–2.14), respectively] after adjusting for potential confounders (including age, lifestyles, dietary intake, personality traits, physical activity and sedentary behaviors).
Conclusions: Our results suggest that mid-life increases in body shape or maintaining a heavy body shape during early and middle life in men and childhood heavy-mid-life increase in women is associated with a higher subsequent risk of developing hypertension in this Mediterranean population.

Acronyms: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; BMI, Body mass index; GBTM, Group-based trajectory modeling; SUN, Seguimiento Universidad de Navarra; FFQ, Food frequency questionnaire.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Introduction

High blood pressure is one of the leading risk factors for cardiovascular disease [1].

In 2013, one of the targets adopted by the World Health Assembly was to lower the prevalence of increased blood pressure, which, at that time, was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg [2].

National Surveys conducted in Europe, USA and Canada, found that the age-and-sex-adjusted prevalence of hypertension (defined as ≥140/90 mmHg) ranged from 20 to 55 percent [3,4]. In United States, according to the NHANES from 2011 to 2014, 46% of adults ≥18 years and older had hypertension (defined as SBP ≥130 mmHg and/or a DBP ≥80 mmHg) [5]. In Spain, according to the Di@bet.es study, a national population-based survey carried out between 2009 and 2010, the age-adjusted prevalence of hypertension was 43% in the adult population, (50% in men and 37% in women) [6].

It is largely known that adulthood overweight/obesity is strongly and independently associated with the development of hypertension [7–11]. Moreover, some studies found that higher body mass index (BMI) levels during childhood play a role in the development of adulthood hypertension [12]. Until now, in epidemiologic studies, BMI has been only considered at one or two time points, in the early or middle life, to assess the relationship with the subsequent development of hypertension. Yet, the duration of obesity or the existence of weight changes during childhood, adolescence or early adulthood may confer differential risks for the development of hypertension in the adult age [13]. Therefore, it seems important to consider the possible effect of intra-individual change of body weight or body shape over a lengthy period of time (at more than 2 points) on hypertension risk. In this context a recent study revealed that the weight change of >2.5 kg or more between early to middle adulthood was associated with higher risk of developing hypertension [14]. However little is known regarding changes in body shape. Advancements in statistical methods might propitiate the identification of groups with similar progression of body shape over time and thus allow for a more detailed investigation on one of the potential factors associated with the development of hypertension, and largely under-researched. For example, statistical methods such as the group-based trajectory modeling (GBTM) represent novel approaches designed to empirically identify clusters of individuals following similar progressions of some behaviors or outcomes [15,16]. In the last years this approach has been successfully used to demonstrate that body shape trajectories from early childhood to the age of 50–60 where associated with the risk of cancer [17], all-cause mortality [18], cardiovascular disease and type 2 diabetes [19].

Therefore, the aim of this study was, using a trajectory-based approach, to characterize distinct trajectories of body shape across early and middle life, and to compare the subsequent risk of hypertension across these trajectories in a Spanish cohort of university graduates.

Methods

Study population

The "*Seguimiento Universidad de Navarra*" (SUN) (1999–2016) project is a Spanish dynamic cohort (participants can enroll to the study at any time) that was originally designed to assess associations between diet and the occurrence of several diseases and chronic conditions including hypertension. Biennially, since enrolment, follow-up questionnaires have been mailed to participants to collect and update information on diet, lifestyle, risk factors, and medical conditions. Information about the design and methods of the SUN project has been published elsewhere [20]. As of December 2016, the SUN project had enrolled 22,560 participants (between 20 and 90 years old). Of these, 496 participants had been recruited after March 2014 or had less than 2 years of follow-up; 5834 were aged less than 42 years at the end of the study and were excluded. We also excluded 2119 participants with total energy intake outside predefined limits (<500 or >3500 kcal/d for women and <800 or >4000 kcal/d for men) [21]. We further excluded 1319 participants who at baseline reported CVD, cancer, or diabetes, and 3719 who reported prevalent hypertension at the beginning of the follow-up. Additionally, we excluded 1365 participants who had no follow-up information, and 194 participants with not enough data on body shape trajectories. After exclusions, 7514 participants (3024 men and 4,490 women) were included in the final analysis (Fig. 1). When comparing the groups of included versus excluded participants, the absolute size of their between-group differences in relevant covariates were all of them meaningless. The maximum observed difference was +0.20 SD, all other differences were of even a smaller magnitude (See Supplemental Table 1).

The project protocol was approved by the Institutional Review Board of the University of Navarra. Voluntary response to the first self-administrated questionnaire was considered informed consent to participate in the study.

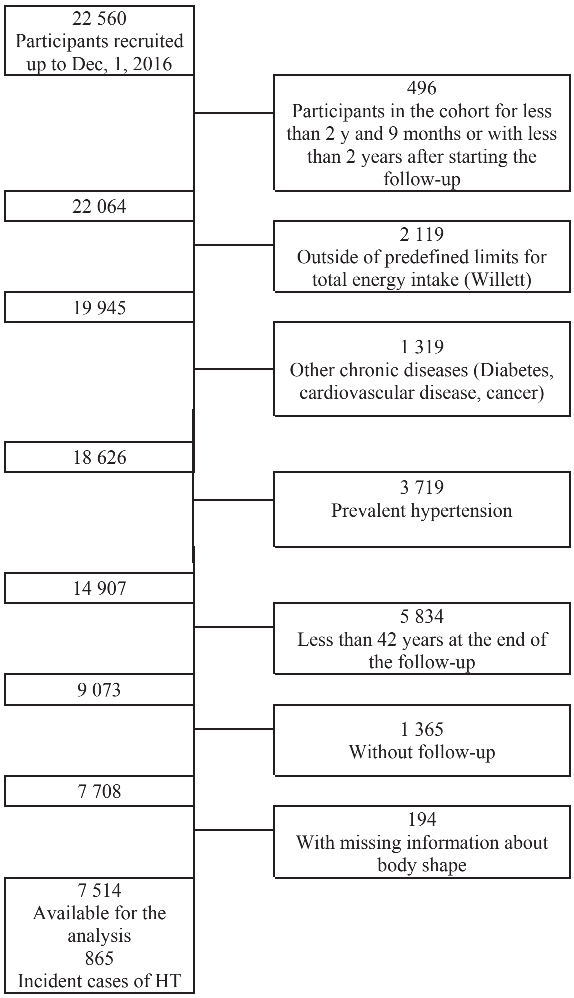

Figure 1 Flow chart.

Assessment of body shape

At baseline questionnaire, participants were asked to report which one of the 9 pictorial body diagrams developed by Stunkard et al. [22] best described their body shape at age 5, 20, 30, 40, and at present, the validity of the remote recall of body shape was assessed previously [23]. Detailed information of the assessment of body shape can be found on supplemental material.

Trajectory modeling

Among participants who had at least 3 different somatotype data at different ages, we used a GBTM to identify distinct body shape trajectories over age (from 5 to 40 years). GBTM method fits longitudinal data as a discrete mixture of two or more trajectories via maximum likelihood [24]. To fit the models, we used the Stata *traj* plug-in, with somatotype figures modeled as a censored normal distribution. Detailed information regarding trajectory modeling can be found on supplemental material.

Ascertainment of outcome

Incident hypertension was the primary endpoint of the study. Participants were asked whether they had ever received a medical diagnosis of hypertension at baseline or during the follow-up and also, we inquired about the date of diagnosis. A validation study of hypertensive status was previously conducted in a subsample of this cohort. That validation study showed an adequate validity of the self-reported diagnosis of hypertension: among those participants who reported a diagnosis of hypertension 82.3% (95% CI:72.8–92.8) were confirmed through conventional measurement of blood pressure, and among those who did not report a diagnosis of hypertension, 85.4% (95% CI:72.4–89.1) were confirmed as non-hypertensive [25].

For the present analyses, participants were considered to have prevalent hypertension if participants have reported a medical diagnosis of hypertension before inception date. Also if they reported a SBP $\geq$140 mmHg, a DBP $\geq$90 mmHg, or any use of antihypertensive medication before inception date [26] [for this study inception date was the date when the initial questionnaire (Q0, time 0) was completed only for those participants who were aged $\geq$ 40 years at the time when they were recruited; whereas, for those participants aged $<$40 years when they were recruited, we defined the inception date as the date when these participants reached age 40 (during follow-up) (43% of the study sample were $<$40 years at baseline questionnaire)]. Incident cases of hypertension were defined as those participants who did not have prevalent hypertension and reported a new medical diagnosis of hypertension after the inception date. In the present study, for either prevalent or incident hypertension we did not use the new definition proposed by the American College of Cardiology/American Heart Association (ACC/AHA) in 2017 guidelines because the medical diagnosis of hypertension in our cohort was done before this new definition was released [27].

Dietary assessment

At baseline questionnaire and using a previously validated 136-items semi-quantitative food frequency questionnaire (FFQ), participants were asked about the past-year food intake [28]. Mediterranean dietary pattern was calculated by the a priori 9-item Mediterranean-diet score proposed by Trichopoulou et al. [29] Measurement of other covariates are described on supplemental material.

Statistical analyses

In 2018 we classified participants into four categories according to body shape trajectories from age 5 to 40 years (Fig. 2a–b); we considered the group of “childhood medium- middle life stable during lifespan” trajectory as the reference category both in women and men.

Nutrient intake was adjusted for total energy intake with sex-specific residuals using the residuals methods [30].

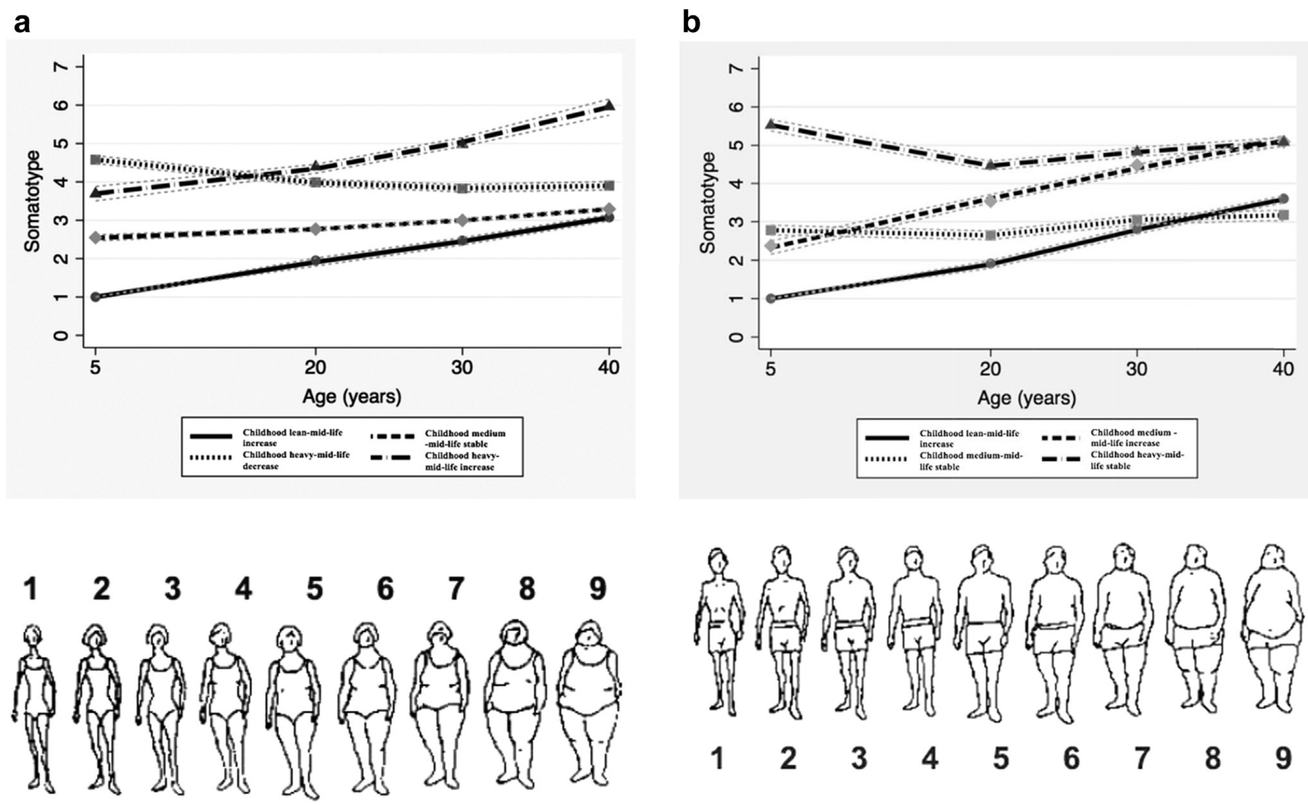

Figure 2 a. Trajectories of body shape by age among women from the SUN Study (1999–2016) Stunkard body diagram in women. b. Trajectories of body shape by age among men from the SUN Study (1999–2016) Stunkard body diagram in men.

As explained before, for participants who were ≥40 years at the time when they entered the cohort, their baseline questionnaire represented the inception date for our analyses. But for those participants who were <40 years when they entered the cohort, we considered as inception date the date when the participant reached age 40 years. Therefore, person-time of follow-up was calculated for each participant, from the inception date till the date of completion of the last follow-up questionnaire, the date of diagnosis of hypertension, or death, whichever occurred first.

Cox regression models were fitted using age as underlying time variable. We fitted a crude univariate model, an age-stratified and period of recruitment-adjusted model, and a multivariable model after additional adjustment for the following potential confounders: family history of hypertension (yes/no), physical activity (METs-h/week as continuous), smoking status (three categories) and package-years of smoking (continuous), alcohol consumption (g/d), sodium and potassium intake (quintiles), total energy intake (quartiles), adherence to the Mediterranean diet [using the score proposed by Trichopoulou (continuous)], whole-fat and low-fat dairy consumption (quintiles), sugar sweetened beverage, artificially-sweetened beverage (three categories), coffee consumption (four categories), personality traits [competitive, dependent and relax (as continuous)], time spent watching TV (continuous), fried food and fast food consumption (tertiles).

Because smoking status has been previously reported as a potential risk factor for hypertension [31,32], and the Mediterranean diet was associated with lower systolic and diastolic blood pressure [33,34], and also these two factors are closely related to body weight, we planned a priori to stratify our analyses by these two variables that might act as effect modifiers of the association. In this way significance of effect modification between smoking status (never/ever), and adherence to the Mediterranean Dietary Score (0–4/5-9 points) and the trajectories of body shape among men and women were calculated through likelihood ratio tests between the fully adjusted model and the same model but introducing the interaction product-term, and stratified analyses were conducted in both cases.

In order to test the proportional-hazard assumption a Cox regression with continuous time varying covariates (*tvc* command in Stata) was conducted using our exposure (dummy variables of the trajectory groups) as *tvc* covariate, obtaining a non-significant time * exposure interaction ($p = 0.63$ for women and $p = 0.80$ for men), and confirming that the relative hazard was constant over time.

Sensitivity analyses were conducted, and all the models were repeated after excluding cases of hypertension diagnosed within 2 and 4 years of follow-up, respectively, and also after excluding participants whose trajectory assignment probability was less than 0.80.

All *p* values presented are two-tailed; $p < 0.05$ was considered statistically significant. Analyses were carried out using STATA/SE version 12.0 (StataCorp, College Station, TX, USA).

Results

Fig. 2a–b shows the estimated mean body shape levels in the 4 trajectories of women and men respectively at each age. The percentages of women assigned to each trajectory were 53% to the "childhood medium- mid-life stable", 20% to the "childhood lean-mid-life increase", 20% to the "childhood heavy-mid-life decrease", and 7% to the "childhood heavy-mid-life increase" trajectory. In men, the body shape trajectories were distributed as follow: 29%, 29%, 28%, and 14% for the "childhood medium-mid-life stable", "childhood lean mid-life increase", "childhood medium-mid-life increase", and "childhood heavy-mid-life stable" trajectories, respectively. Baseline characteristics of participants by trajectories are shown on Tables 1a and 1b. The age range of the study population at inception date was between 40 and 90 years and the range of age at the end of the follow up ranged from 42 to 93 years. Compared to women in the "childhood medium-mid-life stable" trajectory, women in the "childhood lean-mid-life increase" trajectory were older, while women in the "childhood heavy-mid-life decrease" and "childhood heavy-mid-life increase" were younger, the average BMI at inception was very similar to those in the "childhood lean-mid-life increase" category, but lower than the "childhood heavy-mid-life decrease" and "childhood heavy-mid-life increase" trajectories, the percentage of ever smokers were lower than the other groups. Women in this trajectory group were more physically active than women in the other trajectory groups. Other baseline characteristics were similar among all trajectory groups. On the other hand, men in the "childhood medium-mid-life stable" trajectory, were younger than men in the "childhood lean and childhood medium -mid-life increase" trajectories, the BMI at the beginning of the follow-up was lower. Men in this group had lower alcohol consumption, were less frequently ever smokers, were more physically active, and spent less time watching television in comparison with men in the other trajectories.

During a median of 8.2-year and 8.6-year follow-up in women and men, respectively [37,813 and 25,971 person-years in women and men respectively], we observed 381 and 484 incident cases of hypertension in women and men, respectively. Table 2a shows the HRs (95% CI) for the subsequent risk of hypertension in women during the follow-up period. Compared to women in the "childhood

Table 1a Baseline characteristics of women according to trajectories of body shape in the SUN Study from 1999 to 2016 (N = 4490).

Women	Childhood medium-mid-life stable	Childhood lean-mid-life increase	Childhood heavy-mid-life decrease	Childhood heavy- mid-life increase
No. participants (N = 4490)	2396	887	905	302
Persons-years	19,757	7617	7520	2203
Age at inception[a], (y)	44 (5)	46 (6)	43 (5)	42 (4)
BMI at inception of follow-up, (kg/m^2)[a]	22.1 (2.4)	22.2 (2.3)	23.1 (2.4)	28.2 (3.7)
Height, (cm)	163 (6)	163 (6)	163 (6)	163 (6)
Alcohol consumption, (g/d)	4 (7)	5 (6)	4 (6)	4 (6)
Smoking status, (%)				
Former	28	32	28	28
Current	25	24	27	30
Pack-years of smoking	6 (9)	7 (9)	7 (10)	7 (10)
Family history of hypertension, (%)	26	25	30	30
Sodium intake, (g/d)	3.6 (2.4)	3.6 (1.6)	3.6 (1.6)	4.0 (2.0)
Potassium intake, (g/d)	4.9 (1.2)	5.0 (1.3)	5.0 (1.1)	4.9 (1.2)
Whole-fat dairy products, (g/d)	187 (177)	179 (192)	181 (182)	147 (156)
Low-fat dairy products, (g/d)	248 (253)	237 (250)	269 (249)	324 (253)
Artificially-sweetened beverages, (cans/day)	0.6 (1.3)	0.5 (1.2)	0.8 (1.4)	1.2 (1.6)
Sugar-sweetened beverages, (cans/day)	1.1 (1.4)	1.0 (1.3)	1.1 (1.4)	1.3 (1.4)
Adherence to the Mediterranean diet (0–9 score)[b]	4.2 (1.8)	4.3 (1.8)	4.2 (1.8)	4.1 (1.7)
Physical activity, (METs-h/week)	24.7 (20.4)	22.9 (19.5)	23.1 (19.4)	20.4 (17.7)
Self-reported personality traits				
Competitiveness (0–10 score)	6.8 (1.7)	6.8 (1.9)	6.8 (1.8)	6.7 (1.7)
Dependency (0–10 score)	3.6 (2.9)	3.8 (3.1)	3.6 (2.9)	3.5 (27)
Relaxation (0–10 score)	6.0 (2.1)	6.3 (2.2)	6.0 (2.1)	5.9 (2.2)
Time spent watching TV, (hours/d)	1.6 (1.2)	1.6 (1.2)	1.6 (1.2)	1.8 (1.2)
Coffee, (cups/day)	1.3 (1.2)	1.3 (1.3)	1.5 (1.3)	1.5 (1.3)
Fried foods, (times/week)	3.3 (3.9)	3.4 (3.6)	3.1 (4.0)	3.3 (5.0)
Fast food consumption, (g/d)	18 (18)	17 (16)	18 (17)	19 (16)

Values are presented as mean (SD), unless otherwise stated.
Abbreviations: BMI, Body mass index; METs, Metabolic equivalent of task.
[a] Inception date: was the date when the initial questionnaire (Q0, time 0) was completed only for those participants who were aged ≥ 40 years at the time when they were recruited; whereas, for those participants aged <40 years when they were recruited, we defined the inception date as the date when these participants reached age 40 (during follow-up).
[b] Trichopoulou score (range of scores, 0–9, with higher scores indicating greater adherence).

Table 1b Baseline characteristics of men according to trajectories of body shape in the SUN Study from 1999 to 2016 (N = 3024).

Men	Childhood medium-mid-life stable	Childhood lean-mid-life increase	Childhood medium- mid-life increase	Childhood heavy-mid-life stable
No. participants (N = 3024)	869	881	843	431
Persons-years	7558	7824	7124	3465
Age at inception[a], (y)	45 (7)	48 (8)	46 (7)	45 (7)
BMI at inception of follow-up, (kg/m^2)[a]	23.9 (2.0)	25.0 (2.3)	26.9 (2.5)	26.9 (3.4)
Height, (cm)	176 (6)	175 (6)	175 (6)	176 (6)
Alcohol consumption, (g/d)	10 (13)	12 (14)	11 (13)	10 (12)
Smoking status, (%)				
Former	30	36	32	31
Current	20	25	27	25
Pack-years of smoking	7 (10)	11 (13)	10 (12)	9 (12)
Family history of hypertension, (%)	22	22	21	22
Sodium intake, (g/d)	4.1 (2.2)	4.1 (2.3)	4.1 (2.0)	4.1 (2.5)
Potassium intake, (g/d)	4.5 (1.1)	4.6 (1.2)	4.6 (1.2)	4.7 (1.4)
Whole-fat dairy products, (g/d)	231 (200)	203 (202)	201 (171)	194 (175)
Low-fat dairy products, (g/d)	161 (232)	154 (198)	190 (253)	193 (213)
Artificially-sweetened beverages, (cans/day)	0.3 (1.0)	0.4 (1.0)	0.5 (1.2)	0.7 (1.5)
Sugar-sweetened beverages, (cans/day)	1.5 (1.5)	1.4 (1.5)	1.6 (1.5)	1.4 (1.5)
Adherence to the Mediterranean diet (0–9 score)[b]	4.2 (1.9)	4.5 (1.8)	4.3 (1.8)	4.4 (1.9)
Physical activity, (METs-h/week)	32.7 (30.5)	29.0 (24.6)	27.0 (23.1)	31.3 (28.7)
Self-reported personality traits				
Competitiveness (0–10 score)	7.1 (1.7)	7.2 (1.8)	7.1 (1.7)	7.0 (1.8)
Dependency (0–10 score)	3.3 (2.8)	3.3 (3.0)	3.3 (2.9)	3.6 (3.0)
Relaxation (0–10 score)	5.9 (2.2)	6.3 (2.2)	5.9 (2.2)	5.9 (2.2)
Time spent watching TV, (hours/d)	1.3 (0.9)	1.5 (0.9)	1.5 (1.0)	1.5 (1.1)
Coffee, (cups/day)	1.3 (1.3)	1.3 (1.3)	1.4 (1.3)	1.6 (1.4)
Fried foods, (times/week)	4.4 (5.0)	4.3 (4.4)	4.1 (4.0)	3.9 (4.5)
Fast food consumption, (g/d)	23 (21)	20 (21)	22 (19)	21 (21)

Values are presented as mean (SD), unless otherwise stated.
Abbreviations: BMI, Body mass index; METs, Metabolic equivalent of task.
[a] Inception date: was the date when the initial questionnaire (Q0, time 0) was completed only for those participants who were aged ≥ 40 years at the time when they were recruited; whereas, for those participants aged <40 years when they were recruited, we defined the inception date as the date when these participants reached age 40 (during follow-up).
[b] Trichopoulou score (range of scores, 0–9, with higher scores indicating greater adherence).

medium- mid-life stable" category, the multivariable-adjusted HR (95% CI) for hypertension was 1.72 (1.17–2.53) in the "childhood heavy-mid-life increase" group, while the "childhood lean-mid-life increase" and the "childhood heavy-mid-life decrease" groups did not show any significant association. In men (Table 2b), compared with the "childhood medium-mid-life stable" trajectory, the multivariable-adjusted HRs (95% CI) for hypertension were 1.43(1.11–1.85), 1.52(1.17–1.97) and 1.56 (1.14–2.14) for the "childhood lean -mid-life increase", the "childhood medium-mid-life increase" and the "childhood heavy-mid-life stable" groups, respectively.

To examine whether smoking status and adherence to Mediterranean diet modified the association of body shape trajectories with the risk of developing hypertension, we conducted stratified analyses by sex (Tables 2a and 2b). No significant effect modifications were found in either men or women [p for interaction 0.80 and 0.59 in women and 0.79 and 0.88 in men for smoking and adherence to Mediterranean Diet respectively].

We conducted sensitivity analyses (Supplemental Tables 2a–2b.) excluding early cases of hypertension (2 and 4 first years of follow-up), and the results remained essentially unchanged.

In the last sensitivity analysis, we excluded participants who had <80% probability of belonging to the assigned trajectory group. Therefore, we excluded 1068 women and 792 men with modest trajectory assignment. After these exclusions, the point estimates in women slightly increased, and remained statistically significant in the "childhood heavy-mid-life increase" trajectory. Whereas in men, the association remained statistically significant in all trajectories of body shape.

Discussion

In this Mediterranean cohort, our results showed that midlife increases in body shape or maintaining a heavy body shape in men and mid-life increase in women who were heavy at childhood were associated with a higher risk of subsequently developing hypertension. To our knowledge this is the first study to investigate the body shape trajectory using a GBTM during the first 40 years of life in relation to hypertension.

Until now, it is well-known that overweight and obesity are strongly associated with the incidence of hypertension [7–11], the mechanisms through which adiposity

Table 2a Hazard ratio (95% CI) for hypertension in women according to trajectories of body shape, and stratified by smoking status and adherence to Mediterranean Diet in the SUN Study from 1999 to 2016.

Women	Childhood medium-mid-life stable	Childhood lean-mid-life increase	Childhood heavy-mid-life decrease	Childhood heavy- mid-life increase	p for interaction
No. cases (N = 381)	192	100	57	32	
Incidence rate	9.7	13.1	7.6	14.5	
Crude HR (95% CI)	1 Ref.	1.39 (1.09–1.77)	0.78 (0.58–1.04)	1.48 (1.02–2.15)	
Age and period adj.	1 Ref.	1.17 (0.92–1.50)	0.78 (0.58–1.05)	1.65 (1.14–2.41)	
Multivariable adj[a].	1 Ref.	1.19 (0.93–1.53)	0.77 (0.57–1.04)	1.72 (1.17–2.53)	
Stratified by smoking status					
Never smoker					0.799
No. cases/N	76/1060	42/36	18/388	11/121	
Multivariable adj[a,b]	1 Ref.	1.22 (0.82–1.81)	0.70 (0.42–1.18)	1.64 (0.85–3.17)	
Ever smoker					
No. cases/N	116/13,336	58/526	39/517	21/181	
Multivariable adj[a,b]	1 Ref.	1.14 (0.83–1.58)	0.83 (0.57–1.21)	1.77 (1.09–2.88)	
Stratified by adherence to the Mediterranean diet					
0-4 points (low adherence)					0.586
No. cases/N	108/1388	43/471	31/516	17/176	
Multivariable adj[a,b]	1 Ref.	0.99 (0.69–1.43)	0.76 (0.51–1.15)	1.56 (0.91–2.68)	
5-9 points (high adherence)					
No. cases/N	84/1008	57/416	26/389	15/126	
Multivariable adj[a,b]	1 Ref.	1.45 (1.02–2.05)	0.80 (0.51–1.25)	1.89 (1.06–3.38)	

[a] Adjusted for: family history of hypertension, physical activity, smoking status, package-years of smoking (in ever smokers), alcohol consumption, sodium and potassium intake, total energy intake, adherence to Mediterranean diet, whole-fat and low fat dairy consumption, sugar sweetened beverages, non-sugared carbonated beverages, coffee consumption, personality, time spent watching TV, fried food and fast food consumption, age and recruitment period.
[b] In each stratified analysis the variable of stratification was removed from the adjusted model.

Table 2b Hazard ratio (95% CI) for hypertension in men according to trajectories of body shape, and stratified by smoking status and adherence to Mediterranean Diet in the SUN Study from 1999 to 2016.

Men	Childhood medium-mid-life stable	Childhood lean-mid-life increase	Childhood medium- mid-life increase	Childhood heavy-mid-life stable	p for interaction
No. cases (N = 484)	98	175	143	68	
Incidence rate	13.0	22.3	20.1	19.6	
Crude HR (95% CI)	1 Ref.	1.77 (1.38–2.27)	1.56 (1.21–2.02)	1.51 (1.11–2.06)	
Age and period adj.	1 Ref.	1.51 (1.18–1.94)	1.54 (1.19–2.00)	1.57 (1.15–2.14)	
Multivariable adj.[a]	1 Ref.	1.43 (1.11–1.85)	1.52 (1.17–1.97)	1.56 (1.14–2.14)	
Stratified by smoking status					
Never smoker					0.790
No. cases/N	37/420	47/316	46/319	25/184	
Multivariable adj[a,b]	1 Ref	1.36 (0.87–2.14)	1.58 (1.01–2.48)	1.70 (1.01–2.86)	
Ever smoker					
No. cases/N	61/449	128/565	97/524	43/247	
Multivariable adj[a,b]	1 Ref	1.50 (1.09–2.06)	1.45 (1.04–2.02)	1.40 (0.94–2.10)	
Stratified by adherence to the Mediterranean diet					
0-4 points (low adherence)					0.878
No. cases/N	51/492	84/456	73/478	36/221	
Multivariable adj[a,b]	1 Ref	1.51 (1.05–2.17)	1.42 (0.98–2.05)	1.53 (0.99–2.38)	
5-9 points (high adherence)					
No. cases/N	47/377	91/425	70/365	32/210	
Multivariable adj[a,b]	1 Ref	1.37 (0.95–1.97)	1.67 (1.14–2.45)	1.64 (1.02–2.62)	

[a] Adjusted for: family history of hypertension, physical activity, smoking status, package-years of smoking (in ever smokers), alcohol consumption, sodium and potassium intake, total energy intake, adherence to Mediterranean diet, whole-fat and low fat dairy consumption, sugar sweetened beverages, non-sugared carbonated beverages, coffee consumption, personality, time spent watching TV, fried food and fast food consumption, age and recruitment period.
[b] In each stratified analysis the variable of stratification was removed from the adjusted model.

produces high blood pressure are mainly centered in the roles of impaired renal-pressure natriuresis because of physical compression of the kidneys (by fat in and around the kidneys) and by the activation of the renin–angiotensin–aldosterone system and sympathetic nervous system [35].

Previous studies, for example, the study conducted in the late 80's by Sonne-Holm et al. [36], before the novel GBTM approaches were implemented, tried to assess the impact of previous changes in weight on blood pressure. The approach that they used was, to create 4 groups of BMI at the first examination, and then another 4 groups at the final examination, therefore 16 groups were created, and then the prevalence of hypertension was assessed in all groups. Hypertension was more prevalent in subjects who had increased their BMI. For each unit of increment in BMI, the risk of hypertension increases in 7% [OR = 1.07 (1.06–10.8)] in obese subjects, and 15% in non-obese [OR = 1.15 (1.04–1.27)]. More recently, a pooled analysis of 4 cohort studies designed to investigate cardiovascular risk factors that initially involved children and have followed-up participants into adulthood, analyzed data involving 6328 participants to determine whether a change in BMI from childhood to adulthood, was associated with hypertension. In this way, authors created 4 groups and compared children with normal BMI in childhood and continued as normal-BMI adults to the other 3 groups (normal BMI children who became overweight/obese adults, overweight/obese children who became normal BMI adults, and overweight/obese children who remain overweight/obese adults). The relative risks for hypertension were 0.9 (0.5–1.8) for the overweight or obese in childhood, non-obese in adulthood; 2.8 (1.8–4.4), for the overweight or obese in childhood, obese in adulthood group; and 2.1 (1.4–3.3), for the normal BMI in childhood, obese in adulthood group [37], which is in a way in accordance with our results. A recent study found that changes in body weight during early and middle adulthood were associated with higher risk of hypertension. The incident rate ratio (IRR) of hypertension for those who gained from 2.5 to 10 kg were 1.24 (1.20–1.28) and 1.21 (1.12–1.31); for those who gained from 10 to 20 kg were 1.58 (1.53–1.64) and 1.63 (1.50–1.77) and for those who gained more than 20 kg were 2.10 (2.02–2.19) and 2.12 (1.91–2.34) for women and men respectively in each case [14].

A potential limitation of our study is the self-reported nature of both exposure and outcome. However, we published a study that assessed the validity of self-reported diagnosis of hypertension finding an adequate validity for the self-reported diagnosis of hypertension [25]. Another limitation could be that participants may tend to underreport their body shape image, however a previous validation study regarding self-reported weight and BMI and self-reported body shape was conducted [23,38]. To restrict the participation to only university graduates might be thought to be another limitation of our study, because it is not a representative sample. Indeed, this may have affected the generalizability of our findings; and our findings need to be interpreted with caution if we want to extrapolate these results to the general population. Nevertheless, this restriction enhanced the internal validity of our study because the high level of education and homogeneity of the cohort reduced the potential confounding related to socioeconomic status and it also improved the quality of the self-reported information. Moreover, the generalizability of our findings must be based on biological mechanisms and not in the representativeness of the sample. Finally, another possible limitation of our study might be a misclassification in trajectory assignment, however, we conducted diverse sensitivity analyses, also excluding participants whose trajectory assignment probability was less than 0.80, and our sensitivity analyses showed that our results were robust to modest trajectory misclassification. The strengths of our study are the relatively large sample size, the long follow-up period, and the fact that we were able to control for a wide array of potential confounders. Also a strength of our study is the prospective design and the novel statistical method that we used to examine the trajectories of body shape throughout lifespan, which provided a novel alternative to traditional analyses, and help to better understand the developmental course of hypertension in relationship with between-subject differences in within-person change in body shape, and at the same time this statistical approach facilitates causal inference in epidemiological observational studies [39].

In conclusion, our results suggest that in this Mediterranean cohort study, mid-life increases in body shape or maintaining a heavy body shape during the lifespan in men and mid-life increase in women who was heavy at childhood was associated with a higher risk of subsequently developing hypertension. This study strengthens the importance of maintaining a healthy body shape throughout the life span.

Conflict of interest

None.

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MAM-G and MB-R helped to design the study and collect data. CS-O, DH, MS analyzed the data; DH, MS, FBH, LR, MB-R and MAM-G provided insight into result interpretation; CS-O drafted the manuscript. All authors edited and critically reviewed the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2018.12.004.

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